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Systematic Review of Measles, Mumps and Rubella Vaccination Programs in Selected European Countries and the Influence of Migration Movements

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Acronyms

BMG Bundesministerium für Gesundheit, (Austrian Federal Ministry of Health). 21, 47, 106, 398

CDC Centers for Disease Control and Prevention. 3, 5, 21, 307, 398

CHC Child Health-Care Center. 56

CISID Centralized Information System for Infectious Diseases (WHO, Regional Office for Europe). 23, 156, 406

CLIA Chemiluminescence Immunoassay. 358

CMV Cytomegalovirus. 358, 390, 391

CNESPS Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute (Italian National Center for Epidemiology, Surveillance and Health Promotion). 68

CNS Central Nervous System. 9, 14

CRI Congenital Rubella Infection. 18, 341, 368, 369, 392

CRS Congenital Rubella Syndrome. 16–19, 146, 147, 149–151, 154, 156, 194–198, 203, 204, 220, 343, 360, 364, 368, 396

CTV Comité Technique des Vaccinations (French Advisory Board on Vaccination). 48

DHSSPS Department of Health, Social Services and Public Safety (Northern Ireland, UK). 22

ECDC European Center for Disease Prevention and Control. 7, 8, 21, 23, 45, 55, 61, 66–68, 70, 71, 122, 124, 126, 128, 144, 175, 184, 193, 198, 206, 207, 221, 223, 225, 242, 244, 251, 307, 357, 366, 367, 399, 400

EE Eastern Europe. 6, 38

EIA Enzyme-linked Immunoassay. 347, 359, 386, 392

ELFA Enzyme-Linked Fluorescent Assay. 391

ELISA Enzyme-Linked Immunosorbent Assay. 333, 335, 337–340, 344, 349, 352, 354, 356, 369, 377–379, 390

EPHPP Effective Public Health Practice Project. 28, 322

EpiCentro Italian National Center for Epidemiology, Surveillance and Health Promotion. 21, 399

EU European Union. 7, 43, 68, 242, 399, 400

EuroTravNet European Travel Medicine Network. 45

EUVAC.NET European Surveillance Network for Vaccine-Preventable Diseases. 23, 66, 67, 80, 122, 128, 144, 251, 364, 367–369, 373, 396

GDP Gross Domestic Product. 3–6, 27, 36–39, 310, 311

GNI Gross National Income. 3–6, 27, 36, 37, 310

HCDCP Hellenic Centre for Diseases Control and Prevention (Greece). 21

HCSP le Haut Conseil de la Santé Publique (French High Council of Public Health). 48

HE Health Expenditure. 38, 39

HPA Health Protection Agency (United Kingdom). 22, 56

HPS Health Protection Scotland. 22

HPV Human Papillomavirus. 232, 245, 256

HZJZ Hrvatski Zavod za Javno Zdravstvo (Croatian National Institute of Public Health). 21, 58, 401

IgG Immunoglobulin G. 105, 108–110, 115, 116, 140, 141, 168, 172, 174, 176–178, 180–182, 185–187, 189, 191, 192, 218, 333, 335, 337–340, 342, 343, 347, 349–352, 355, 356, 358–360, 377–379, 389–392

IgM Immunoglobulin M. 204, 333, 343, 344, 347, 352, 356, 360, 386, 387, 390–392

INPES Institut National de Prévention et d'Éducation pour la Santé (French National Institute for Prevention and Health Education). 48

InVS Institut de Veille Sanitaire (French Institute for Public Health Surveillance). 21, 48, 109, 345, 387, 402

ISCIII Instituo de Salud Carlos III (Spain). 22, 54, 55, 401

JCVI Joint Committee on Vaccination and Immunisation (UK). 57

KiGGS Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (Health of Children and Adolescents in Germany Study). 104, 105, 108–111, 113, 115, 116, 137, 140, 141, 175, 176, 178, 180, 184, 188, 190, 191, 218, 375–380

MCV Measles-Containing Vaccine. 11–13, 62, 96, 97, 99, 104, 106, 107, 109, 110, 114, 116, 117, 306, 373

MCV-1 Primary MCV Dosage. 12, 96, 97, 104–106, 110, 112, 113, 115, 116, 214, 222, 336

MCV-2 Secondary MCV Dosage. 12, 96, 97, 103–107, 109, 113, 121–123, 211

MeaNS Measles Nucleotide Surveillance. 10

Medline Medical Literature Analysis and Retrieval System Online®. 21, 24, 31, 61, 123, 146

MEIA Microparticle Enzyme Immunoassay. 343, 355, 360

MM Measles-Mumps Vaccine. 11, 306

MMR Measles-Mumps-Rubella Vaccine. 11, 13, 15, 18, 22, 30, 31, 47, 49, 60, 62, 63, 65, 104, 105, 108, 113, 115, 117, 120, 124, 136, 137, 140, 144, 149, 166, 176, 179, 183, 184, 188, 190, 213–218, 220, 221, 223–225, 229, 231–237, 239, 240, 246, 256, 257, 259, 306, 335–337, 355, 359, 360, 366, 382, 389, 390, 399, 403, 406

MMR-1 Primary MMR Dosage. 62, 238, 256

MMR-2 Secondary MMR Dosage. 107, 108, 137, 139, 171, 212, 213, 215, 216, 228, 233–235, 238, 256

MMRV Measles-Mumps-Rubella-Varicella Vaccine. 11, 149, 306

MR Measles-Rubella Vaccine. 11, 306

MSPSI Ministerio de Sanidad, Servicios Sociales e Igualdad (Spanish Ministry of Health, Social Services and Equality). 105, 402

NE Northern Europe. 5, 38

NFZ Narodowy Fundusz Zdrowia (Polish National Health Fund). 59

NIP National Immunization Program. 52, 53, 55, 59, 60

NIZP Narodowy Instytut Zdrowia Publicznego (Polish National Institute of Public Health). 22

NRW North Rhine-Westphalia (German federal state). 112, 114, 382, 383

PCR Polymerase Chain Reaction. 204, 354, 369

PHE Public Health England. 22

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses. 20

r Pearson correlation coefficient. 209

$\mathbf{R}_o$ Basic Reproductive Number. 10, 14, 17

RCV Rubella-Containing Vaccine. 18, 166, 168, 175, 176, 178, 180, 183, 184, 193, 306

RKI Robert Koch Institut (Germany). 21, 52, 335, 404

RNA Ribonucleic Acid. 10, 14, 17, 345, 347, 362, 364, 366, 380, 390, 391

SA Surface Area. 32

SCI-Expanded Science Citation Index Expanded™. 21, 24, 31, 61, 124, 146

SE Southern Europe. 4, 5, 38

SES Socioeconomic Status. 113–115, 141, 189, 325

SIA Supplementary Immunization Activities. 217, 235, 239, 245

SMI Smittskyddsinstitutet (Swedish Institute for Infectious Disease Control). 22, 56

SSCI Social Sciences Citation Index®. 21, 24, 31, 61, 124, 146

SSPE Subacute Sclerosing Panencephalitis. 9, 17

STIKO Ständige Impfkommission (German Standing Committee on Vaccinations). 51, 52, 404

TESSy The European Surveillance System. 66

TORCH Toxoplasma gondii, (Other), Rubella, Cytomegalovirus, Herpes simplex Viruses. 392

UK United Kingdom of Great Britain and Northern Ireland. 3, 5, 33, 36, 39, 41, 44, 125–127, 145, 202–206, 208, 218, 220, 222, 231, 235, 249, 355, 361, 395

UN United Nations. 3, 4, 6

UNICEF United Nations International Children's Emergency Fund, since 1953 United Nations Children's Fund. 21, 96–99, 122, 136, 144, 166, 167, 175, 198, 307, 396, 407

USA United States of America. 90, 220, 229, 234, 240, 356, 398

VENICE Vaccine European New Integrated Collaboration Effort. 22, 49, 106, 224, 225, 233, 366, 406

VPD Vaccine-Preventable Disease. 2, 8, 25, 45, 55, 311

WE Western Europe. 3, 4, 38

WHO World Health Organization. 2, 3, 5, 8, 10, 12, 13, 15, 18, 19, 21, 23, 29, 30, 55, 61, 62, 66–68, 71, 80, 96–100, 105–107, 109, 122–124, 126, 136, 144, 146, 150, 151, 154, 156, 166–168, 175, 178, 197–200, 202–204, 206, 208, 209, 211, 213, 214, 221, 227, 230, 238, 242, 244, 250, 251, 255, 256, 258, 259, 307, 338, 341, 355, 362–364, 366, 369, 371, 373, 377, 380, 384, 386, 387, 393, 395, 396, 406–408

1. Introduction and Background

1.1. Aims

The World Health Organization has established the goal of eliminating measles and rubella from the European region by the of 2015.[310] The primary aim of this dissertation is to assess the progress various selected European nations have made in reaching this objective. A comprehensive overview of current vaccination recommendations, immunization statistics and epidemiological data is provided for the vaccine-preventable diseases measles, mumps and rubella. A secondary aim is to evaluate the role travel and migration play in the sustenance of these diseases in Europe. The question of whether a uniform, European-wide immunization recommendation would be feasible is discussed.

The European countries included in the research are Austria, Croatia, France, Germany, Greece, Italy, Poland, Spain, Sweden, Turkey, and the United Kingdom. A comparison between these countries is made regarding various demographic, epidemiological and vaccination variables. Literature-supported analyses of the success of each nation's measles, mumps, and rubella immunization plans are performed based on annual disease incidences and national vaccination rates. Furthermore, the susceptibility among various populations are identified in order to determine the necessity for a standardized international immunization schedule.

1.2. Background

In modern medicine, disease prevention is becoming increasingly relevant. The most established prevention method available for infectious diseases, next to proper hygiene, is immunization. Since the introduction of vaccinations, the number of outbreaks and deaths due to communicable disease has been reduced tremendously. According to the World Health Organization (WHO), an estimated 2 to 3 million deaths are averted annually as a result of vaccinations.[29]

Due to the unambiguous preventative effects of immunizations in improving public health, the WHO strongly urges all member states to "achieve and maintain high levels of population immunity" against such vaccine-preventable diseases (VPD) as measles and rubella.[304] In 2005, the WHO Regional Committee for Europe initiated a plan for the elimination of these two diseases in the entire European region by 2010.[310] Five years later, the European Member States recommitted to the measles and rubella elimination goal, with the new target set to 2015.[310]

Each European country follows its own strategies for attaining high levels of immunity among their resident populations. The immunization plans differ widely and are in some nations inconsistent even among regions of the same country. Such variances in vaccination strategies are addressed for selected European nations regarding the VPDs measles, rubella and the frequently co-vaccinated mumps. A systematic literature search of the immunization recommendations, vaccination rates and epidemiological statistics for the European nations listed above is performed, and the success of each program analyzed. The "best practice" immunization plans are summarized and the feasibility of a homogeneous, European-wide vaccination schedule is discussed.

In the following sections, the countries chosen in this report, as well as the influence of migration to and from these nations, are briefly introduced. A further section outlines the three diseases focused on in this research.

1.2.1. Selected European Nations

In 2010, the WHO Regional Office for Europe and the United States Centers for Disease Control and Prevention (CDC) evaluated the likelihood of measles elimination among all European member states.[175] Several nations had already been successful at continually preventing the transmission of measles, including Finland, Norway and Iceland.[175] Most of the other European nations had been assessed as less likely to reach the elimination goals by the end of the year, however.[175]

For the purposes of this report, countries that had not yet achieved measles control as of 2010 were selected in order to evaluate the progress made since. Due to logistic reasons, not all of these nations could be included, however. Eleven countries of four different geographic subregions were therefore chosen as representatives for the European continent: Austria, Croatia, France, Germany, Greece, Italy, Poland, Spain, Sweden, Turkey and the United Kingdom of Great Britain and Northern Ireland (UK). Their geographic allocation is based on the division provided by the United Nations (UN),[288] with the exception of Croatia and Turkey (see below). The nations are briefly introduced below in terms of indicators pertinent to communicable diseases and vaccinations. More detailed information about each country regarding population, health, education, and economic development indicators is provided in Section 3.1.

Western Europe

The representative Western European (WE) countries selected are Austria, France, and Germany. All three nations were assessed by the WHO and CDC as "unlikely" to eliminate measles as of 2010.[175]

Like most Western European nations, these countries have stable economies with high gross domestic products (GDP) and gross national incomes (GNI).[285] The public expenditures on health and education, measured as percentages of GDP, are also

higher than for most other countries included in this report.[285] The infrastructure in each of these nation is highly developed, and all residents have access to basic and advanced health care.

Due to their stable economies and centralized location in Europe, all three nations are commonly frequented by migrants and travelers. Germany has the largest immigrant population, France the most annual tourists, and Austria one of the highest migrant-to-native population ratios of all countries included in this report.[285] Though the countries' population indicators, including population growth and density, vary (see Section 3.1.2), they are overall comparable and representative for the Western European region.

Southern Europe

The countries chosen as representative for Southern Europe (SE) are Greece, Italy and Spain. (Croatia, classified as Southern European by the UN,[288] is here grouped among the Eastern European nations based on its geographic location as well as its similarities to those nations.) The elimination of measles by 2010 was evaluated as "probable" in Greece and Spain and "unlikely" in Italy.[175]

Economically, these three countries have somewhat lower GDPs and GNIs than the Western European nations do.[285] The spending on health care and education is also less than among the WE-states.[285] All three nations have unemployment rates that are among the highest in Europe.[285]

The population indicators, including annual growth, birth and death rates, are comparable to those of most other European nations and have been slightly decreasing in the past years.[285] Population densities vary among this group, however. While Spain and Greece have fairly low densities, Italy has one of the highest in Europe (see Section 3.1.2).[285]

The SE countries have been particularly affected by recent increases in migrant and refugee arrivals. Spain has the third highest immigrant population, after Germany and France, and Italy has one of the highest net migration rates as of 2012.[285] Nearly 12 million immigrants and refugees were reported in all three of the SE countries in 2010.[285] In addition, more than 82,500 people were seeking Asylum in these nations in 2011 and 2012.[23]

Northern Europe

Both Sweden and the United Kingdom of Great Britain and Northern Ireland were chosen as representative nations for Northern Europe (NE). Only two countries were selected due to the comparatively low number of nations that had not yet achieved measles control. Sweden was classified by the WHO and CDC as "probable" and the UK as "unlikely" to achieve the 2010 elimination goals.[175]

Overall, both of these countries have stable economies. The UK has the third highest GDP and GNI, after Germany and France.[285] Sweden's economy is not quite as strong, but also stable, and the county's public education expenditure is among the highest in the world.[285] The proportions of the GDPs dedicated to health expenditure in both countries are slightly lower than among the Western nations, but are higher than those among the Southern and Eastern European countries.[285]

The UK population has the highest density of all included European nations.[285] The annual net migration rate to the UK is also among the highest and was matched with that of Italy in 2012 (see Section 3.1.6).[285] Sweden, on the other hand, has a comparatively low population density and lower immigration rate.[285] The population growth rates are nonetheless higher in both Sweden and the UK than in most other European nations, predominantly due to fairly high annual birth rates.[285] The only country surpassing these nations in annual population growth is Turkey (see below).

Eastern Europe

The Eastern European (EE) representative nation chosen was Poland. For the purpose of analysis, Croatia (classified as Southern European by the UN) and Turkey (classified as Western Asian by the UN) are also included in this group. In 2010, the elimination of measles was assesses as "probable" in Poland and Turkey and "feasible" in Croatia.[175]

Economically, these countries are among the least wealthy in Europe. Based on the 2010 national GDPs and GNIs, Croatia was the poorest of the European nation included in this report.[285] The poverty rate is very high among many Eastern European populations, having reached up to 18.1% in Turkey in 2009.[285] As such, not all citizens of these nations have access to improved water sources and sanitation facilities, particularly in rural areas.[285]

The population indicators show that the Eastern European population growths rates are widespread. Turkey has the highest birth rate of all European nations, whereas Croatia has one of the lowest.[285] The Turkish population also experiences a tremendous annual growth rate of $>1.2\%$, whereas Croatia's population is declining by about 0.3% annually (2012 data).[285] Poland's population dynamics, on the other hand, are stable and average compared to those of the other European nations.

While the 2012 net migration rates were positive in most European nations, they were negative in Croatia and Poland due to a higher number of people emigrating than immigrating.[285] The total immigrant and refugee populations living in these two countries are also the lowest among all included nations.[285] However, because of the low overall population in Croatia, the country has the highest immigrant-to-native population ratio.[285] Turkey, on the other hand, has a larger immigrant and refugee population than several of the other selected countries do, but the lowest immigrant-to-native population ratio of all included countries.

The European nations briefly described above all differ in economical development and population indicators. In spite of the geographic proximity of all these nations, they face distinct demographic situations that influence the epidemics of communicable diseases and the prevention thereof through available vaccinations. As a result of travel and migration, these demographics are changing, however, and impacting the immunization statuses of people residing in Europe.

1.2.2. Migration and Travel

Migratory activities are a not to be disregarded factor influencing disease outbreaks and immunization statistics. Since the establishment of the European Union (EU), travel and migration between its member states has become much simpler and the subject of immigration has gained increasing relevance. As more people are moving to different countries, the populations within Europe are changing and with them, the immunization statuses of regional populations. Due to differences in health care systems, vaccination recommendations, and exposure to communicable diseases, most foreign-born residents' immunization statuses differ from those of non-foreign residents. Next to tuberculosis and hepatitis B, measles and rubella infections are described frequently among immigrant populations, as stated in a report on migrant health by the European Center for Disease Prevention and Control (ECDC).[104] Furthermore, vaccines against rubella are not readily available in many immigrants source countries, including most African and Eastern Mediterranean nations, thus resulting in a high susceptibility among migrants from these regions.[304]

From an infection control and prevention point of view, such tremendous variances in vaccination recommendations may pose a considerable concern, as the diverse immunization statuses disrupt the herd immunity effect within a population. The concept of herd immunity signifies that those persons with weaker immune systems, such as infants, pregnant women, the elderly, chemotherapy patients or other immunocompromised individuals, who are at risk for a myriad of infectious diseases, may be shielded from disease through the immunocompetent persons around

them.[147] Hence, consistent vaccinations of the general population keep the collective immunity high. Pockets of low levels of immunity within a population, however, pose an increased risk for disease outbreaks and resulting complications, particularly among the immunodeficient subpopulations. The need for consistent immunizations of all persons able to be vaccinated thus becomes evident.

The ECDC has identified several hard-to-reach groups that may contribute to the perpetuation of vaccine-preventable diseases in Europe: vaccine-opposing groups, such as some religious and anthroposophic communities, and migrating populations, such immigrants and traveling ethnic minorities.[180] This report focuses on the latter. Measles, mumps and rubella cases among migrants as well as the level of susceptibility among these populations are therefore analyzed below.

1.3. Overview of Vaccine-Preventable Diseases

The following section introduces the three VPDs analyzed and discussed in this report: measles, mumps and rubella. Each of these infectious diseases is described with regard to the underlaying pathogen, its infectivity and transmission, as well as the symptoms and complications of the disease. The disease-specific immunization mechanisms and available vaccination types are also introduced.

1.3.1. Measles

Measles is a viral infectious disease with a high global disease burden. According to the WHO, approximately 158,000 people died of measles worldwide in 2011, most of them young children below the age of five years.[311] Globally, this preventable disease is still a leading cause of death among children. Although about 95% of measles fatalities occur in low-income nations with weak health infrastructures, the mortality rate is with 1-3 per 1000 cases considerably high in high-income nations

with well-developed health care systems as well.[107,311] These fatalities are mainly due to the serious complications that may occur through a measles infection.[107]

Symptoms and Complications

Measles typically presents with a high fever and enanthema, followed by a maculopapular exanthema. During the prodromal phase of the disease, patients may have unspecific coryza syndromes, including a barking cough, runny nose and conjunctivitis or keratitis.[311] Typically one or two days after the onset of symptoms, the fever drops slightly and so-called *Koplik's spots*, or clustered white, chalk-like lesions, appear on the darkened oral mucosa. Another three to four days later, the exanthematous phase begins with a new rise in temperature and a maculopapular rash that starts behind the ears and spreads across the face, trunk and finally the extremities. The exanthema usually lasts for about three days and then fades quickly. The fever drops rapidly as well, but a generalized lymph-node swelling may persist.

Atypical clinical presentations are possible and include *mitigated measles*, typically seen among young infants with persistent maternal antibodies and patients who have received immunoglobulins, *atypical measles*, occasionally seen among adults who had received an inactivated measles immunization as a child, and *non-exanthematous* (or "white") *measles*, typically seen among patients with T-cell immunodeficiencies.[277] The latter two may present with serious pulmonary infection and, in the case of immunodeficiency, a giant-cell pneumonia, frequently associated with a high mortality rate.[277] Besides pneumonia (occurring in 1-6% of all cases), other common complications of a measles infection are otitis media (in 7-9%), diarrhea (in 7-8%), and other secondary bacterial infections.[107,277]

More serious complications include encephalitis (occurring in 0.05-0.2%) and the rare but fatal subacute sclerosing panencephalitis (SSPE), which occurs in 7-11/100.000 measles cases.[277] SSPE is a degenerative central nervous system (CNS) disease

occurring through the persistence of measles viruses in the brain and a reappearance thereof 5-10 years after the original measles infection.[107] The disease typically affects children between the ages of 8 and 11 years and is marked by dementia, neurological deficits, myoclonic and cerebral seizures, severe central and vegetative regulatory disorders and death.[277] To date, no specific therapy exists.[277] Prevention through vaccination against measles is the only effective method against these complications.

Pathogen and Transmission

The measles pathogen is a single-stranded ribonucleic acid (RNA) morbillivirus of the family *Paramyxoviridae*. To date, 24 viral genotypes in eight clades (A through H) have been isolated worldwide, but only one serotype exists.[261,305] The identification of genotypes through molecular analysis of clinical samples from infected individuals allow for the epidemiological linking of cases and the recognition of importation sources in outbreak situations. The WHO-associated Measles Nucleotide Surveillance database (MeaNS), for instance, provides comprehensive information regarding measles epidemiology.[257]

Humans are the only reservoir for measles, signifying that they are only spread from one human to another and do not affect other species.[107] The transmission route is through respiratory droplets, so that these pathogens can be transmitted via close contact, coughing or sneezing.[107] The live viruses are able to remain in the air for several hours[107]- a fact that must be taken into consideration when trying to prevent the transmission of measles.

The virulence and force of infection of the measles viruses are extremely high, with a basic reproductive number (R_o) of 12 to 18.[107] This value indicates that when one person with measles enters into a population of non-immune individuals, on average, 12 to 18 other persons will be infected with the virus during the infectious period. These individuals will then each spread the disease to, on average, another

12 to 18 persons, and the chain of infection continues in a similar pattern. The contagiosity (or ease with which the disease spreads from one person to another) is 90% among non-immune individuals, and the infectivity (or abilitiy of the virus to infect the host, once contracted) is 100%.[107] Measles are thus one of the most highly contagious diseases that may spread rapidly among a non-immune population.

The incubation period of measles is 8-12 days, and the contagiosity period spans from about 3-5 days before the onset of symptoms until about 4 days after the clinical signs subside.[107,277] The period before the first symptoms appear, or before they are diagnosed correctly, may be the most critical in regard to disease transmission, as the infected person may not yet know that he is contagious. Particularly at-risk for disease contraction are infants, immunocompromised individuals, non-vaccinated individuals and those with a primary or secondary vaccine failure.[107]

Prevention and Vaccination

The only effective preventative method against measles is vaccination. Measles vaccines consist of live attenuated (live but non-pathogenic) viruses that induce cellular and humoral immune responses in vaccinated individuals.[301] They are available as monovalent or polyvalent inoculants. The polyvalent vaccines may consist of a combination of a measles vaccine with a rubella vaccine (MR), with a mumps vaccine (MM), with a rubella and mumps vaccine (MMR), or with a rubella, mumps and varicella vaccine (MMRV).[305] These inoculants are frequently grouped under the name measles-containing vaccines (MCV).

Various strains of the measles vaccines exist, most of them derived from the *Edmonston strain*, first isolated in 1954; these include the Edmonston-Zagreb, Moraten and Schwartz strains.[305] Others include the TD 97, CAM-70, Leningrad-16 and Shanghai 191 (or Ji-191) strains.[305] These strains do not differ in their clinical effectiveness and are all deemed safe and interchangeable by the WHO.[301] In Europe, the

Schwarz and Edmonston strains are most commonly used in commercially available vaccines.[325]

Recommendations for the age at which measles vaccination should be given and the number of dosages to achieve optimal protection are made by the WHO in vaccine position papers based on extensive studies performed worldwide.[301] The first MCV dosage (MCV-1) is recommended for all infants (for whom the vaccine is not contraindicated) as soon as protective maternal antibodies have faded. This typically occurs after the first 6-9 months of life. However, studies have shown that a single vaccination at age 8-9 months only leads to a median seroconversion of 89.6% (interquartile range: 82%-95%), whereas a vaccination at age 11 to 12 months leads to a median seroconversion of 99% (interquartile range: 93%-100%).[301] The antibody response and subsequent protection against measles is thus improved if the children are vaccinated around their first birthday. Regardless of the age of the primary dosage, a secondary dosage (MCV-2) is recommended during childhood so that those with a failed initial immune response may achieve immunity. The WHO does not recommend a specific age for the MCV-2 dosage, but urges all countries to include both dosages in their national immunization programs either at a scheduled age or through routine mass vaccination campaigns.[301] In Section 3.3.2, the included nations' individual recommendations for both MCV dosages are detailed.

The WHO European Region member states are currently aiming to eliminate measles by 2015.[310] An elimination is defined by the WHO as "the absence of endemic measles transmission in a defined geographical area (e.g. region or country) for $\geq$12 months in the presence of a well-performing surveillance system".[307] Endemic transmission is, in turn, defined as "the existence of continuous transmission of indigenous or imported measles virus...that persists for $\geq$12 months in any defined geographical area".[307] In addition, it is noted that the absence of endemic measles transmission must be sustained for a period of at least 36 months in order to verify the elimination.[307] For the European nations to reach this objective, an overall population immunity of $>$95% is necessary.[301] Furthermore, surveillance systems that not only detect all measles cases but can also identify whether or not they

are endemically linked are crucial. The current measles immunization situation in Europe, the progress that has been made in reaching the elimination target, and the potential need for standardized MCV immunization recommendations are analyzed and discussed below in Chapters 3 and 4.

1.3.2. Mumps

Mumps, also known as Parotitis epidemica, is an infectious disease of the salivary glands, typically affecting children and young adults. The most frequently affected age group is between 5 and 9 years old, though a trend towards higher incidences among adolescents and young adults is being observed.[247,306] The global disease burden of mumps is considerably lower than that of measles and rubella, and as such, the WHO does not consider the control of mumps to be as high a priority.[306] Nonetheless, routine mumps vaccinations are recommended in nations with existing measles and rubella immunization programs, as these inoculants are easily combined in the form of MMR-vaccinations.[306]

Symptoms and Complications

Mumps is typically a mild, self-limiting disease, but complications may occur, particularly among males.[306] The disease symptoms vary widely, from clinically silent or mild, cold-like symptoms (about 50% of all cases) to severe complications (rare).[277] In about 30-40%, mumps presents with a typical bilateral or (less often) unilateral swelling of the parotid salivary glands, accompanied by fever, headache, myalgia, and malaise.[277,306] Other glands and organs may be affected by the virus as well, including the pancreas (pancreatitis), ears (deafness), heart (myocarditis), kidneys (nephritis), breast tissue (mastitis), ovaries (oophoritis) and testes (orchitis).[247] Especially an infection of the testes, occuring in about 15-30% of males, can cause severe pain and complications for adolescents and young men, leading to atrophy of the testes, reduction in sperm production and sterility.[247] After puberty, an orchitis

may be the only mumps symptom infected males present with.[277] Further complications include permanent deafness, viral meningitis, and encephalitis. Particularly the CNS symptoms may leave permanent damage or even lead to death.[247] No specific therapy for mumps exist. Vaccination is therefore the only effective prevention of these rare, but severe complications.

Pathogen and Transmission

Mumps, like measles, is caused by a single-stranded RNA virus of the family *Paramyxoviridae*, but of the *Rubulavirus* genus. Only one mumps serotype exists, but 14 different viral genotypes (A through N) have been isolated.[247] These genotypes vary by geographical location; in Europe, particularly the genotypes A, C, D, G and H are observed, whereby G is the most prevalent.[247]

Humans are the only reservoir for mumps.[247] The transmission route is through respiratory droplets and contact to saliva or saliva-coated objects. Because the virus predominantly affects mucous glands, the saliva of affected individuals is highly contagious.[277] However, the mumps virus is also very susceptible to damage through heat, light, ultraviolet-rays, soaps and disinfectants, making it is easier to control than many other pathogens.[247]

The virulence of the mumps virus is only slightly lower than that of the measles virus, with an average R_o of 10 to 12.[127] This high level of contagiosity causes the disease to spread easily among a non-immune population. After a very long incubation period, ranging from 12 to 25 days (most frequently 16-18 days), an infected individual can transmit the disease in a period of 7 days before until 9 days after the onset of symptoms.[247] Persons with clinically non-apparent infections may also spread the disease to others. From an infection control point of view, these clinically silent or very mild cases (up to 50%) may pose a threat to at-risk individuals who are not or can not be immunized against mumps.

Prevention and Vaccination

As with the other diseases included in this report, the only effective preventative against mumps method is vaccination. Like the measles vaccines, available mumps vaccines consist of live attenuated viruses and are obtainable as monovalent or polyvalent inoculants. The most frequently used vaccine combination is the trivalent measles-mumps-rubella (MMR) vaccine.[306] (See Section 1.3.1 for other available polyvalent inoculants).

The different attenuated strains of mumps include the Jeryl-Lynn, Leningrad-3, Leningrad-Zagreb, RIT 4385, S79 and Urabe AM-9 strains.[306] The seroconversion of these strains is near or above 90% after one dosage.[300] Commonly used strains in commercial preparations available in Europe are the Jeryl-Lynn , RIT 4385 and Urabe AM-9 strains.[325]

WHO recommendations for the age and dosages of mumps vaccines closely match those of the measles and rubella vaccines, since they are often applied as combination preparations (see Section 1.3.1).[300] As with measles, two dosages are necessary to establish adequate long-term immunity. The first dose is recommended at age 12-18 months and the second dose at least one month later but at any time between age 1 and 6 years.[300] The mumps immunization recommendations in the countries included in this report, as well as the individual vaccination success data, will be further analyzed in the Results (Chapter 3) and Discussion (Chapter 4) below.

1.3.3. Rubella

Rubella, also known as German measles because of its first mention in Germany, was endemic to Europe and the cause of frequent large outbreaks prior to the introduction of vaccines.[112] Acute rubella is typically a mild, exanthematous disease affecting children as well as adults. Though the exanthematous disease itself rarely presents with major complications, its teratogenic effects can cause severe disabili-

ties among the children of infected pregnant women and may lead to the termination of a pregnancy through fetal death. The disease burden of rubella, and particularly the congenital rubella syndrome (CRS), thus remains high.

Symptoms and Complications

The symptoms of a non-congential rubella infection include fever, malasie and conjunctivitis. Occipital, cervical and postauricular lymph node swelling often accompanies these symptoms. After about 5-10 days, the for rubella characteristic pink, small-sized, maculopapular and pruritic rash starts behind the ears and generalizes within 24 hours. After another 1-3 days, the rash starts to fade and disappear. Up to 50% of infected individuals may show no symptoms at all.[302]

The most frequently occurring complications of non-congential rubella affect the joints in form of arthritis and arthralgias. As many as 70% of adolescent girls and adult women experience joint symptoms during a rubella infection.[302] Children and men are less commonly affected. Other complications are rare and include thrombocytopenia (approximately 1 in 3,000 cases), post-infectious encephalitis (approximately 1 in 6,000 cases), and the Guillain-Barré syndrome (extremely rare).[112,302]

While the complications of an acute rubella infection are mild or rare, those of the congential infection are frequent and often severe. Particularly an infection during the first trimester of a pregnancy will lead in an about 90% of cases to fetal defects and/or death.[183] The risk of fetal complications associated with a maternal rubella infection declines after about 10-12 weeks of pregnancy and is low after the 16th week, with the exception of sensorineural hearing deficits, which may appear even if rubella was contracted at a later stage of pregnancy.[112] The complete clinical picture of the congenital rubella syndrome includes auditory, opthalmic, craniofacial and cardiac defects: sensorineural deafness, cataracts, glaucoma, micropthalmia, microcephaly, ventricular septal defects, pulmonary artery stenosis, and persisting ductus arteriosus, among others.[302] CRS may also appear after the

child has been born, leading to neonatal meningoencephalitis, hepatosplenomegaly, hepatitis, thrombocytopenia, and other complications.[302] Even after the neonatal period, affected infants may show signs of severe developmental delay and disabilities. Though rare, progressive encephalopathies similar to SSPE (see Section 1.3.1) have been described.[286]

Pathogen and Transmission

The Rubella pathogen is a single-stranded RNA virus of the *Togaviridae* family and *Rubivirus* genus. The spherical virus consists of a lipid sheath with glycopeptides E1 and E2. The E1 peptide is responsible for hemagglutination and infection of the host cells, and is thus frequently used in diagnostics.[248] In the mature virus, the E1 and E2 peptides exist as a heterodimer, which serves as target for neutralizing antibodies.[248] To date, only one serotype is known, but 13 different genotypes in two phylogenetic clades have been isolated.[302] In spite of the varying genotypes, no antigenic differences have been found.[112]

The sole reservoir for the rubella virus is humans. Though structurally similar alphaviruses of the *Togaviridae* family may cause encephalitides among non-human vertebrates, no antigenic cross reactions between these viruses and the rubella virus have been documented.[70,248] The transmission of rubella occurs, like measles, through respiratory droplets in form of coughing, sneezing, and direct contact to infected individuals. Pharyngeal secretions and the urine of children with CRS may be infectious for well over a year.[302]

The virulence of the rubella virus is comparatively low, with an R_o averaging about 6 in Europe (compared to 12-18 for measles, see Section 1.3.1).[181] Higher values up to an R_o of 12 are estimated for other parts of the world, such as Africa, however.[181] Rubella is with an approximate 10-30% risk of transmission much less contagious than measles and mumps are.[112] The infectivity, on the other hand, is close to

100%, signifying that a susceptible (non-immunized) individual who has contracted the disease will in nearly all cases be infected by the virus.

After an incubation period of 12-23 days (on average, 18 days), the virus can be transmitted to others in a period of 7 days before until 6 days after the onset of the typical rash.[112,302] Infected individuals without symptoms may also transmit the disease. In pregnant women, the virus passes the placenta and can lead to a congenital infection. Through rare, secondary re-infections among adults have been documented and may lead to CRS when occurring during a pregnancy.[302]

Prevention and Vaccination

No specific treatment for rubella exists. Immunization is the only effective strategy to prevent both the acute and congenital rubella diseases. Live attenuated rubella-containing vaccines (RCV) are available, often in combination with measles and mumps vaccines (see Section 1.3.1).

The most commonly used strain for rubella vaccinations is the Wistar RA 27/3 strain, which has a seroconversion rate of 98% and is therefore highly effective.[112,302] Other strains include the BRD-2, Takahashi, Matsuura and TO-336 strains, predominantly used in Asian regions.[302]

Historically, most European countries vaccinated only adolescent or pre-adolescent girls in order to prevent the occurrence of congenital rubella infections (CRI). This strategy, while reducing CRS cases, still proved insufficient, however, and epidemiological models suggest that the wide-spread vaccination of both males and females would lead to a greater reduction in CRS incidences due to herd immunity.[42] As a result of such studies, rubella vaccination recommendations were changed to now include the immunization of both boys and girls.[112] The WHO recommends at least a single RCV dosage for the immunization of children, though the vaccination as part of two-dosage MMR-immunization schemes are common.[302]

As with measles, the WHO European Member States have committed to eliminating rubella by 2015.[310] Rubella elimination is defined by the WHO as "the absence of endemic rubella virus transmission in a defined geographical area (e.g. region or country) for $\geq$ 12 months and the absence of CRS cases associated with endemic transmission in the presence of a well-performing surveillance system," whereby, the "*verification* of rubella elimination takes place after 36 months of interrupted rubella virus transmisson", as for measles.[307] In order to reach this objective, the following strategies have been established by the WHO Regional Office for Europe (excerpt):[310]

- "*achieve and sustain high coverage ($\geq$ 95%) with two doses of measles and at least one dose of rubella vaccine through high-quality routine immunization services;*
- *provide measles and rubella vaccination opportunities, including supplementary immunization activities (SIA), to all population groups at risk for and susceptible to measles and/or rubella;*
- *strengthen surveillance systems through rigorous case investigation and laboratory confirmation of suspected sporadic cases and outbreaks*"[310]

Details about the selected nations' individual vaccination plans and progress towards the elimination of rubella are described below in Section 3.5. For each country, the national vaccination coverage, number of reported acute and congenital rubella cases, performance of surveillance systems, and susceptibility among various population groups are addressed.

2. Materials and Methods

All pertinent epidemiological and immunization data collected and described in this paper, including vaccination recommendations, disease outbreak rates, immunization coverage and antibody seroprevalence rates, were extracted from publications and accredited organizations using the guidelines of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement.[164]

Additionally, supplementary data regarding country demographics and migratory activities were included in the search, but did not follow the criteria outlined in the PRISMA statement for systematic reviews. Instead, information provided by authorized organizations, such as *The World Bank* database and the *Eurostat* statistics database of the European Commission,[23] were relied upon for the accumulation of these variables.

In the following sections, details regarding the literature search methods, the study selection procedures, and the data collection and analysis processes are described.

2.1. Literature Search Method and Eligibility Criteria

Prior to performance of the literature research, all variables to be incorporated in the search were specified and a list of eligibility and exclusion criteria for reports and studies was composed. These lists can be found in Appendices A and B. The

inclusion and exclusion criteria were amended and expanded during the research, as the necessity for the further limitation of the literature topics became apparent once the research had started. These amendments are included in the list of eligibility criteria found in Appendix A.

Three separate literature searches, each regarding the topic of either measles, mumps or rubella, were preformed by the author between August 2013 and February 2014. The following electronic databases were used for all three searches: *Pubmed*® (source: United States National Library of Medicine, National Institute of Health), the *Medical Literature Analysis and Retrieval System Online*® (Medline) (source: United States National Library of Medicine, National Institute of Health; accessed via Ovid® Technologies, Wolters Kluwer Health) and the Web of Science® Core Collection Citation Indexes—*Social Sciences Citation Index*® (SSCI) and *Science Citation Index Expanded*™(SCI-Expanded) (source: Thomas Reuters). Reference lists of included publications were also used to identify further relevant studies.

In addition, publicly available online data from official and accredited organizations and government agencies were incorporated into the study. These organizations include the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), the European Center for Disease Prevention and Control (ECDC), the Centers for Disease Control and Prevention (CDC), and the appropriate governmental public health departments of the countries included in this study. These government agencies are responsible for vaccinations, disease surveillance and public health education, among other things, and include the following: the Austrian Federal Ministry of Health, *Bundesministerium für Gesundheit* (BMG); the Croatian National Institute of Public Health, *Hrvatski Zavod za Javno Zdravstvo* (HZJZ); the French Ministry of Social Affairs and Health, *Ministère des Affaires sociales et de la Santé*, and the Institute for Public Health Surveillance, *Institut de veille sanitaire* (InVS); the German *Robert Koch Institute* (RKI); the Greek Ministry of Health and the *Hellenic Centre for Diseases Control and Prevention* (HCDCP); the Italian Ministry of Health, *Ministero della Salute*, and the *National Centre for Epidemiology, Surveillance and Health Promotion* (EpiCentro); the Polish National Insti-

tute of Public Health, *Narodowy Instytut Zdrowia Publicznego* (NIZP); the Spanish Ministry of Health, Social Services and Equality, *Ministerio de Sanidad, Servicios Sociales e Igualdad*, and the Institute of Health "Carlos III", *Instituo de Salud Carlos III* (ISCIII); the Swedish Institute for Infectious Disease Control, *Smittskyddsinstitutet* (SMI); the Turkish Ministry of Health, *Sağlık Bakanlığı*; the United Kingdom *Department of Health*, the *Health Protection Agency* (HPA), *Public Health England* (PHE); *Health Protection Scotland* (HPS), and the *Department of Health, Social Services and Public Safety* (DHSSPS) in Northern Ireland. Data from international collaborative projects, such as the Vaccine European New Integrated Collaboration Effort (VENICE), were also included. Not used as data sources were unofficial websites or articles, newspaper reports, or opinions and statements of organizations or individuals not backed up by sufficient scientific evidence.

Further eligibility limitations for reports and studies included publications in either English or German language, publication dates between the years 2009 and 2013, and human subjects of any age and gender. Scientific articles, books, conference scripts, data bases and data tables, periodicals, technical reports and webpages were considered. Only those scientific publications for which an abstract was available were included, however. Excluded were all other publication types, as listed in Appendix A. Furthermore, certain terms were specifically eliminated from the literature search so as to narrow the number of hits obtained in each database. The following terms, often abbreviated as *MMR* but not referring to the measles-mumps-rubella vaccination, were omitted: "major molecular response", "maternal mortality ratio", "maternal mortality rate", and "mismatch repair".

As additional criterion for studies, a sole or high pertinence to the selected countries and to the respective disease analyzed needed to be evident. For studies involving more than one country or more than one disease, high pertinence of the respective variable was defined as having at least equal consideration in comparison to all other related variables. As an example, during the literature search for studies on measles, those publications involving equal amounts of data for various immunizations (including, but not limited to, measles) would be included. However, if studies

involving mostly a different disease, such as rubella, were found, and measles was simply mentioned because of the frequent co-vaccination, then these publications would not qualify for inclusion in the measles results.

Table 2.1 shows an excerpt of the literature search strategy, as exemplified for measles. An overview of the search terms and limitations, as well as the resulting number of publications found though each database are provided. Similar literature searches were performed for mumps and rubella. Those studies and reports pertaining to vaccination coverage or antibody seroprevalence were selected, as were those related to outbreaks or immunizations among migrants and travelers. The rubella search additionally included the term *congential**, as prenatal rubella infections have a high relevance to the topic. The full search strategy is specified in Appendix C.

National disease and immunization surveillance data were not obtained using the literature search, but instead through other sources, including the WHO, ECDC and governmental agencies. Vaccination coverage reports and estimates were accessed via the *WHO vaccine-preventable diseases monitoring system* (2013)[309,312,324] as well as the respective public health agencies listed above. Measles, mumps and rubella case reports were also obtained through each nation's respective governmental agencies. In addition, case data were retrieved from the *Centralized information system for infectious diseases* (CISID) of the WHO European Regional Office,[326] surveillance data and annual epidemiological reports published by the ECDC,[26,103,105,106,109,110,113,114] and past records (up to 2010) of the former European surveillance network for vaccine-preventable diseases (EUVAC.NET).[189–199] All publications found through theses public health agencies as well as the electronic database searches were further analyzed according to the selection process described below.

Term 1	Term 2	Term 3	Term 4	Excl. 1	Excl. 2	Lang.	Pub. Date	Species	Abstract	Pubmed	Medline	SSCI/SCI
Measles (af)	-	-	-	-	-	all	all	all	-	23,699	21,571	16,756
Measles (af)	-	-	-	-	-	English, German	2009-2013	humans	-	2,744	2,243	3,260
Measles or MMR (t/a)	-	-	-	-	-	English, German	2009-2013	humans	-	2,955	2,731	4,751
Measles or MMR (t/a)	[Included Nations] (af)	-	-	-	-	English, German	2009-2013	humans	-	793	2807	1,550
Measles or MMR (t/a)	[Included Nations] (t/a)	Outbreak* or Case* or Incidence* or Epidemic* (af)	Migrant* or Immigrant* or Refugee* or Import* or Travel*(af)	[Excluded publication types]	[Other MMR terms]	English, German	2009-2013	humans	available	51	35	35
Measles or MMR (t/a)	[Included Nations] (t/a)	"Vaccination coverage" or "Immunization coverage" or "Vaccination Rate" or "Immunization Rate" (af)	-	[Excluded publication types]	[Other MMR terms]	English, German	2009-2013	humans	available	65	42	63
Measles or MMR (t/a)	[Included Nations] (t/a)	Vaccination* or Immunization* (af)	Migrant* or Immigrant* or Refugee* or Import* or Travel*(af)	[Excluded publication types]	[Other MMR terms]	English, German	2009-2013	humans	available	74	28	42
Measles or MMR (t/a)	[Included Nations] (t/a)	Seroprevalence or seropositiv* or seronegativ* (af)		[Excluded publication types]	[Other MMR terms]	English, German	2009-2013	humans	available	36	14	24

(af): term(s) searched in all fields
(t/a): term(s) searched in title or abstract (title or topic in SSCI/SCI-Expanded)
[Included Nations]: Austria, Croatia, Germany, Greece, Italy, Poland, Spain, Sweden, Turkey, United Kingdom
[Excluded publication types]: addresses, autobiography, biography, classical article, dictionary, directory, duplicate publication, historical article, interview, legal cases, letter, news, newspaper article, patient education handout, personal narratives, pictorial works, portraits, video audio media, or webcasts
[Other MMR terms]: "major molecular response", "maternal mortality ratio", "maternal mortality rate" or "mismatch repair"

Table 2.1. Literature Search Method and Results: Measles (Excerpt). Selected search terms and limitations for the literature search as well as the number of results obtained using the databases Pubmed, Medline and Social Sciences Citation Index (SSCI)/Science Citation Index Expanded(SCI-Expanded) are shown for the topic of measles. Similar searches were also performed for mumps and rubella. The complete search strategy is provided in Appendix C.

2.2. Publication Selection Process

Studies and reports were chosen according to the predefined inclusion and exclusion criteria listen in Appendix A. After completion of the literature searches, those publication that appeared more than once were removed and the remaining screened for content based on their titles and abstracts. Articles that were clearly irrelevant due to pertinence to different countries, diseases or pathogens were excluded. Studies focusing solely on certain employment groups, such as health care workers, teachers/child-care employees or military personnel, were excluded as well. While these groups certainly play a role in the potential transmittance of communicable diseases due to their frequent interactions with other people, they are not the main focus of this report. Likewise, literature focusing on patient groups with chronic or co-morbid diseases or conditions were omitted. Instead, articles regarding the overall vaccination rates and disease epidemiology among entire countries or sub-national regions were selected. Studies and reports involving groups of migrants and travelers to or from the countries selected for this report, on the other hand, were included in order to address the issue of VPD susceptibility among these populations.

For those publications remaining after the titles and abstracts had been screened, available full-text articles were read and the relevance of the provided information analyzed. More studies were excluded in this step, using the same criteria as above. For all of the discarded articles, the main reason for exclusion was noted, though more than one reason may have applied to some. A complete list of the omitted literature, including reasons for exclusion, is provided in Appendix G. The remaining publications were grouped according to their pertinence to either case reports, immunization coverage, or antibody seroprevalence studies. Finally, the data obtained from the included studies was summarized and further analyzed in the corresponding Results and Discussion Sections.

Further details regarding the publication selection processes for each of the three diseases, including the numbers of excluded and included studies and reports, are provided in the respective Results Sections 3.3 to 3.5.

2.3. Data Collection

Once all pertinent publications of the literature search had been screened and selected, epidemiological and immunization data were extracted based on the pre-established list of variables (see Appendix B). Particularly of interest were data regarding disease incidences and vaccination rates in each country. Annual epidemiological data were collected in terms of notified, confirmed, and imported case numbers. Reported hospitalizations and deaths were also included. National immunization rate estimates as well as reported age-related coverages were recorded separately for preschool-aged children (1-5 years old), school-aged children (6-14 years old) and adolescents (15-19 years old). Vaccination coverages among various subpopulations were collected in terms of variables potentially affecting measles, mumps or rubella susceptibility, including age, gender, educational status, migratory background or pregnancy. Available antibody seroprevalence studies were furthermore considered, as they are reflective of the level of protection among individual populations.

Vaccination schedules and recommendations were obtained from the official government and health agencies responsible for issuing such recommendations. They include data on the diseases vaccinated against, the age and gender recommendations for each vaccine's primary and booster immunizations, as well as the types of vaccinations used.

Demographic data was extracted from official sources, predominantly *The World Bank Database* and the *Eurostat* statistics database. The demographic indicators obtained include the following: geographic and development indicators (such as country size, infrastructure and urban and rural development), population indica-

tors (such as population size, birth rate, age distribution, and gender distribution), economy and labor indicators (such as GDP, GNI, and employment rate), health indicators (such as physician density, health expenditure, and vaccination financing), education indicators (such as literacy rate and school enrollment), and travel and migration indicators (such as international tourism and immigrant and refugee populations). For a complete list of all data variables, see Appendix B.

2.4. Data Analysis

Data obtained from the literature search and accredited organizations or agencies were summarized and analyzed for each country and disease included in this report. The national epidemiological and vaccination data variables extracted from the literature are reported in the appropriate measles, mumps and rubella Results Sections 3.3 to 3.5.

For each disease, the progress towards its elimination has been assessed by reporting international differences in immunization plans, surveillance systems, case reports and vaccination coverages. Outbreaks and immunizations among traveling and migrating populations that play a potential role in the persistence of these communicable disease in Europe are addressed as well. Furthermore, other demographic variables, such as age, gender, residence, education and socioeconomic status, are analyzed regarding their impact on measles, mumps or rubella susceptibility.

Comparisons between the countries were made with caution, as heterogeneity in the reporting methods was observed. For example, some nations use predominantly a clinical and others a laboratory-based surveillance system. Reporting variances may also be due to mandatory vs. voluntary systems, estimates and underreporting. Even for the same country, diverging data values are provided by different sources. In order to account for such reporting discrepancies, averages were determined and used

for the analysis. The extend of inter-report variance was measured by calculating the standard deviation (SD) of recorded case numbers.

In terms of vaccination coverage reports and seroprevalence studies, a wide heterogenity in immunization recommendations, data collection methods and targeted populations prevented a sensible combination of the results. For instance, some nations presented only regional data whereas others reported nation-wide estimates. Differences were also observed in the ages at which vaccination coverages were surveyed. The results of each study were therefore assessed separately. In some instances, data within a study or report was combined or adapted to match the indicated age-groups, however.

The quality of the data and risk of bias was evaluated for each included publication. A slightly altered version of the *Quality Assessment Tool for Quantitative Studies*, provided by the *Effective Public Health Practice Project* (EPHPP),[5] was used to rate studies according to the following components: *Selection Bias*, *Study Design*, *Confounders*, *Blinding*, *Data Collection Method*, and *Withdrawls and Drop-outs*. Each component was rated individually as *strong*, *moderate* or *weak* according to predefined, objective definitions.[6] The *Study Design* component was modified slightly to include cross-sectional and epidemiological studies and reports in the *moderate* rating category, as these were frequently encountered study designs that had not been included in the tool. A *Conflict of Interest* item was also added. Studies that had no "*weak*" component ratings were classified as having an overall *strong* quality, those with one "*weak*" rating as having a *moderate* quality, and those with two or more "*weak*" component ratings as having a *weak* quality.[5] The amended version of the quality assessment tool employed is shown in Section 1 of Appendix D.

Literature reviews were evaluated separately using the eleven-item AMSTAR Checklist, a valid and reliable tool for assessing the quality of systematic reviews.[11,265] The complete checklist can be found in Section 2 of Appendix D. The quality of each review was categorized according to the AMSTAR score (number of items with positive responses as a proportion of all eleven items), with *strong* corresponding to a

score of at least 72% (8/11), *moderate* to a score of 36% (4/11) to 63% (7/11), and *weak* to a score of 27% (3/11) or less.

The quality of reports from public health and governmental agencies was assessed separately as well: well-founded data reports were assumed to be accurate and labeled as *strong*, reliable estimates and regional data reports were labeled as *moderate*, and voluntary or underreported data reports were labeled as *weak*.

Taking the qualitative and quantitative differences of the epidemiological and immunization data into account, an analysis of the nations' immunization programs was performed. The success of each country's individual vaccination plan was assessed based on disease prevention through high immunization rates and low disease incidences. A rating system was developed in order to objectively measure success using a school grading system, whereby 1 was defined as the highest possible and 5 as the lowest possible level of success. Evaluated were both current vaccination rates and recent annual disease incidences, whereby the quality of the national surveillance system also affected the grading. The following evaluation scheme was used:

Level 1 Vaccination rate of 95.0% or above *and* max. disease incidence $\leq$ 0.10/100,000

Level 2 Vaccination rate of 95.0% or above *or* max. disease incidence $\leq$ 0.10/100,000

Level 3 Vaccination rate between 90.0% and 94.9% *or* max. disease incidence 0.11–1.00/100,000

Level 4 Vaccination rate between 80.0% and 89.9% *or* max. disease incidence 1.01–10.00/100,000

Level 5 Vaccination rate below 80% *or* no vaccination recommendation *or* max. disease incidence above $\geq$ 10.00/100,000

Immunization rates were based on the 2012 coverages among children aged 1-5 years with either one (rubella) or two (measles, mumps) dosages, as recommended by the WHO. The 95%-threshold needed for a level 1 or 2 grade has been adapted from the WHO recommendation for adequate herd immunity within a population.[307,310]

Annual incidences were averaged based on the number of cases per 100,000 people reported between 2006 and 2013. The highest attainable levels also comply with the WHO recommendation for the elimination of the included diseases.[307] If the disease surveillance in a country is not mandatory or under-reporting is known to occur (*weak* data reports), only the vaccination coverage data was used to determine the grade (best possible: level 2). Likewise, if the second-dosage immunization rates (for measles and mumps) were not known, only the incidence was used to determine the grade. If more than one criterion was fulfilled, the best attainable grade was given.

Efforts have been made to determine a "best practice" recommendation for the immunization against each vaccine-preventable disease on the basis of the most successful vaccination schemes. Other factors, such as demographic indicators and migratory activities have also been taken into consideration, as they may play a role in the potential spread of infectious diseases and may impact the local immunization status of a particular population. Finally, an MMR immunization schedule that combines these literature-supported "best" vaccination practices has been established and the feasibility of an European-wide implementation of this schedule is discussed below.

3. Results and Analysis

In order to assess the measles, mumps and rubella elimination progress among the selected European nations and to determine whether a single, synchronized MMR vaccination plan would be feasible in Europe, a comparison between the countries has been made in terms of demographic indicators, current immunization programs, and disease epidemiology. In the sections below, each of these constituents is addressed separately. Section 3.1 (Demographic Indicators) compares the nations by geographic, population, financial, health, education, and migration indicators. Overall vaccination programs currently in effect in each country are briefly described in Section 3.2 (National Immunization Profiles). Measles, mumps and rubella vaccination coverages, case data and immunization program evaluations, are covered in Sections 3.3 to 3.5. The results of the systemic literature search using the databases Pubmed, Medline and SSCI/SCI-Expanded, as well as data obtained from official governmental or agency sources, are indicated. Study characteristics and quality assessments of the included studies can be found in Appendix E.

3.1. Demographic Indicators

To compare and contrast the various European nations included in this report, geographic and demographic data have been obtained using *The World Bank DataBank*[285] and the *Eurostat* statistics database of the *European Commission*.[23] Unless otherwise indicated, all data are for the year 2010, due to higher data set completion during that year.

3.1.1. Geographic and Development Indicators

The countries included in this study were chosen as representatives for the European continent and separated into four sub-regions based on their geographic locations, as described in the Introduction (Section 1.2.1). The European regions and included nations are as follow:

Western Europe: Austria, France, Germany

Southern Europe: Greece, Italy, Spain

Northern Europe: Sweden, United Kingdom of Great Britain and N. Ireland

Eastern Europe: Croatia, Poland, Turkey

Of these nations, Turkey is the largest with a surface area (SA) of more than 780,000 km^2 and Croatia the smallest, with a SA of under 57,000 km^2 (see Table 3.1).[285] In terms of population, Germany has the highest with about 81.8 million, followed by Turkey with 72.1 million.[285] Croatia, Austria and Sweden have the lowest populations, each with under 10 million people.[285] The population density ranges from a low of about 23 people/km^2 in Sweden to a more than 10-fold increased high of nearly 258 people/km^2 in the United Kingdom.[285] Data for all included nations are shown in Table 3.1.

The majority of residents in the European nations live in urban areas. As indicated in Table 3.1, the proportions of the total populations residing in urban areas averaged 71.5% (range: 57.5% - 85.2%) in 2010.[285] Both population density and urban population percentage are important factors in the spread of communicable diseases, and will be further addressed in the Discussion section below (see Chapter 4).

3.1.2. Population Indicators

As reported above, the total populations of the nations included in this study range from about 4.5 million in Croatia to about 82 million in Germany.[285] In 2010, both

Countries	Surface Area (km^2)	Total Population (in millions)	Population Density (people/km^2)	Rural Population (% of total)	Urban Population (% of total)
Western Europe					
Austria	83,879	8.39	101.8	32.5	67.5
France	549,190	65.03	118.7	14.8•	85.2*
Germany	357,127	81.78*	234.6	26.2	73.8
Southern Europe					
Greece	131,960	11.31	87.7	38.8	61.2
Italy	301,340	60.48	205.6	31.8	68.2
Spain	505,600	46.07	92.4	22.7	77.3
Northern Europe					
Sweden	450,300	9.38	22.9•	14.9	85.1
UK	243,610	62.27	257.4*	20.5	79.5
Eastern Europe					
Croatia	56,590•	4.42•	78.9	42.5*	57.5•
Poland	312,680	38.18	125.5	39.1	60.9
Turkey	783,560*	72.14	93.7	29.5	70.5

Table 3.1. Population Distribution by Country, 2010. Country size, total population, population density and rural or urban distribution are shown for comparability between the indicated nations and geographical regions. All data are for the year 2010. The highest (∗) and lowest (•) values for each indicator have been marked. ***Source**: The World Bank: DataBank: World Development Indicators, 2013*.[285]

Croatia and Germany were decreasing in population, as indicated by their negative population growth rates of -0.3% and -0.2%, respectively (see Table 3.2).[285] In the following years, the total population of Germany increased, however, and showed a positive annual growth rate of 0.1% in 2012.[285] Austria, the UK, and Poland also increased in population, whereby the latter experienced a sharp rise in 2011 (from 0.1% to 0.9% growth rate), which then dropped again in 2012.[285] The populations of France and Turkey continue to grow at about the same annual growth rates as in 2010. Croatia's 2012 growth rate remained at -0.2% as well.[285] Other nations with decreases in population growth over the past years were Italy, Spain, Sweden and Greece.

The factors influencing these population changes are birth and death rates as well as immigration and emigration, addressed below in Section 3.1.6. The country with the by far largest birth and lowest death rates is Turkey. Approximately 1.3 million children are born in the country each year, leading to a crude birth rate of nearly 18/1,000 people/year, one of the highest on the European continent.[287] All other

countries included in this study have crude birth rates that range between 8 and 13/1,000/year (see Table 3.2).[285] Turkey also has the lowest crude death rate among the selected European countries; with about 5.5 deaths/1,000 people/year, it is much lower than the remaining countries' average of 9.6 deaths/1.000 people/year.[285] The country with the highest death rate is Croatia (11.8/1,000/year), closely followed by Germany (10.5/1,000/year).[285] The much higher mortality rates may be due to the larger populations of elderly people living in these countries (17.5% and 20.8% respectively, see Table 3.2).[285]

The population age distribution shown in Table 3.2 provides a rough overview of the proportions of children, adults and elderly living in the individual countries. In accordance with the high birth rate, Turkey has the highest percentage of children under the age of 14 (26.7% or 19.3 million children).[285] Germany, on the other hand, has the lowest proportion with 13.4% of the total population, or about 11.0 million, being under the age of 14 years.[285] Table 3.3 shows a finer breakdown of the age distribution among children and adolescents. These data are relevant for age-specific immunization recommendations and vaccination rates, which will be further addressed in Sections 3.3.2, 4.4 and 4.5.

Countries	Population Indicators							
	Total Population (in millions)	**Female Population** (% of total)	**Population Growth** (annual %)	**Birth Rate** (crude, per 1,000)	**Death Rate** (crude, per 1,000)	**Population Ages 0-14** (% of total)	**Population Ages 15-64** (% of total)	**Population Ages ≥65** (% of total)
Western Europe								
Austria	8.39	51.3	0.3	9.4	9.2	14.8	67.4	17.8
France	65.03	51.6	0.5	12.9	8.5	18.4	64.8•	16.8
Germany	81.78*	51.0	-0.2	8.3•	10.5	13.4•	65.8	20.8*
Southern Europe								
Greece	11.31	50.7	0.2	10.1	9.6	14.5	66.5	19.0
Italy	60.48	51.5	0.5	9.3	9.7	14.0	65.7	20.3
Spain	46.07	50.6	0.4	10.5	8.3	14.9	68.0	17.1
Northern Europe								
Sweden	9.38	50.2•	0.9	12.3	9.6	16.5	65.3	18.2
UK	62.27	50.8	0.7	13.0	9.0	17.6	65.9	16.6
Eastern Europe								
Croatia	4.42•	51.8*	-0.3•	9.8	11.8*	15.3	67.2	17.5
Poland	38.18	51.7	0.1	10.8	9.9	15.0	71.5*	13.5
Turkey	72.14	50.9	1.3*	17.9*	5.5•	26.7*	66.2	7.1•

Table 3.2. Population Indicators by Country, 2010. Shown are selected population indicators for each included European nation. All data are for the year 2010. The countries have been grouped by geographical region for easier comparability. The highest (∗) and lowest (•) values have been marked, as shown. ***Source**: The World Bank: DataBank: World Development Indicators, 2013*.[285]

Countries	Population by Age Group (in millions and % of total Pop.)							
	0-5 years		5-9 years		10-14 years		15-19 years	
Austria	0.4	4.7%	0.4	4.9%	0.4	5.3%	0.5	6.0%
France	4.0	6.2%	4.0	6.3%	4.0	6.1%	4.0	6.2%
Germany	3.4	4.2%	3.6	4.5%	4.0	4.8%	4.3	5.3%
Greece	0.6	5.0%	0.5	4.7%	0.5	4.7%	0.6	5.1%
Italy	2.8	4.7%	2.8	4.7%	2.8	4.6%	3.0	4.9%
Spain	2.5	5.4%	2.3	5.0%	2.1	4.6%	2.3	4.9%
Sweden	0.5	5.9%	0.5	5.4%	0.5	5.3%	0.6	6.8%
UK	3.8	6.1%	3.5	5.5%	3.7	5.9%	4.0	6.4%
Croatia	0.2	4.8%	0.2	4.7%	0.3	5.7%	0.3	5.8%
Poland	2.0	5.1%	1.8	4.7%	2.0	5.3%	2.5	6.6%
Turkey	6.2	8.5%	6.2	8.5%	6.5	9.0%	6.2	8.6%

Table 3.3. Child Population by Age Group and Country, 2010. Shown are the 2010 populations of children and adolescents between the ages of 0 and 19 years. The first column of each age group corresponds to the population in millions, the second to the percentage of the total population for that country and year. ***Source**: European Commission: Eurostat Statistics Database, 2013*.[285]

3.1.3. Economy and Labor Indicators

As with all medical and preventative health measures, vaccination programs require financing. In Section 3.2, each country's national immunization program is briefly described, including which government agencies, institutions or persons are responsible for covering the charges accrued through vaccinations. Most of these costs are financed by the national or state governments through their ministries of health. National economic factors, such as the GDP or GNI as well as the strengths of the labor force, are therefore relevant for the comparison of vaccination programs. Each nation's public and private expenditure on health will be detailed below in Section 3.1.4. Table 3.4 gives and overview of the national income and labor force indicators of each included country.

As shown in the table, Germany has the largest economy of all the selected European nations. The 2010 German GDP and GNI were $3.28 trillion and $3.35 trillion, respectively, ranking Germany 4th in the world.[285] France, Italy, Spain and the UK also have very strong economies, with respective 2010 GDPs and GNIs over $1

trillion.[285] The country with the lowest national income in 2010 was Croatia, with a $59 billion GDP and $57 billion GNI.[285]

Countries	**GDP** (in billions)	**GDP per capita**	**GNI** (PPP, in billions)	**Employment rate** (% of ≥15 Pop.)	**Unemployment rate** (% of labor force)
Western Europe					
Austria	$377	$44,916	$376	57.9	4.4•
France	$2,548	$39,186	$2,600	51.2	9.4
Germany	$3,284*	$40,164	$3,351*	55.4	7.1
Southern Europe					
Greece	$292	$25,851	$284	47.7	12.5
Italy	$2,042	$33,761	$2,032	44.3	8.4
Spain	$1,380	$29,956	$1,363	47.3	20.1*
Northern Europe					
Sweden	$463	$49,360*	$373	58.4*	8.4
UK	$2,256	$36,233	$2,275	57.0	7.8
Eastern Europe					
Croatia	$59•	$13,327	$57•	46.3	11.8
Poland	$470	$12,302	$451	50.5	9.6
Turkey	$731	$10,135•	$724	43.6•	11.9

Table 3.4. Economic Indicators by Country, 2010. 2010 gross domestic products (GDP, in billions) and gross national incomes (GNI, in billions) are shown for the included countries. They are measured in current U.S. and international dollars (using purchasing power parity (PPP) rates), respectively. Each nation's 2010 employment rate (proportion of employed individuals over the age of 14 years among the total population for that age range) and unemployment rate (proportion of individuals seeking employment among the total population able to work) are also provided. The highest (∗) and lowest (•) values for each indicator have been marked. ***Source**: The World Bank: DataBank: World Development Indicators, 2013*.[285]

When examining the countries in regard to GDP per capita, more similarities can be observed between them. The Northern and Western European nations have comparable per capita GDPs averaging about $42,000.[285] The Southern as well as the Eastern European states also have similar GDP per capita values within their individual geographic regions, averaging nearly $30,000 and $12,000, respectively.[285] Table 3.4 shows each country's individual per capita GDP.

National employment and unemployment rates are two further important economic indicators. On average, 51% of the populations above the age of 15 years living in the selected European countries were employed during 2010.[285] The lowest annual employment rate was observed in Turkey (43.6%) and the highest in Sweden (58.4%).[285] Individual national population age structures (see Tables 3.2 and 3.3) should also be considered when comparing these rates, however, as the size of the

elderly population unable to work or adolescent population still attending school has an impact on the overall employment rate. When considering the employed to total population ratio of only those between the ages of 20 and 64 years, for example, the average lies by 66.5% (range: 50.0% in Turkey to 78.1% in Sweden).[23] Of those populations able to work, an average of 10% were seeking employment in 2010. Greece, Croatia, Turkey and Spain reported even higher unemployment rates, whereby the later indicated a rate as high as 20.1%.[285] The with 4.4% lowest proportion of unemployed individuals was observed in Austria (see Table 3.4).[285] Low unemployment and high employment rates are important factors determining the economic strength of a country and thus the ability to finance national health care systems, among others.

3.1.4. Health Indicators

Various health indicators provide an insight into the health care system of a nation and allow for an understanding of the availability of essential medical resources.

One of these indicators is the amount of monetary resources allocated to health care. Each nation included in this study spends a significant proportion of its national income on medical and preventative care funding. Table 3.5 indicates the total, public and private health expenditures (HE) of each nation as well as the remaining out-of-pocket expenses for their residents. The annual total spending on health ranges from 6.7% of the national GDP in Turkey to 11.7% of the national GDP in France.[285] The Western European nations tend to spend a larger proportion of their GDPs on medical care than the nations of other European regions do, as can be observed by the regional total HE averages: WE: 11.7%, SE: 10.0%, NE: 9.6% and EE: 7.2%. In accordance with this, the per capita HE is also distributed in a similar fashion, with the exception of Sweden, which has a per capita HE more comparable to those of the WE nations (see Table 3.5). On average, $3,093/person are spent on health in the included nations.[285] Of the total annual HE, approximately 60-85% are financed publicly through government, social security or public health

insurance funds, among others.[285] Sweden, the UK and Croatia provide with more than 80% the largest proportions of public funds in relation to their total HEs. In Greece, nearly 40% of the funds come from private persons, institutions and health insurances, whereby the largest proportion (36.4% of the total HE) is paid directly by patients out-of-pocket.[285] The percentages of out-of-pocket expenditures range from 7.4% to 22.1% among the other nations, as shown in Table 3.5.

Countries	**Total HE** (% of GDP)	**Total HE per capita**	**Distribution** (% of Total HE)		
			Public	**Private**	**Out-of-Pocket**
Western Europe					
Austria	11.0	$4,964	76.2	23.8	15.9
France	11.7	$4,618	76.9	23.1	7.4
Germany	11.5	$4,654	76.8	23.2	11.9
Southern Europe					
Greece	10.8	$2,873	61.5	38.5	36.4
Italy	9.5	$3,247	77.6	22.4	19.6
Spain	9.6	$2,896	74.2	25.8	19.7
Northern Europe					
Sweden	9.6	$4,708	81.0	19.0	16.8
UK	9.6	$3,495	83.2	16.8	8.9
Eastern Europe					
Croatia	7.8	$1,051	84.8	15.2	14.6
Poland	7.0	$851	71.7	28.3	22.1
Turkey	6.7	$668	74.8	25.2	16.2
Average	**9.5**	**$3,093**	**76.3**	**23.7**	**17.2**

Table 3.5. National Health Expenditure by Country, 2010. The 2010 total expenditures on health care (HE), measured as percentage of the national gross domestic product (GDP), are indicated for the respective countries. The per capita health expenditures, measured in current U.S. dollars, are also provided, with notable differences between the geographic regions. Furthermore, the proportions of the total health expenditures financed through public (i.e. government) and private agencies and institutions have been included in the table. Out-of-pocket expenditures are those covered directly by the persons receiving health care and make up the largest proportion of private expenditure in most countries, as shown. Overall averages have been calculated for each indicator.
***Source**: The World Bank: DataBank: World Development Indicators, 2013*.[285]

Other important national health indicators include the availability of medical resources, such as hospitals and health care professionals. Figure 3.1 shows the hospital bed, physician and nurse densities of each nation in relation to the total population. Hospital bed density is defined as the number of available acute and chronic, inpatient and rehabilitation clinic beds per 1,000 residents. The average hospital

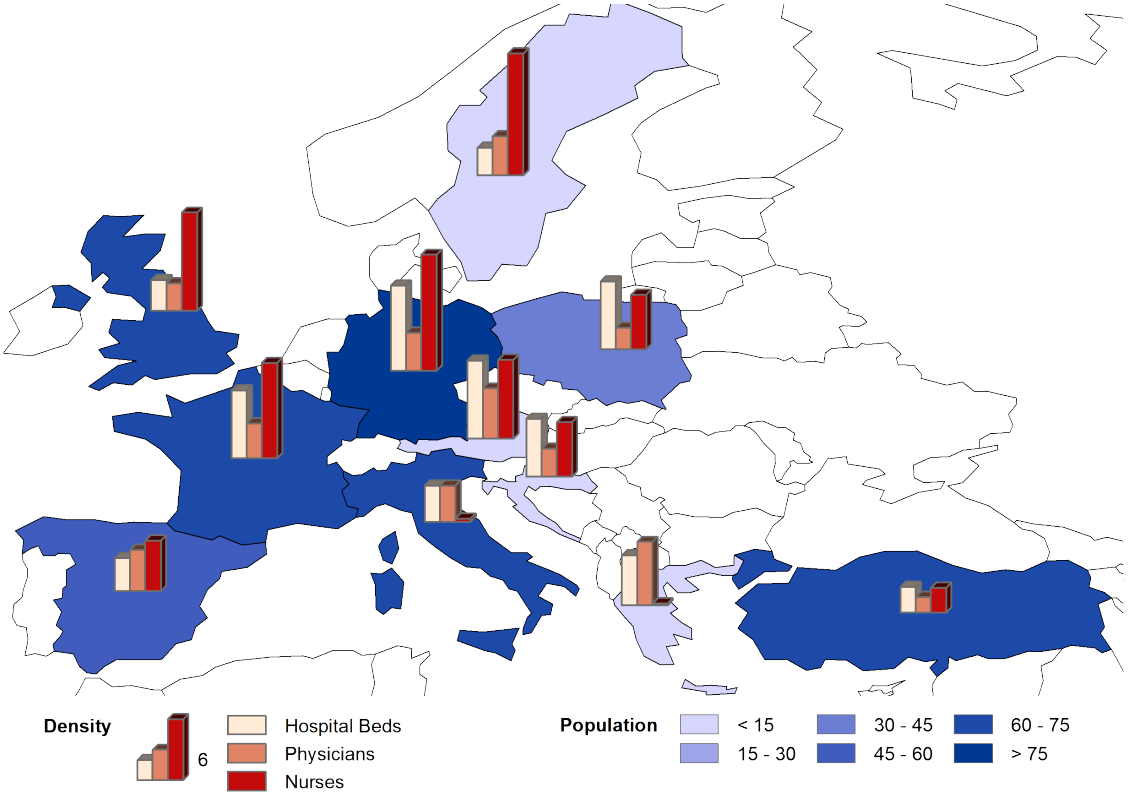

Figure 3.1. National Health Care Indicators: Hospital Bed, Physician and Nurse Densities, 2010. The bar graphs illustrate the relative densities of available medical resources in the form of hospital beds, physicians and nurses per 1,000 people. The background colors indicate the respective total populations (in millions) of the included European nations (see Table 3.2 for exact numbers). All Data are as of 2010. ***Sources***: *Eurostat Statistics Database: Nursing and caring professionals, 2013*,[23] *The World Bank: DataBank: World Development Indicators, 2013*.[285] Geographic data obtained from www.naturalearthdata.com.

bed density for the included nations is 5.0/1,000 people (2009-2010 data), whereby the highest ratios are found in Germany (8.3) and Austria (7.6) and the lowest in Turkey (2.5) and Sweden (2.7).[285] Physician and nurse densities describe the number of all physicians and nurses in general and field-specific areas as well as in inpatient an outpatient care per 1,000 residents. On average, 3.5 doctors and 6.2 nurses are available for every 1,000 people in the selected European countries (2010-2011 data).[23,285] The by far largest proportion of doctors to residents is found in Greece, with 6.2 physicians per 1,000 people.[285] Austria and Spain also have considerably high physician densities. The density of nurses, including all primary care, long-term care, hospital, midwife, dental and auxiliary nurses, is highest in Sweden and Germany, with 11.9 and 11.3 nurses for every 1,000 people, respectively.[23,285] The lowest nurse to resident ratios are found in Greece (0.2) and Italy (0.3), though under-reporting is likely.[23,285]

In Section 3.2, the vaccination practices in the included European nations are described, including the professions administering vaccines. Although immunizations are mostly performed by physicians, they are in some countries, i.e. Sweden, primarily administered through nurses. Further details will be described below in Section 3.2.7 (National Immunization Profiles - Sweden).

3.1.5. Education Indicators

Next to the health system, the education system of a nation is relevant to the analysis of immunization practices. On one hand, communicable diseases may be easily transmitted in educational facilities, on the other, schools are establishments where vaccination campaigns may be conducted. Pertinent education indicators include the primary school starting age, the intended duration of primary and secondary education and the enrollment rates in various educational stages.

The age at which children are enrolled in schools varies slightly between the European nation. In the UK and in Germany, children begin their primary education as early as at age five; in Sweden, Croatia and Poland, they start school at the age of seven.[285] All other nations enroll their children at age six.[285] Primary education lasts four (Austria, Croatia and Germany), five (France, Italy and Turkey) or six (Greece, Poland, Spain, Sweden and the UK) years.[285] The duration of secondary education varies between six (Greece, Poland, Spain and Sweden) and eight (Austria, Croatia, Germany and Italy) years.[285] In some parts of Germany, higher secondary education lasts nine years. The total length in which children and adolescents are intended to be enrolled in schools is thus 12 to 13 years and the age of secondary school completion 18 to 19 years.

Enrollment in schools varies substantially between the included nations. Table 3.6 shows the gross enrollment rates in pre-primary to tertiary educational institutions. The rates are expressed as the number of registered students of all ages in proportion to the population corresponding to the intended age range for that educational level

Countries	Enrollment by Educational Level (%)			
	Pre-Primary	**Primary**	**Secondary**	**Tertiary**
Austria	99.6	99.2	98.9	68.2
France	108.7	110.0	113.2	56.7
Germany	113.5	102.3	103.3	-
Greece	74.4	100.8	109.5	-
Italy	98.0	101.8	100.4	65.0
Spain	126.4	105.5	124.7	78.1
Sweden	95.0	101.4	99.2	73.8
UK	83.4	106.9	105.3	59.7
Croatia	61.3	93.0	95.7	54.1
Poland	71.1	98.6	97.0	72.4
Turkey	26.4	104.3	82.1	55.4

Table 3.6. School Enrollment by Educational Level and Country, 2010 The gross enrollment in pre-primary to tertiary educational institutions are shown. The rates are calculated based on the number of registered students of any age within an educational stage in proportion to the population corresponding to the intended age range for that school level. Due to the inclusion of younger or older students at the same educational level, the enrollment rates may exceed 100%, as shown. Students in pre-primary educational institutions are typically younger than 6 to 7 years (the starting age of primary education in most of the included nations). Primary education typically lasts 4 to 6 years and secondary education another 6 to 8 years. Tertiary, or higher learning, institutions include universities and vocational schools, and the enrollment therein is measured as a percentage of the up to 5-year post-secondary school aged population. ***Source**: The World Bank: DataBank: World Development Indicators, 2013*.[285]

and may therefore exceed 100% if younger or older students are enrolled at the same educational stage.[285] Pre-primary (kindergarten or pre-school) enrollments are very high (near or above 100%) in Austria, France, Germany, Italy and Spain.[285] Low registration rates in pre-primary institutions are found in Croatia (61.3%) and Turkey (26.4%).[285] Primary and secondary school enrollments, on the other hand, are very high in nearly all the selected nations. Croatia has the lowest enrollment rate in primary education (93.0%) and Turkey in secondary education (82.1%).[285] Tertiary education enrollment reflects the number of students enrolled in higher learning institutions, such as universities or vocational schools, as proportion of the total five-years post-secondary school age group. High enrollment rates above 70% can be observed in Spain, Sweden and Poland (Data for Germany and Greece not available).[285] Specific enrollment numbers for each educational level are shown in Table 3.6.

In some nations, such as Croatia, Turkey and Sweden, schools are used for the administration of vaccinations because a large proportion of the age-specific populations

are reached there. Mass-vaccination campaigns are conducted at particular grade levels in order to ensure a wide-spread protection of the population at a specific age. Other countries, such as France, do not typically administer vaccines at school, but require that students entering the school system are vaccinated against particular diseases. Further details about each nation's individual vaccination practices will be provided below in Section 3.2.

3.1.6. Travel and Migration Indicators

International travel and migratory activities are pertinent to the topic of immunizations as they may influence disease outbreaks and vaccination statuses within a population. Over the course of the past years, both travel and migration to and within Europe have increased tremendously. International tourist arrivals to the EU increased by nearly 65 million between 2000 and 2011, and the number of immigrants in the EU by over 12 million during the same decade.[285]

Figure 3.2 shows the 2010 total numbers of international arrivals and departures for the selected European nations. Most travelers were reported in France and Germany, as shown, likely due to the central geographic locations of these nations. The most frequently visited nations (with the highest numbers of international arrivals) were France, Spain and Italy.

In a separate map shown in Fig. 3.3, international migration has been illustrated. The 2010 immigrant and refugee populations, as proportion of the total populations, are shown. The largest percentages of foreign-born residents were observed in Croatia (15.8%) and Austria (15.6%), followed by Sweden (13.9%), Spain (13.8%) and Germany (13.2%).[285] The lowest immigrant to total population ratios were reported in Poland (2.2%) and Turkey (2.0%). In regard to the total number of immigrants and refugees, most were residing in Germany as of 2010 (10.2 million and 0.6 million respectively).[285] Of these, roughly 3.5 million (32.5%) were from EU Member States and 3.9 million (36.8%) from other European countries.[27] Other large immigrant

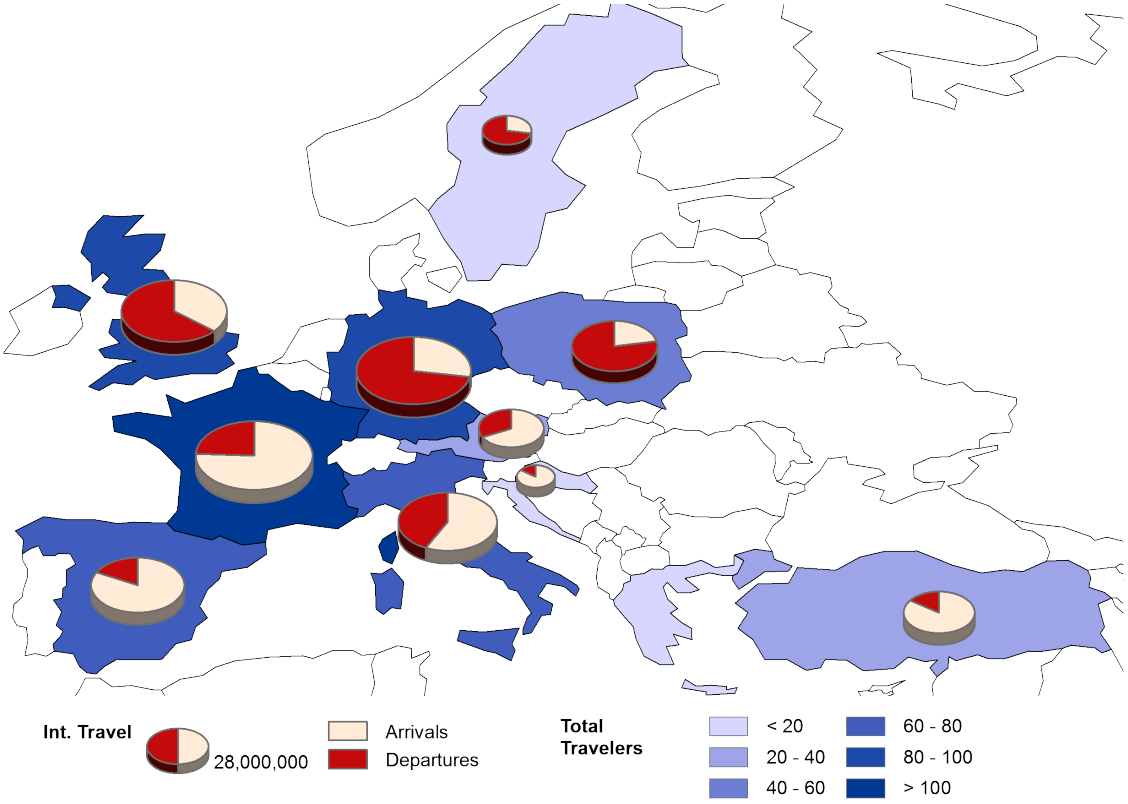

Figure 3.2. International Travel: Arrivals, Departures and Total Travelers, 2010. Relative international travel rates are shown for the indicated European nations. Most travelers (in millions) have been reported in France, Germany and the United Kingdom. Respective arrival-to-departure rates are highest in Croatia, Spain and Turkey and lowest in Germany, Sweden and Poland. Exact data for Greece is unavailable. All Data are as of 2010. ***Source***: *The World Bank: DataBank: World Development Indicators, 2013*.[285] Geographic data obtained from www.naturalearthdata.com.

and refugee populations have been observed in France, Spain, and the UK, as shown in Fig. 3.3.

The 2010 most frequent immigrant nationalities have been determined for some of the nations included in this report. They are shown in Fig. 3.4. The pie charts indicate that particularly Romanian and Polish citizens migrated to other European countries in 2010. Large proportions of immigrants with nationalities corresponding to the countries of residency were also observed; these persons were living abroad prior to migrating back to their country of citizenship in 2010.[27]

The tourism and migration data are relevant to the analysis of epidemiology statistics as the introduction and transmission of communicable diseases may occur through travel. Furthermore, the vulnerability towards these diseases is higher among insuf-

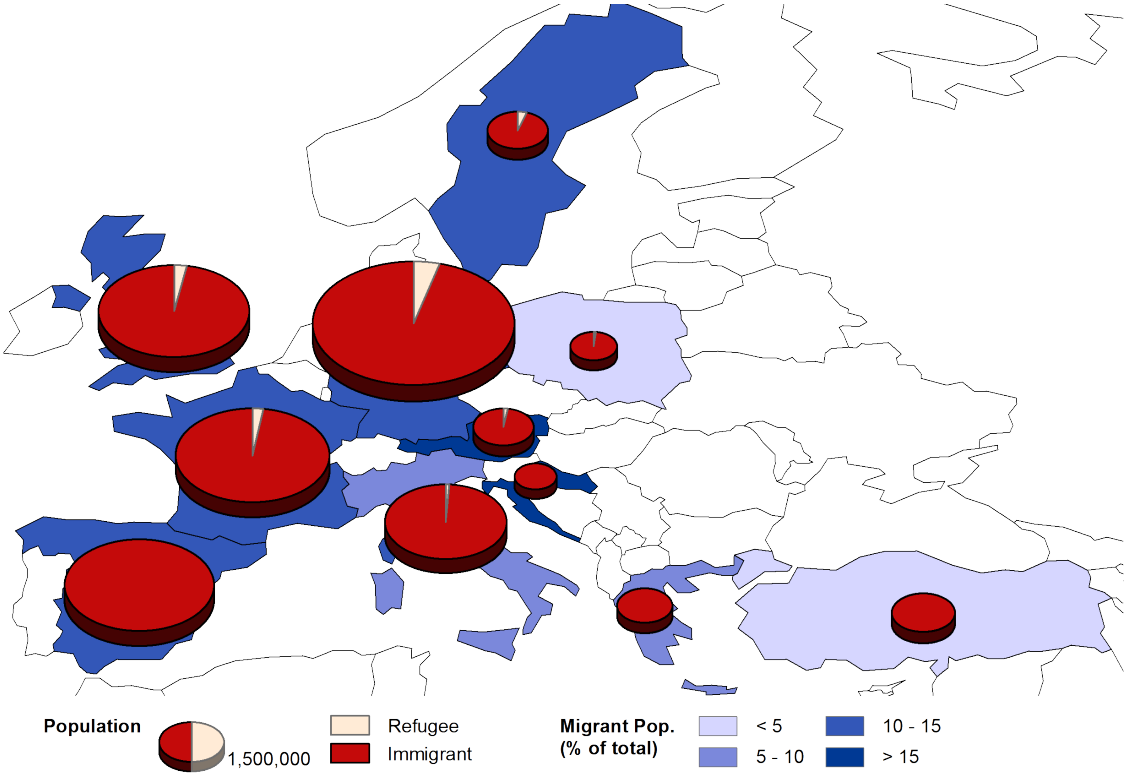

Figure 3.3. Total and Relative Migrant Populations in Europe, 2010. The total immigrant and refugee populations residing in the respective European nations in 2010 are shown. Most migrants were reported in Germany, France, Spain and the United Kingdom. The background colors indicate the relative migrant populations as proportions of the total national populations. The highest migrant-to-total population ratios were reported in Austria and Croatia. See text for further details. ***Source***: *The World Bank: DataBank: World Development Indicators, 2013*.[285] Geographic data obtained from www.naturalearthdata.com.

ficiently vaccinated tourists, immigrants and refugees entering regions in which outbreaks are occurring.[220] According to the ECDC and the *European Travel Medicine Network* (EuroTravNet), a network for the surveillance of tropical and travel-related communicable diseases, the most frequent VPDs reported among travelers and migrants in Europe are tuberculosis, influenza, hepatitis B, measles and rubella.[104,204] Details about the vaccination statuses of immigrants and migration-related outbreaks of diseases will be further addressed in Sections 3.3 to 3.5 below.

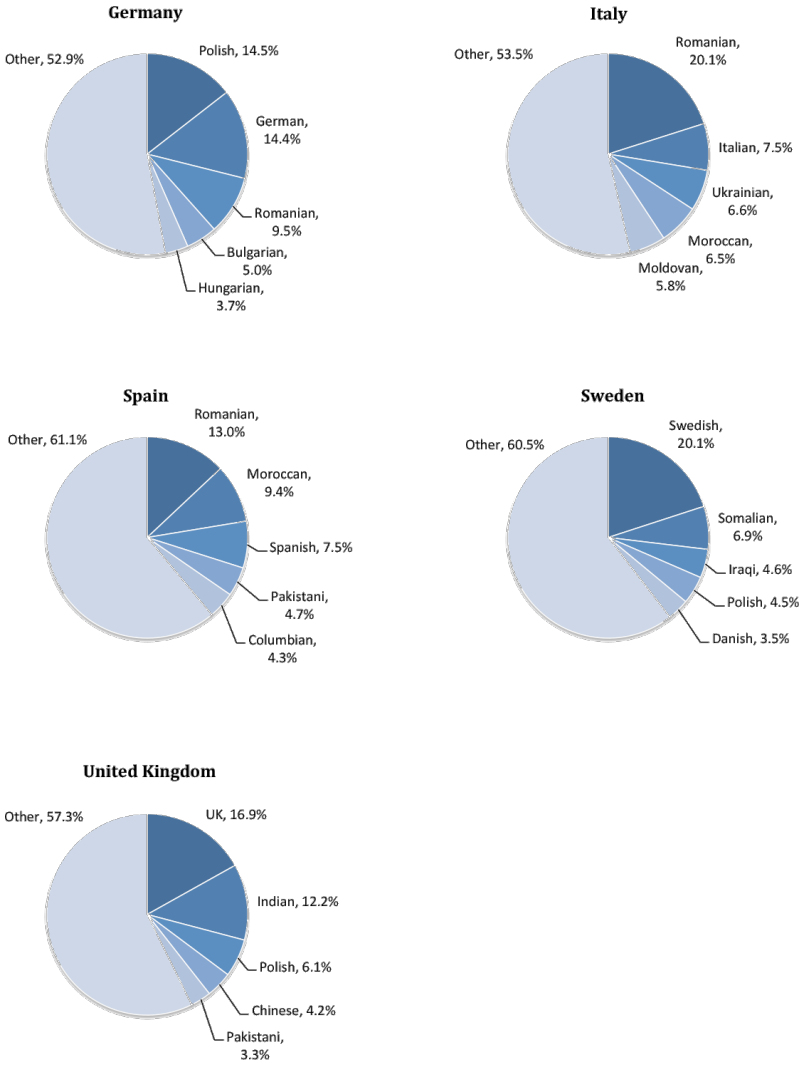

Figure 3.4. Immigrant Populations by Nationality and Country of Residence, 2010. Proportions of immigrants from various source nations are shown for the indicated European countries. Returning citizens from foreign nations of residency are also counted as immigrants, as shown (i.e. German immigrants in Germany). ***Source***: Figures adapted from *Bundesamt für Migration und Flüchtlinge, 2013: Migrationsbericht 2011*.[27]

3.2. National Immunization Profiles

Immunization schedules and recommendations provided by each nation vary considerably. Specific vaccination schemes for the prevention of measles, mumps and rubella are detailed in Section 3.3.2 below. Here, a brief overview of each nation's general immunization program is given, including vaccine administration practices, funding, and implementation modalities.

3.2.1. Austria

Information about vaccine-preventable diseases and immunization recommendations are provided by the Austrian federal ministry of health (*Bundesministerium für Gesundheit*, BMG).[293] The BMG, in collaboration with the national immunization advisory board, annually publishes a current nationwide vaccination schedule as well as pertinent information for specific groups of people with high infection risks.[24] Austrian residents are strongly advised to acquire all appropriate vaccines, but doing so is not compulsory. The overall recommendation is that "every person who wishes to protect himself and his family or contact persons should be immunized"[24] [translation].*

A national child vaccination program has been in effect for about 20 years and provides free routine immunizations to all children up to the age of 15 years.[24] Exceptions apply to varicella and influenza vaccines as well as to non-routine vaccinations.[24] For adolescents and adults, most vaccines are financed privately by the vacinees or their families.[293] Due to national measles eradication efforts, the MMR vaccine is provided free of charge for all people up to the age of 45 years, however.[24] Figure 3.5 compares the immunization financing among the selected European nations. As shown, an estimated 70% of the vaccination costs are covered by the Austrian national and local governments and 15% by social security institutions; the remaining 15% are paid out-of-pocket.[24,139]

The administration of vaccines occurs both in public and private institutions. For school-aged children, immunizations are offered in schools and are administered by public health officials.[124] Regional public health centers also provide vaccinations.[293] The majority of immunizations among non-school-aged children, adolescents and adults generally occur through the private health sector and are administered by general practitioners and pediatricians.[293] Austria's vaccination administration practices in comparison with those of other countries are shown in Fig. 3.6.

* "Jeder, der sich und seine Familienangehörigen (Kontaktpersonen) schützen will, soll sich impfen lassen."[24] (translated by author)

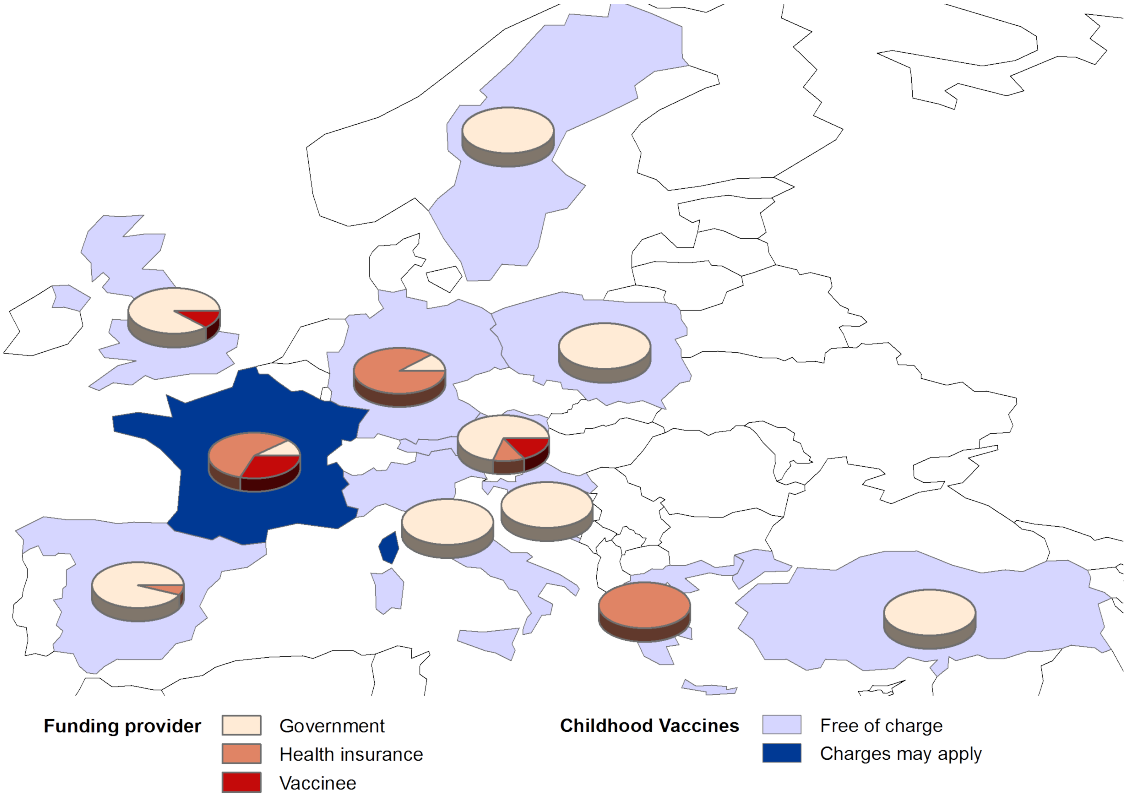

Figure 3.5. Immunization Financing in Selected European Countries. The pie charts indicate the proportions of routine vaccines funded by national and local government, health insurance and social security schemes, as well as the vaccinees or their families themselves. In most nations, all routine immunizations are financed publicly, as shown. In France, Austria and the United Kingdom, small proportions of routine immunizations are paid out-of-pocket. Routine childhood and adolescent vaccines are free of charge in all nations, with the exception of France. ***Sources***: *Akdağ, 2011*,[39] *Bundesministerium für Gesundheit: Impfplan Österreich 2013*,[24] *Ceyhan, 2010*,[74] *Hofmarcher, 2013*,[139] *Pavlopoulou et al., 2013*,[215] *Tesovic, 2012*,[284] *Vaccine European New Integrated Collaboration Effort (Venice II): Immunization Programs*.[293] Geographic data obtained from www.naturalearthdata.com.

3.2.2. France

In France, immunizations are regulated by the Ministry of Social Affairs and Health (*Ministère des Affaires sociales et de la Santé*), which annually publishes a current vaccination schedule, as proposed by the Advisory Board of Immunizations (*Comité Technique des Vaccinations* (CTV)) of the High Council of Public Health (*Haut Conseil de la santé publique* (HCSP)),.[293] The CTV's recommendations are based on data obtained from various government agencies responsible for epidemiological surveillance, vaccination coverage evaluations and vaccination attitude and practice analyses, such as the *Institut de veille sanitaire* (InVS) or the *Institut national de prévention et d'éducation pour la santé* (INPES).[293] The immunization schedule applies to all regions of the country equally, and local district governments do not

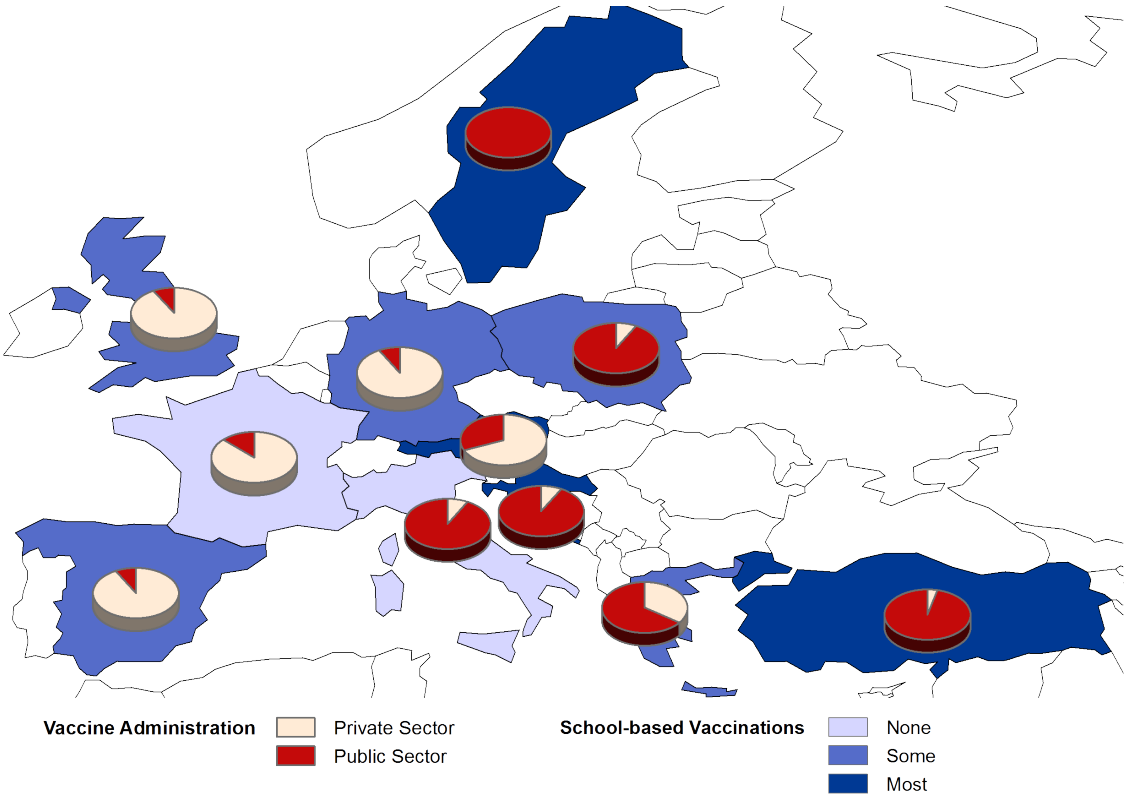

Figure 3.6. Private and Public Vaccine Administrations in Selected European Countries. Estimated proportion of immunizations administered in the private and public health sectors of each nation are shown. In Austria, France, Germany, Spain and the United Kingdom, most vaccines are administered in private practices and clinics. In Croatia, Greece, Italy, Poland, and Turkey, public vaccine administrations are more common. In Sweden, immunizations are distributed almost exclusively through the public health sector. The map's background colors indicate the approximate frequency of school-based vaccinations. Immunizations are commonly provided through schools in Sweden, Croatia, Turkey and Austria, whereby the later does not include MMR vaccines. In Italy and France, on the other hand, vaccinations are not typically administered in schools. All other nations have policies that include some school-based immunizations campaigns. ***Sources***: *Decreto del Presidente della Repubblica 26 gennaio 1999, n. 355*,[1] *Hofmarcher, 2013*,[139] *Hrvatski Zavod za Javno Zdravstvo, 2013*,[25] *Kaic et al., 2007*,[150] *Ministére de l'éducation nationale, 2012*,[17] *Öffentliches Gesundheitsportal Österreichs, 2013*,[124] *Pavlopoulou et al., 2013*,[215] *T.C. Milli Eğitim Bakanlığı, 2013*,[28] *Vaccine European New Integrated Collaboration Effort (VENICE II): Immunization Programs*.[293] Geographic data obtained from www.naturalearthdata.com.

have the authority to make changes, even in local outbreak situations.[293] Although most of the routine vaccinations are non-compulsory, some are mandatory for children under the age of 14 years, including vaccines against diphtheria, tetanus and poliomyelitis.[133] These immunizations, as well as vaccines against tuberculosis and hepatitis B are also mandatory for health care workers.[133] Measles, mumps and rubella vaccinations are not compulsory, however (See Table 3.7 for details).

All mandatory vaccines are free of charge for the public.[293] In addition, MMR and influenza vaccines are also free for children under the age of 13 years, the elderly and at-risk patients.[293] In the private sector, where about 85% of vaccines are

administered, approximately 65% of the routine immunizations are financed through the social security system.[293] The remaining costs are either funded by optional health insurance coverage or paid out-of pocket by the families themselves.[293] France is the only included nation that does not provide all routine childhood immunizations free of charge. (See Figs. 3.5 and 3.6 for further details).

Public vaccine administration, making up about 15% of all distributed vaccines, are provided by local public health care clinics for children up to the age of six years, and in some regions for older children and adults as well. Immunizations are not administered in schools, but proof of mandatory vaccination is required for entry into the primary school system.[17]

Nation	Recommended Vaccines		Mandatory Vaccines	
	General Population	Specific Groups	General Population	Specific Groups
Austria	MMR, V, TD, aP, IPV, HB, HiB, Inf, MV, PCV	V[1], Inf[1,2]		
Croatia		Inf[2], PCV[2]	MMR, TD, aP, IPV, HB, HiB, BCG	
France	MMR, aP, HB, HiB, MV, PCV	V, TD[3], IPV[3], Inf, BCG	TD[4], IPV[5]	TD[6], HB[6], BCG[6]
Germany	MMR, V, TD, aP, IPV, HB, HiB, MV, PVC	Inf[2,7]		
Greece	MMR, V, aP, HiB, MV, PCV, BCG	Inf	TD[8], IPV[8], HB[8]	
Italy	MMR, V[9], TD[9], aP, IPV, HiB, MV[9], PCV[9]	V[9], MV[9], PCV[9], Inf, BCG	TD,[10]IPV, HB	
Poland		MMR[10], V[2], Inf[2,7], HB[2], MV[2]	MMR, TD, wP/aP, IPV/OPV, HB, HiB, BCG	DT[2], HiB[2], HB[2,6], PCV
Spain	MMR, TD, aP, IPV, HB, HiB, MV, PCV	V[9], Inf[2], PCV[9], BCG[9]		
Sweden	MMR, TD, aP, IPV, HiB, PCV	Inf[2,7], HB[2], BCG[2]		
Turkey	MMR, TD, aP/oP, IPV, HiB, PCV, HB, BCG	V[2], Inf[2]		
UK	MMR, TD, aP, IPV, HiB, MV, PCV	V[2], aP[3], Inf[3], PCV[3], HB[2], BCG[3]		

Note: MMR: mumps-measles-rubella, *V*: varicella, *TD*: tetanus-diphtheria, *aP*: acellular pertussis, *wP*: whole-cell pertussis, *IPV*: inactivated polio, *OPV*: oral polio, *HB*: hepatitis B, *HiB*: *Haemophilus influenzae* type B, *Inf*: influenza, *MV*: meningococcal, *PCV*: pneumococcal, *BCG*: Bacillus Calmette-Guérin (tuberculosis)

Source: Austrian Ministry of Health, 2013,[24] Haverkate et al., 2012,[133] Robert Koch Institut, 2013,[245] Tešovic, 2012,[284] Turkish Ministry of Health, 2011,[39] UK Department of Health,[98] Vaccine European New Integrated Collaboration Effort (VENICE II), 2013[293]

[1] Recommended for women of child-bearing age and/or pregnant women.
[2] Recommended for those at clinical, epidemiological or occupational risk of infection.
[3] Recommended for children $\geq$ 13 years of age and adults.
[4] Mandatory for children $\leq$ 18 months of age.
[5] Mandatory for children $\leq$ 13 years of age.
[6] Mandatory/Recommended for health-care workers.
[7] Recommended for the elderly (>55 years).
[8] Non-compliance with mandatory vaccination is not penalized.
[9] Regional differences in recommendations.
[10] Recommended for insufficiently vaccinated girls and women with occupational exposure risks.

Table 3.7. Recommended and Mandatory Vaccines by Nation. Listed are the non-compulsory and compulsory vaccinations for each country. Whereas most immunizations apply to the general public, some are only recommended for specific groups of people, such as those with occupational exposure risks or severe chronic illnesses. Croatia, France, Greece, Italy, and Poland lawfully require their residents to receive certain vaccinations, most notably those against tetanus, diphtheria and poliomyelitis. Routine immunizations in Croatia and Poland are mandatory for the entire population, as shown.

3.2.3. Germany

In Germany, information about vaccine-preventable diseases, vaccination recommendations and immunization schedules are provided by the *Ständige Impfkommission*

(STIKO), a committee of the Federal Public Health Department associated *Robert Koch Institut* (RKI). Responsibilities of the STIKO and RKI include, among others, the management and prevention of disease, with particular focus on communicable and vaccine-preventable diseases.[244] The STIKO regularly updates and publishes a current vaccination schedule that includes all infant, child and adult immunization recommendations as well as specific information for certain high-risk groups.[245] These recommendations do not necessarily apply on a national level, however.[293] The German federal states can decide individually which vaccines their residents should receive.[293] Most follow the STIKO recommendations closely and some even provide additional recommendations.[293] As in Austria, all vaccinations in Germany are voluntary and there are no penalties for those choosing not to vaccinate themselves or their children.[293]

The administration of immunizations occurs largely (about 90%) through the private health sector.[293] These vaccines are not financed by the government, but are mainly covered through statutory health insurances.[293] About 10% of the vaccines, typically those that are non-routine, are not financed by statutory insurance schemes, however, and must be paid either by the vaccinees or through private health insurance companies.[293] Publicly administered immunizations, in public health institutions or schools as part of specific vaccination programs, are financed by the individual state governments; these cover about 10% of all vaccinations in Germany.[293] Figures 3.5 and 3.6 show how these vaccination practices compare with those of other nations.

3.2.4. Greece

Vaccinations in Greece are administered according to the National Immunization Program (NIP), maintained and published by the Ministry of Health. A National Committee on Vaccinations regularly proposes amendments to the NIP according to current research on vaccines, vaccine safety and epidemiology, and the Ministry of Health approves or revises these proposals, as necessary.[123]

Some immunizations are mandatory for all residents, including diphtheria, tetanus, polio and hepatitis B vaccines, whereas others are voluntary, such as the measles, mumps and rubella vaccines.[133] Non-compliance with this mandate is not usually penalized, however.[133] Further details as well as comparisons to other nations' mandatory and recommended vaccines are provided in Table 3.7.

Since 2008, all vaccines included in the NIP are free of charge for children residing in the country, regardless of migratory background or nationality.[215] Although immunizations must be paid privately, public health insurance companies fully reimburse families for the costs of vaccines.[215] The administration of immunizations occur in the private and public primary health care sectors as well as in health insurance clinics. According to a recent study by Pavlopoulou et al.,[215] about one-third of preschool children are vaccinated by pediatricians in private practice and about two-thirds by health insurance doctors or clinics. Public health clinics were visited for immunization in less than 1% of cases.[215] This study illustrates, among other things, the important role health insurance companies play in regard to the Greek vaccination program.

3.2.5. Italy

Italy, like France and Greece, has a national immunization plan that includes both mandatory and voluntary vaccines. Mandatory vaccinations are those against diphtheria, tetanus, polio and hepatitis B.[133,293] All others are recommended, but not compulsory, and vary according to region.

Each region of Italy is responsible for the implementation of an immunization program on a local level.[293] A national plan is regularly published by the Italian Ministry of Health and serves as a reference guideline for the local public health authorities.[185,293] It is established in collaboration with the National Institute of Health (*Istituto Superiore di Sanitá*) and the Directorate General of Health Prevention.[185] Italian's federal regions can either adhere to the national plan, recommend

additional vaccines, or make changes depending on the local epidemiological situation.[293] This has lead to a wide heterogeneity among the vaccination programs in the country.[185]

The administration of vaccines, both mandatory and voluntary, is predominantly performed by vaccination clinics within the Italian National Health Service.[293] All vaccines are free of charge for Italian and immigrated children, who can receive immunizations in any vaccination clinic throughout the country.[293] Immunizations are not administered in schools. Children in the Italian school system who are not inoculated with the compulsory vaccines are reported to the local public health authorities and the Ministry of Health, but are not excluded from attending school.[1]

3.2.6. Spain

The Spanish Ministry of Health, Social Services and Equality (*Ministerio de Sanidad, Servicios Sociales e Igualdad*), while responsible for the coordination of public health services and institutions, such as the National Institute of Health (*Instituto Nacional de la Salud*, INSALUD) and the Institute of Health "Carlos III" (*Instituo de Salud Carlos III*, ISCIII), does not oversee immunizations on a national level.[293] Instead, the country's 19 autonomous regions provide vaccination recommendations and funding for their local residents.[293] Nonetheless, a national immunization schedules is in place and is regularly amended by an Inter-Territorial Council, made up of representatives of each of the autonomous communities.[293] The Council's Commission on Public Health oversees a Technical Working Group on Vaccines that makes immunization recommendations based on currently available vaccines, safety and efficacy studies, as well as epidemiological considerations.[293] These recommendations, once approved by the Commission on Public Health and the Council, are incorporated into the national schedule.[293] The autonomous communities generally adhere to the agreed upon schedule, though variances do occur, particularly among the recommended vaccination ages.[293] Some regions also offer additional vaccines to their residents.[293]

All vaccines in Spain are voluntary and free of charge for the general public.[133] Universal public health care coverage is available for all residents and about 94% of all citizens are enrolled in the National Health Care Plan.[293] Programs for the health coverage of legal and illegal immigrants are also available.[293] Those people not covered through public health plans typically have private health insurances.[293] The out-of-pocket expenditure for routine vaccinations is therefore effectively zero (See Fig. 3.5).

The administration of vaccines generally occurs through pediatricians, who are the primary health care providers for children up to the age of 14 years.[293] In some regions, public health clinics may also provide immunizations.[293] Whereas most vaccines are not administered in schools, the menigococcal vaccine is an exception; public health care workers visit schools to vaccinate students, thus ensuring a higher coverage.[293]

Vaccination coverage is also monitored by the autonomous communities.[293] Various regional surveillance systems exist and include electronic registries of immunizations as well as vaccination cards.[293] Aggregated data from each community are passed on to the Ministry of Health and, more specifically, the *National Immunization Program* (NIP), which serves to coordinate the vaccination activities of the communities and upholds correspondence with international organizations, such as the ECDC or WHO.[293] Surveillance of the VPDs themselves is carried out by the ISCIII,[142] as further addressed in Sections 3.3 to 3.5 below.

3.2.7. Sweden

The Swedish national immunization program is maintained and regulated by the National Board of Health and Welfare (*Socialstyrelsen*).[276] The Board proposes and regulates the vaccination programs within in the country's individual counties and municipalities, which are responsible for the implementation of the national schedule and administration of immunizations.[293] The Swedish Institute for Infectious

Disease Control (*Smittskyddsinstitutet*, SMI), as well as expert advisory groups, regularly recommend immunization schedule improvements to the Board based on current vaccination and epidemiology research. The Board takes these proposals into consideration when amending the current national schedule.[293] The SMI is also responsible for national disease, seroepidemiology and vaccination coverage surveillance.[272,293]

In Sweden, vaccines are predominantly administered by nurses. Young children up to the age of six years are vaccinated in Child Health-Care Centers (CHC); older children are vaccinated in schools.[293] In some instances, physicians administer the vaccines, if the child belongs to a high-risk group or has a severe chronic disease, for example.[293] The CHC and school immunizations reach nearly all children in the Swedish communities. More than 99% of children are registered in the health care system and all children, including non-registered immigrants and refugees, are enrolled in the school system.[293] All immunizations are voluntary and there are no penalties for parents choosing not to vaccinate their children. The coverage rates are nonetheless high[276](See Sections 3.3 to 3.5 for details).

Routine vaccination costs are financed by local counties and communities; no charges for the vaccinees or their families apply.[293] The cost of non-routine vaccines, including travel immunizations, may be charged to the patients, however, depending on the vaccine and region.[293] Particularly adult immunizations, such as annual influenza shots and diphtheria and tetanus boosters, are not part of the national vaccination program. Official recommendations for these vaccines do exist however, and they are provided free of charge in some regions of the country.

3.2.8. United Kingdom

The United Kingdom immunization program falls under the domain of the Department of Health, which, in collaboration with the HPA, publishes national immunization recommendations in a so-called "green book" ("Immunisation against infectious

disease").[98] The currently effective recommendations are from the 2006 edition, whereby regular updates are included as changes to the program are being made. An independent advisory group consisting of scientific medical, clinical and immunization experts, the *Joint Committee on Vaccination and Immunisation* (JCVI), regularly proposes amendments to the vaccination schedule, which are generally included by the Department of Health.[98]

All recommendations in the national vaccination program are non-compulsory. The schedule includes immunizations for children and adolescents up to the age of 14 or 15 years and for adults 65 years and older.[98,232] Groups with a high risk of infection may also receive additional vaccinations, such as against tuberculosis or varicella, as indicated in Table 3.7.[98,232] Details regarding measles, mumps and rubella immunizations are shown in Table 3.8 of Section 3.3.2.

Nearly all immunizations are free of charge. Vaccine financing for children is generally covered by the government.[232] Adults, however, may need to pay for certain immunizations, including influenza, pneumococcal and hepatitis B, out-of-pocket.[232] Charges for non-routine (i.e. travel) vaccines may also need to be covered by the vacinees themselves.

Vaccinations are offered in private and public health care clinics and practices. Most are performed by general practitioners. Immunizations are also administered in schools in some areas of the country or during specific vaccination campaigns. Adolescents 16 years of age and older can chose themselves whether or not to be vaccinated.[98] For minors, the choice to receive an immunization is either made by the parents or by "Gillic competent" children (judged to be fully aware of the involved health procedures) themselves, regardless of the parental decision.[98] See Fig. 3.6 for a comparison of these vaccination administration practices among the included European nations.

3.2.9. Croatia

Unlike most other European countries, Croatia has an immunization policy in which nearly all vaccines are mandatory for the general public, as regulated by law.[150] The Minister of Health annually declares an immunization schedule with infant and childhood vaccinations for the entire nation, as based on recommendations by the National Institute of Public Health (*Hrvatski Zavod za Javno Zdravstvo*, HZJZ).[284] Nearly all included vaccines are part of the Croatian Childhood Vaccination Program, which covers children up to 19 years of age and provides the immunizations free of charge.[284] Some vaccines, including those against influenza and pneumococcal disease, are not compulsory, bur are recommended for high-risk groups.[284] For further details about which vaccines are compulsory and which are not, see Table 3.7.

The administration of vaccines occurs through different institutions, depending on the age of the child. Young preschool-aged children are vaccinated by primary health care providers or through public health care institutions.[150] Older children receive their immunizations at school through the local school medical services in grade levels one, six, seven, eight and twelve.[25,150] In addition, a Tetanus booster at 60 years of age is also included in the mandatory schedule.[25]

3.2.10. Poland

In Poland, the National Immunization Program is regulated and upheld by the Ministry of Health and the General Sanitary Inspectorate.[293] A health and epidemiology advisory board (*Rada Sanitarno-Eppidemilogiczna*), consisting of physicians, epidemiologists, microbiologists and health inspectors, regularly makes recommendations for changes to the program.[293] A new schedule is published annually and includes predominantly mandatory and some voluntary vaccines.

Mandatory childhood immunizations in Poland include those against measles, mumps, rubella, tetanus, diphtheria, polio, hepatitis B, *H. influenzae* and tuberculosis[133] (see Table 3.7). Additionally, some vaccinations are mandatory for certain high-risk groups, such as health care workers, or people who have been exposed to a disease, such as rabies or tetanus.[293] Furthermore, non-compulsory recommendations are in place for previously unvaccinated adults or people at risk for infection due to occupation or travel.[293] Vaccines against meningococcal disease, influenza and varicella are also voluntary and recommended only for those with a clinical or epidemiological risk.[133]

The costs of all mandatory vaccines are financed through the Ministry of Health and the National Health Fund, *Narodowy Fundusz Zdrowia* (NFZ).[293] They are administered at hospitals, public health clinics or practices that are affiliate with the NFZ.[293] Voluntary vaccines are not free of charge, however, and must be paid privately by the vaccinees.[293] Some employers and insurance companies also cover these charges.[293] Immunizations are typically not administered at schools.[293]

3.2.11. Turkey

In 2003, Turkey launched a *Health Transformation Program*, with the goal of providing better health care to all citizens through improved policies and regulations as well as the implementation of new health programs.[39] In the course of this transformation program, Turkey has increased its total expenditure on health, including available funding for vaccines and immunization programs. According to an evaluation report of the program, resources available for immunizations were increased nearly ten-fold between 2002 and 2010.[39] In accordance with this, all routine childhood vaccination expenditures are covered completely by government funds.[39,74]

The Turkish Ministry of Health oversees the National Immunization Program (NIP) that includes non-compulsory vaccinations for children and adolescents up to their 8^{th} year in school (age 13-14 years).[39] Over the course of the past decade, many

changes have been made to the NIP, as recommended by an Advisory Board of Immunizations, consisting of pediatricians and public health, epidemiology and immunology experts. In 2004, general immunization recommendations existed for measles, diphtheria, tetanus, pertussis, polio, hepatitis B and tuberculosis, but the national coverage rates averaged $\leq$85% and were even below 50% in some regions of the country.[39,74] In the following years, vaccines against mumps, rubella, *H. influenzae* and *S. pneumoniae* were added, as well as against influenza and varicella for high-risk groups.[39,74] Improved immunization campaigns reaching much wider populations were also implemented.[74] These NIP amendments lead to an overall increase in immunization rates that are comparable with those of most other European nations.[74]

Immunizations are mainly offered in the public health care sector by health centers, hospitals and schools and, to a lesser degree, in the private heath care sector by family practitioners.[74] Prior to entry into the school system, most children are vaccinated in public health centers associated with the Ministry of Health.[74] Children attending a preschool/kindergarten may also receive vaccinations there, in particular the MMR inoculation.[28] Vaccines for school-aged children are administered at schools during the first and eighth grades.[28,39] Additionally, catch-up vaccination campaigns have been used to vaccinate children and adolescents against measles and rubella.[39] Within the framework of a Maternal Neonatal Tetanus Elimination Program, wide-spread tetanus (and diphtheria) immunizations for previously unvaccinated women of childbearing age have also been provided.

Through these extensive vaccination measures, the reported case rates for many vaccine-preventable diseases were sharply reduced in Turkey. Nonetheless, the spread of communicable diseases continues to be a concern and the infection rates for several diseases, including measles and rubella, have risen again in recent years.[326] More detailed information about the occurrences of measles, rubella and mumps are provided in the respective sections below.

3.3. Measles

The WHO European Region is aiming to eliminate measles by the end of 2015.[310] All Member States have committed to reaching this goal, which includes the nationwide absence of endemic measles cases for a period of at least one year, or three years for verification, as measured by a well-functioning surveillance system.[307,310] High national vaccination rates are needed to reach this goal. This section analyzes various studies and reports among the eleven included European nations in order to determine which immunization programs are the most effective in controlling measles outbreaks and eliminating the disease.

3.3.1. Study and Report Selection

The literature search resulted in a total of 333 studies and reports. Of these, 227 were found using Pubmed, 117 using Medline, 109 using the SSCI/SCI-Expanded database and 55 through other sources, such as the WHO, ECDC and governmental agencies. After screening the titles and abstracts, 186 articles could be excluded because they were not relevant to the search. The most common reasons for exclusion were the focus on different pathogens (predominantly mumps and rubella), method analyses (such as laboratory testing methods), subjects belonging to specific employment groups (mainly health care workers) and studies regarding countries other than the ones included in this report. The full-text articles of the remaining 146 sources were analyzed and another eight studies excluded. Missing or insufficient epidemiological data was the most common reason for exclusion after full-text examination. In Appendix G, a list of all excluded publications and reasons for exclusion is provided.

A total of 138 studies and reports were included in the literature analysis. These were separated into groups based on their pertinence to either measles case reports, vaccination coverage, or seroepidemiological antibody studies. A flow diagram of

the study selection process, including the number of excluded studies and reasons for exclusions as well as the number of included studies in each category, is shown in Fig. 3.7.

3.3.2. National Immunization Plans

Current national childhood vaccination schedules of measles-containing vaccines (MCV) have been compared for all included countries and are delineated in Table 3.8 below. As recommend by the WHO, two-dosage, polyvalent MMR combination preparations are used in each country. Three of the indicated nations—Croatia, Poland and Turkey—mandate MMR vaccinations. All other countries strongly recommend, but do not require, the vaccination of all their citizens (see Table 3.7).[39,133] MMR vaccines are provided either free of charge or are covered through statutory health insurances in each included nation, with the exception of France (see Fig. 3.5).

As shown in Table 3.8, nearly all countries recommend or mandate the first MMR vaccination dosage (MMR-1) around the age of one year (11 to 14 months). Slightly later first-dose immunizations up to 15 and 16 months are recommended by Greece and Italy, respectively, while the latest recommendation at 18 months is made by Sweden. Much larger international differences can be observed for the suggested second-dosage immunization age. While both Austria and Germany recommend this dosage soon after the first and before the child's second birthday, other countries, including Sweden, Croatia, Poland and Turkey, do not recommend or mandate the vaccine until the child is at least 6 years old (the typical age for entry into the primary school system, see Section 3.1.5).

Most nations have catch-up plans in effect, targeted towards those children, adolescents and adults who were not previously vaccinated or who only received one prior MMR dosage. France, Germany and Spain additionally provide measles immunizations to infants as young as 6 months old (9 months in Germany) if exposure to

an infected individual has occurred or is likely to occur. In all three nations, the regularly scheduled MMR vaccines are additionally recommended for these children to ensure sufficient seroconversion. For further details, see the Table 3.8 notes.

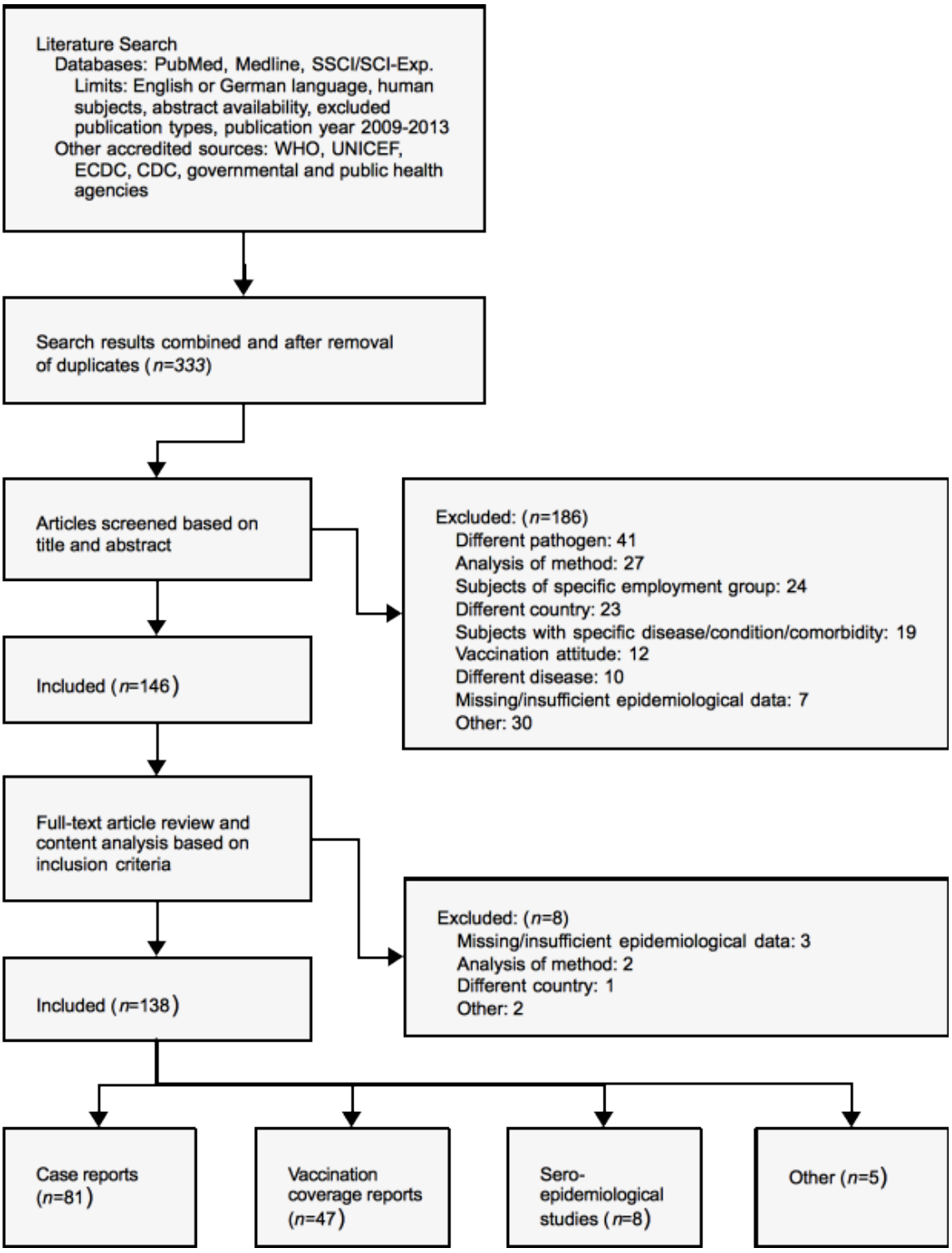

Figure 3.7. Publication Selection Flow Diagram: Measles. The literature search process for studies and reports pertaining to measles is shown. Pre-defined inclusion and exclusion criteria, as listed in Appendix A, were used. Figure adapted from Liberati et al., 2009, *The Prisma Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration*, Figure 1.[164]

Country	Age in Months (M) or Years (Y)																	
	0-5M	6-10M	11M	12M	13M	14M	15M	16M	17M	18M	19-23M	2Y	3Y	4Y	5Y	6Y	7-10Y	11-14Y	15-18Y
Austria[a]			1, 2														catch-up		
France[b]		P		1				2								catch-up			
Germany[c]		P	1				2								catch-up				
Greece[d]				1										2					
Italy					1										2			catch-up	
Spain[e]		P		1							2			catch-up					
Sweden[f]										1						2		(2)	
UK[g]				1									2					catch-up	
Croatia[h]				1												2			
Poland[i]					1												2	catch-up	
Turkey[j]				1												2			

[a] Minimum interval of 4 weeks between dosages; catch-up vaccinations recommended for residents with no or only one prior MMR vaccination; vaccine included in the national child vaccination program and free of charge for citizens up to the age of 45 years. *Source: Austrian Federal Ministry of Health, 2013 Vaccination Schedule*.[24]

[b] Additional monovalent measles dosage recommended for infants 6-12 months of age in case of measles exposure or travel to a high-prevalence area; vaccine free of charge. *Source: French High Council of Public Health, 2013 recommendations*.[132]

[c] Additional MMR dosage recommended for infants 9-11 months of age in case of measles exposure; post-exposure MMR vaccine also recommended for older children with no or only one prior dosage; strongly recommended for those born after 1970 and insufficiently vaccinated; immunization costs covered through statutory health insurance providers. *Source: Robert Koch Institut, 2013 Vaccination Schedule*.[245]

[d] Post-partum MMR vaccination of seronegative pregnant women recommended.

[e] Additional single MMR dosage *or* non-specific immunoglobulins recommended for children 6-12 months of age in case of measles exposure; vaccine free of charge. *Source: "Immunization schedule of the Spanish Association of Pediatrics: 2012 recommendations", Moreno-Pérez, et al.*[188]

[f] Second dosage recommended at age 6-8 years for children born during or after 2002 and at age 12 years for children born prior to 2002; post-partum MMR vaccination of seronegative pregnant women strongly recommended; immunization is part of the general vaccination program and free of charge. *Source: Swedish Institute for Communicable Disease Control, Vaccination program*.[272]

[g] Catch-up program for children born 1997-2003; vaccine free of charge. *Source: National Health Service, 2013/14 routine vaccination schedule*.[232]

[h] Immunization mandatory at age 12 months an 6-7 years; vaccine free of charge.

[i] Immunization mandatory at age 13-14 months and 10 years; catch-up immunizations mandatory for insufficiently vaccinated children and young adults <20 years; vaccine free of charge. *Source: Szczepienia.info, Polish National Insitute of Public Health, 2013*[18,31,35]

[j] Vaccine free of charge. *Source: Turkish Ministry of Health, 2011 Childhood Vaccination Schedule*.[39]

Table 3.8. MMR Immunization Schedules for Children (Ages 0-18 Years). Shown are the measles-mumps-rubella (MMR) immunization dosages (1^{st}, 2^{nd}) at the appropriate vaccination ages for children, as recommended or mandated by the indicated European nations. Darker shaded cells indicate the routine immunization schedules, lighter shaded cells post-exposure (P) and catch-up recommendations. Unless otherwise indicated, data was adapted from the European Center for Disease Prevention and Control (ECDC)[115]

3.3.3. Surveillance Systems

The WHO definition of measles elimination includes the absence of cases "in the presence of a well performing surveillance system".[307] Indicators for the performance of measles surveillance systems include, among others, the regular and timely reporting of suspected cases and the laboratory confirmation of at least 80% of these cases.[307]

Measles is a mandatory notifiable disease in all of the nations included in this report.[98,110,196] According to annual epidemiological reports published by the ECDC, all of these nations, with the exception of Turkey and Croatia (not included), require the notification of measles cases either by laboratories (all but Italy and Spain), physicians (all but UK) and/or hospitals (all but Sweden).[109,110] All nations report case-based data, allowing for further insight into demographic variables, vaccination history, course of the infection and complications, among others (known as enhanced surveillance).[198]

Nearly all included countries report nation-wide enhanced surveillance statistics to *The European Surveillance System* (TESSy) on a regular basis. The data are then analyzed and published by the ECDC in a monthly monitoring report.[26] Important exceptions are Croatia, for which case numbers were not published until 2013, and Turkey, for which data are not currently available through the ECDC. Prior to September of 2011, measles cases were reported to EUVAC.NET by all of the nations included in this report. The numbers of notified, confirmed and hospitalized cases up to 2010, as published through EUVAC.NET, have been included in Table 3.10 below.

Although the laboratory or epidemically-linked confirmation rates were reported to be very high by some countries, such as Sweden, Turkey, and the UK, only 43% of the total European-wide cases were confirmed in 2011.[110] This number is lower than the overall confirmation rates reported by the ECDC for the previous three years: 48% in 2008, 63% in 2009 and 91% in 2010.[105,106,109] With the exception of 2010,

the WHO goal of confirming at least 80% of suspected measles cases has not yet been reached for the European region.

In addition, the under-reporting of measles cases, in spite of mandatory disease notification laws, may be a problem in several nations. Under-reporting has been described to occur in Germany, where regional data from health insurance carriers regarding measles case numbers were significantly higher than the numbers of officially reported cases.[182] In France, reported case numbers have also been described as inaccurate because of a lack of notification by physicians, particularly in regard to secondary cases after the primary case had been reported.[270] Under-reporting is suspected to occur in some parts of Italy as well, where large differences in measles incidence have been reported by various sub-national regions, ranging from 0.2/100,000 to 246.6/100,000 during the same year.[118] Similar circumstances may lead to incorrect case reporting in other countries as well.

While the studied nations' current surveillance systems for measles do require case-based reporting by physicians, hospitals and laboratories in a timely manner, the confirmation rates do not quite meet the standards set forth by the WHO and case numbers may be under-reported. These potential reporting errors will be further addressed in Section 4.1.2 of the Discussion.

3.3.4. Case Reports and Incidences

A total of 81 studies and epidemiological reports were analyzed regarding national measles case numbers for the included countries (see Fig. 3.7). Data obtained from the WHO, ECDC, EUVAC.NET and governmental and public health organizations have been summarized in Table 3.10. The numbers of confirmed cases (laboratory tested or epidemiologically linked) and imported cases, as well as reported hospitalizations and deaths are also indicated in the table. Annual incidences have been calculated for each country.

Varying national measles surveillance data from different sources has been averaged and the standard deviation determined, as shown. Particularly large variances are found for data reported by Italy. According to the WHO, 1,619 measles cases occurred in Italy during 2008.[326] However, the ECDC annual surveillance report states that 5,311 cases were reported by the country during the same year.[105] The Italian National Center for Epidemiology, Surveillance and Health Promotion (CNESPS) comments on their website that a new measles surveillance system was established in 2007; the older system continued to be in use until 2009, however, possibly explaining the reporting differences.[102] Data available through the CNESPS indicates that during 2008, 5,312 cases were reported through the older system, but only 4,132 (1,180 less) through the new system.[102] Similarly, in 2009, 759 cases were reported through the older system and 253 (506 less) through the new system.[102] Potential reasons for these rather large discrepancies will be further addressed in the Discussion.

Variances in the reporting of confirmed cases was also found, though the discrepancies were comparatively small. Some sources only reported laboratory-confirmed cases, whereas most also included epidemically linked cases (or *probable* cases, according to the 2008 EU case definition[291]). Whenever discrepancies in reporting of confirmed cases occurred, the higher number was included, as confirmation may have taken place at a later point in time. The majority of the included nations (Germany, Poland, Italy, Spain, Sweden, Turkey and the UK) surpassed the 80% confirmation rate threshold, though not all of these cases were confirmed by laboratories. The other four countries reported lower rates, ranging between 43% in France and 77% in Croatia, as shown.

Overall, a total of 72,592 measles cases (53,487 confirmed) were reported by the selected countries between 2006 and 2013. During 2011 alone, more than 26,000 individuals were infected, corresponding to an incidence of 5.66 per 100,000 population. The countries with the highest measles incidences during 2011 were Italy (7.55/100,000), Spain (7.70/100,000) and France (22.87/100,000). Next to these three countries, Germany, Turkey and the UK also reported high overall case num-

bers, the majority of them in the more recent years (2011-2013). An overall increasing trend in measles infections can be observed over the course of the past eight years.

Of those cases in which an importation status could be determined, a total of 1,615 cases were imported from other countries between 2006 and 2013. Most of the studied nations report 2% to 5% importation rates, as shown in Table 3.10. In Italy, $<$1% of the cases had been imported. In Austria, Turkey, Croatia, and Sweden, on the other hand, the rates were higher, reaching 8%, 14% and as high as 45%, respectively. The sources of importation could be identified for a large number of these cases, as further delineated below (see Table 3.11).

During 2006 to 2013, a total of 11,643 measles-related hospitalizations and 18 deaths were reported. As seen in Table 3.10, the countries with the highest numbers of hospitalized measles cases were France, Italy, Spain and the United Kingdom. Particularly during the 2011 outbreaks, seven mortalities were reported, six of them from France.[326] The overall case fatality rate among confirmed cases was calculated to be 0.03% for the 2006-2013 time period. This number is in accordance with previously described case-fatality ratios in industrialized nations.[107,217,280]

The fatalities reported were mostly among young children.[45,200] A review by Perry and Halsey[217] regarding measles infections in the United States between 1987 and 2000 also showed that children below the age of 5 years were predominantly affected by severe complications and had an increased fatality rate compared to older children. A young age is therefore an increased risk factor for severe disease progression. Affected children are often too young to be vaccinated or have not yet received the full two-dose measles immunization. In Table 3.9 below, the number of cases that have been reported among children younger than the recommended vaccination age, according to the respective national immunization schedule, are shown. Though age-based data was not available for all case reports, the table does indicates that several thousand children were affected prior to receiving complete immunization.

Next to national measles surveillance, local outbreaks have been described in several studies and reports, some of them focusing on particular populations. Based on these and similar reports, the ECDC has identified certain high-risk groups for measles infections, among them tourists, immigrants and traveling minority groups.[180] The following section provides details about reported measles outbreaks among these subpopulations.

Measles Cases among Children Younger than the Recommended Vaccination Age

Source	Country (Region/Pop.)	Vaccination Age and Cases Among Children Too Young to be Vaccinated		Total Cases	Study Quality
		Measles Dose 1	Measles Dose 2		
	Croatia	**12 Months**	**6-7 Years**		
Kaic et al., 2009[149]	Slavonski Brod	0 (0%)	3(10)[a] (15%)	20	Strong
Kaic et al., 2009[149]	Zagreb	2 (7%)	4 (14%)	29	Strong
	France	**12 Months**	**16-18 Months**		
CDC, 2011[72]	Nation-wide	955 (7%)	-	13,933	Strong
InVS, 2013[143]	Nation-wide	1,650 (7%)	-	22,627	Strong
Huoi et al., 2012[140]	Lyon	129 (32%)	-	407	Strong
	Germany	**11-14 Months**	**12-24 Months**		
RKI, 2013[249]	Nation-wide	452 (5%)	995 (11%)	8,857	Strong
Arenz et al., 2009[45]	Nation-wide	-	40[b] (42%)	96[b]	Strong
Hegasy et al., 2012[137]	Hamburg	19 (17%)	35 (33%)	107	Strong
	Italy	**13-16 Months**	**5-6 Years**		
Filia et al., 2011[119]	Nation-wide	69 (3%)	289 (14%)	2,079	Strong
Bassetti et al., 2011[51]	Genoa	0 (0%)	0 (0%)	83	Moderate
D'Agaro et al., 2011[96]	FVG	-	4 (10%)	42	Strong
Curtale et al., 2010[83]	Lazio	44 (10%)	152 (34%)	449	Strong
	Spain	**12-14 Months**	**2-5 Years**		
CDC, 2011[72]	Nation-wide	349 (13%)	833 (30%)	13,933	Strong
Barrabeig et al., 2011[50]	Catalonia	60 (78%)	74 (96%)	77	Strong
	Andalusian Region	**15 Months**	**3 Years**		
Mayoral Cortes et al., 2012[178]	Region-wide	285 (16%)	408 (23%)	1,759	Strong
López Hernandez et al., 2010[167]	Granada	6 (24%)	14 (56%)	25	Moderate
	Valencian Region	**15 Months**	**5 Years**		
Delgado de Los Reyes et al., 2012[168]	Elche	15[c] (14%)	19 (17%)	109	Strong

Measles Cases among Children Younger than the Recommended Vaccination Age

Source	Country (Region/Pop.)	Vaccination Age and Cases Among Children Too Young to be Vaccinated		Total Cases	Study Quality
		Measles Dose 1	Measles Dose 2		
	UK	**13-15 Months**	**3-5 Years**		
Cohuet et al., 2009[79]	(Irish travelers)	9 (5%)	57 (33%)	171	Strong
	Europe	**≈12 Months**	**N/A**		
CDC, 2011[72]	WHO European Region[†]	2,343 (9%)	-	25,832	Strong
Muscat et al., 2009[200]	EUVAC[‡] (2006)	1,223 (15%)	-	8,121	Strong
Muscat et al., 2009[200]	EUVAC[‡] (2007)	357 (9%)	-	3,845	Strong

Note: CDC: Center for Disease Control and Prevention (USA); *FVG*: Friuli Venezia Giulia region (Northeastern Italy); *InVS*: Institut de Veille Sanitaire (Institute for Public Health Surveillance, France); *RKI*: Robert Koch Institut (Germany).

[†] Includes EU countries, Albania, Andorra, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Iceland, Israel, Kazakhstan, Kyrgyzstan, Monaco, Montenegro, Norway, Republic of Moldova, Russian Federation, San Marino, Serbia, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine and Uzbekistan

[‡] Includes EU countries, Iceland, Norway, Switzerland and Turkey

[a] Cases were reported for 3 children below the age of 5 years and a further 7 children below the age of 10 years. The exact ages were not provided.

[b] Only hospitalized cases were included.

[c] Study indicated that some children were vaccinated at a younger age than the recommended vaccination age; these children have not been included here.

Table 3.9. Measles Cases among Children Younger than the Recommended Vaccination Age. Shown are recent reports of measles infections among children who were younger than the recommended immunization age in the respective country or region. Of note are the different immunization recommendations in various regions of Spain. Based on these data reports, thousands of children were infected by measles before they had reached the recommended vaccination age. Quality of the included studies has been assessed as indicated (see Study Characteristics, Appendix E for details). Hard data reports by the WHO, ECDC and governmental agencies were assumed to be accurate and assigned a "strong" quality; estimates were assigned a "moderate" quality.

Reported Measles Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Imported	Hospit.	Deaths			
	Austria	**2006-2013**	**797**	-	**383** (48%)	**60** (8%)	**263**	**-**			
ECDC, 2014,[116] WHO, 2013[326]		2013	**77**	2.8	59	5	32	-	-	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2013,[113] WHO, 2013[326]		2012	**30**	9.2	35	6	17	-	0.35	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2013,[113] WHO, 2013[326]		2011	**114**	13.3	69	13	76	-	1.36	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2012& 2013,[109,113] EUVAC.NET, 2011,[198] WHO, 2013[326]		2010	**50**	5.7	15	9	31	-	0.60	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2011,[106] EUVAC.NET, 2010,[197] WHO, 2013[326]		2009	**49**	3.0	13	2	11	-	0.58	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2010,[105] EUVAC.NET, 2009,[196] WHO, 2013[326]		2008	**437**	10.4	157	14	74	-	5.24	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2009,[103] EUVAC.NET, 2008,[195] WHO, 2013[326]		2007	**21**	1.2	20	8	7	-	0.25	Sur (M)	Strong
BMG, 2013,[62] EUVAC.NET, 2007,[194] WHO, 2013[326]		2006	**25**	3.2	15	3	15	-	0.30	Sur (M)	Strong
	Croatia	**2006-2013**	**82**	-	**62** (77%)	**11** (14%)	**14**	**-**			
ECDC, 2014[116]		2013	**1**	0.0	0	-	-	-	-	-	
WHO, 2013[326]		2012	**3**	-	3	3	-	-	0.07	Sur (M)	Strong
WHO, 2013[326]		2011	**7**	-	7	2	-	-	0.16	Sur (M)	Strong
EUVAC.NET, 2011,[198] WHO, 2013[326]		2010	**7**	0.0	7	1	1	-	0.16	Sur (M)	Strong
EUVAC.NET, 2010,[197] WHO, 2013[326]		2009	**2**	0.0	1	2	1	-	0.05	Sur (M)	Strong

Reported Measles Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	**Confirmed•**	**Imported**	**Hospit.**	**Deaths**			
EUVAC.NET, 2009,[196] WHO, 2013[326]		2008	**61**	14.8	44	2	11	-	1.36	Sur (M)	Strong
EUVAC.NET, 2008[195]		2007	**0**	-	0	0	0	-	0.00	Sur (M)	Strong
EUVAC.NET, 2007[194]		2006	**1**	-	0	1	1	-	0.02	Sur (M)	Strong
	France	**2006-2013**	**23,342**	-	**10,066** (43%)	**423** (2%)	**5,237**	**10**			
ECDC, 2014,[116] WHO, 2013[326]		2013	**272**	0.0	121	23	54	-	-	Sur (M, E)	Strong
ECDC, 2013,[113] InVS,[143] WHO, 2013[326]		2012	**847**	20.2	396	37	181	-	1.29	Sur (M, E)	Strong
ECDC, 2013,[110] InVS,[143] WHO, 2013[326]		2011	**14,948**	268.0	4,991	269	2,960	6	22.87	Sur (M, E)	Strong
ECDC, 2012,[109] EUVAC.NET, 2011,[198] InVS,[143] WHO, 2013[326]		2010	**5,041**	67.1	3,225	19	1,479	2	7.75	Sur (M, E)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[197] InVS,[143] WHO, 2013[326]		2009	**1,546**	36.8	928	35	422	2	2.39	Sur (M, E)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[196] InVS,[143] WHO, 2013[326]		2008	**602**	15.8	363	22	112	-	0.93	Sur (M, E)	Strong
ECDC, 2009,[103] EUVAC.NET, 2008[195]InVS,[143] WHO, 2013[326]		2007	**43**	8.7	24	8	15	-	0.07	Sur (M, E)	Strong
EUVAC.NET, 2007,[194] EUVAC.NET, 2007,[194] InVS,[143] WHO, 2013[326]		2006	**45**	0.7	18	10	14	-	0.07	Sur (M, E)	Strong
	Germany	**2006-2013**	**8,701**		**7,087** (82%)	**409** (5%)	**917**	**3**			
ECDC, 2014,[116] WHO, 2013[326]		2013	**1,776**	6.4	1,467	62	25	-	-	Sur (M, E)	Strong
ECDC, 2013,[113] RKI,[249] WHO, 2013[326]		2012	**167**	1.3	144	26	3	-	0.20	Sur (M, E)	Strong
ECDC, 2013,[113] RKI,[249] WHO, 2013[326]		2011	**1,606**	4.1	1,481	97	1	1	1.96	Sur (M, E)	Strong

Reported Measles Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	**Confirmed•**	**Imported**	**Hospit.**	**Deaths**			
ECDC, 2012,[109] EUVAC.NET, 2011,[198] RKI,[249] WHO, 2013[326]		2010	**790**	15.7	719	75	224	-	0.97	Sur (M, E)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[197] RKI,[249] WHO, 2013[326]		2009	**575**	5.0	533	26	149	-	0.70	Sur (M, E)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[196] RKI,[249] WHO, 2013[326]		2008	**921**	10.8	780	74	97	-	1.12	Sur (M, E)	Strong
ECDC, 2009,[103] EUVAC.NET, 2008,[195] RKI,[249] WHO, 2013[326]		2007	**569**	2.4	487	16	74	-	0.69	Sur (M, E)	Strong
EUVAC.NET, 2007,[194] RKI,[249] WHO, 2013[326]		2006	**2,298**	16.5	1,476	33	344	2	2.79	Sur (M, E)	Strong
	Greece	**2006-2013**	**710**		**387** (54%)	**18** (3%)	**499**	**0**			
ECDC, 2014,[116] HCDCP,[138] WHO, 2013[326]		2013	**3**	0.7	3	0	2	-	-	Sur (M)	Strong
ECDC, 2013,[113] HCDCP,[138] WHO, 2013[326]		2012	**3**	0.6	3	3	3	-	0.02	Sur (M)	Strong
ECDC, 2013,[113] HCDCP,[138] WHO, 2013[326]		2011	**39**	2.3	36	5	29	-	0.34	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2011,[198] WHO, 2013[326]		2010	**149**	0.6	128	10	105	-	1.32	Sur (M)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[197] WHO, 2013[326]		2009	**2**	0.0	1	0	1	-	0.02	Sur (M)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[196] WHO, 2013[326]		2008	**1**	0.0	1	0	1	-	0.01	Sur (M)	Strong
ECDC, 2009,[103] EUVAC.NET, 2008,[195] WHO, 2013[326]		2007	**2**	0.6	0	0	1	-	0.01	Sur (M)	Strong
EUVAC.NET, 2007,[194] WHO, 2013[326]		2006	**512**	0.0	215	0	357	-	4.59	Sur (M)	Strong

Reported Measles Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Imported	Hospit.	Deaths			
	Italy	**2006-2013**	**14,026**		**11,746** (84%)	**77** (<1%)	**1,069**	**1**			
ECDC, 2014,[116] WHO, 2013[326]		2013	**1,792**	909.3	5,468	47	-	-	-	Sur (M, E)	Moderate
ECDC, 2013,[113] WHO, 2013[326]		2012	**658**	34.6	375	4	-	-	1.08	Sur (M, E)	Moderate
ECDC, 2013,[113] WHO, 2013[326]		2011	**4,585**	856.3	3,091	23	-	-	7.55	Sur (M, E)	Moderate
ECDC, 2012,[109] EpiCentro,[102] EUVAC.NET, 2011,[198] WHO, 2013[326]		2010	**1,894**	1,196.7	3,064	0	282	-	3.13	Sur (M, E)	Moderate
ECDC, 2011,[106] EpiCentro,[102] EUVAC.NET, 2010,[197] WHO, 2013[326]		2009	**413**[a]	294.0	705	0	41	-	0.69	Sur (M, E)	Moderate
ECDC, 2010,[105] EpiCentro,[102] EUVAC.NET, 2009,[196] WHO, 2013[326]		2008	**3,599**[a]	1870.3	1,503	0	335	-	6.02	Sur (M, E)	Moderate
ECDC, 2009,[103] EpiCentro,[102] EUVAC.NET, 2008,[195] WHO, 2013[326]		2007	**505**[a]	104.0	595	3	118	1	0.85	Sur (M, E)	Moderate
ECDC, 2012,[109] EpiCentro,[102] EUVAC.NET, 2007,[194] WHO, 2013[326]		2006	**580**	11.4	571	0	293	-	0.98	Sur (M, E)	Moderate
	Poland	**2006-2013**	**665**		**425** (83%)	**31** (5%)	**372**	**0**			
ECDC, 2014,[116] WHO, 2013[326]		2013	**86**	0.7	60	8	42	-	-	Sur (M)	Strong
ECDC, 2013,[113] WHO, 2013[326]"		2012	**67**	8.5	61	4	38	-	0.17	Sur (M)	Strong
ECDC, 2013,[113] NIZP, 2012,[87] WHO, 2013[326]		2011	**38**	0.0	32	1	23	-	0.10	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2011,[198] NIZP, 2012,[87] WHO, 2013[326]		2010	**18**	11.1	9	0	9	-	0.05	Sur (M)	Strong

Reported Measles Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	**Confirmed•**	**Imported**	**Hospit.**	**Deaths**			
ECDC, 2011,[106] EUVAC.NET, 2010,[197] NIZP, 2010,[86] WHO, 2013[326]		2009	**138**	50.1	147	1	79	-	0.36	Sur (M)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[196] NIZP, 2010,[86] WHO, 2013[326]"		2008	**122**	43.5	89	14	83	-	0.32	Sur (M)	Strong
ECDC, 2009,[103] EUVAC.NET, 2008,[195] NIZP, 2008,[85] WHO, 2013[326]		2007	**76**	70.0	59	0	23	-	0.20	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2007,[194] NIZP, 2008,[85] WHO, 2013[326]		2006	**121**	1.7	91	3	75	-	0.32	Sur (M)	Strong
	Spain	**2006-2013**	**5,855**		**4,951** (85%)	**139** (2%)	**1,219**	**1**			
ECDC, 2014,[116] WHO, 2013[326]		2013	**127**	0.0	119	12	44	-	-	Sur (M)	Strong
ECDC, 2013,[113] ISCIII,[142] WHO, 2013[326]		2012	**958**	443.7	1,062	17	233	1	2.07	Sur (M)	Strong
ECDC, 2013,[113] ISCIII,[142] WHO, 2013[326]		2011	**3,554**	75.2	2,629	52	701	-	7.70	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2011,[198] ISCIII,[142] WHO, 2013[326]		2010	**299**	9.1	281	24	64	-	0.65	Sur (M)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[197] ISCIII,[142] WHO, 2013[326]		2009	**43**	1.3	42	7	7	-	0.09	Sur (M)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[196] ISCIII,[142] WHO, 2013[326]		2008	**285**	37.3	227	7	24	-	0.62	Sur (M)	Strong
ECDC, 2009,[103] EUVAC.NET, 2008,[195] ISCIII,[142] WHO, 2013[326]		2007	**248**	18.8	255	0	43	-	0.55	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2007,[194] ISCIII,[142] WHO, 2013[326]		2006	**342**	7.5	336	20	103	-	0.78	Sur (M)	Strong

Reported Measles Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Imported	Hospit.	Deaths			
	Sweden	**2006-2013**	**162**		**162** (100%)	**73** (45%)	**16**	**0**			
ECDC, 2014,[116] SMI,[273] WHO, 2013[326]		2013	**51**	0.6	51	15	4	-	-	Lab (M)	Strong
ECDC, 2013,[113] SMI,[273] WHO, 2013[326]		2012	**30**	0.6	30	9	6	-	0.32	Lab (M)	Strong
ECDC, 2013,[113] SMI,[273] WHO, 2013[326]		2011	**26**	0.0	26	17	5	-	0.28	Lab (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2011,[198] SMI,[273] WHO, 2013[326]		2010	**7**	1.5	7	7	0	-	0.07	Lab (M)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[197] SMI,[273] WHO, 2013[326]		2009	**3**	0.0	3	3	1	-	0.03	Lab (M)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[196] SMI,[273] WHO, 2013[326]		2008	**25**	0.5	25	11	0	-	0.27	Lab (M)	Strong
ECDC, 2009,[103] EUVAC.NET, 2008,[195] SMI,[273] WHO, 2013[326]		2007	**1**	0.0	1	0	0	-	0.01	Lab (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2007,[194] SMI,[273] WHO, 2013[326]		2006	**19**	0.0	19	11	0	-	0.21	Lab (M)	Strong
	Turkey	**2006-2013**	**8,267**		**8,237** (100%)	**68** (8%)[b]	**82**	**0**			
WHO, 2013[326]		2013	**7,406**	-	7,370	-	-	-	-	Sur (A)	Strong
WHO, 2013[326]		2012	**698**	-	698	45	28	-	0.94	Sur (A)	Strong
WHO, 2013[326]		2011	**105**	-	105	11	35	-	0.14	Sur (A)	Strong
EUVAC.NET, 2011,[198] WHO, 2013[326]		2010	**11**	5.7	15	8	7	-	0.02	Sur (A)	Strong
EUVAC.NET, 2010,[197] WHO, 2013[326]		2009	**6**	2.8	8	3	8	-	0.01	Sur (A)	Strong
EUVAC.NET, 2009,[196] WHO, 2013[326]		2008	**4**	0.7	4	1	2	-	0.00	Sur (A)	Strong

Reported Measles Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	**Confirmed•**	**Imported**	**Hospit.**	**Deaths**			
EUVAC.NET, 2008,[195] WHO, 2013[326]		2007	**3**	0.0	3	0	1	-	0.00	Sur (A)	Strong
EUVAC.NET, 2007,[194] WHO, 2013[326]		2006	**34**	0.0	34	-	1	-	0.05	Sur (A)	Strong
	UK	**2006-2013**	**9,985**		**9,858** (98%)	**300** (3%)	**1,955**	**3**			
ECDC, 2014,[116] WHO, 2013[326]		2013	**1,897**	4.2	1,893	51	348	1	-	Sur (M)	Strong
ECDC, 2013,[113] HPS, 2012,[135] PHE, 2013,[233] WHO, 2013[326]		2012	**1,978**	130.8	2,058	53	589		3.13	Sur (M)	Strong
ECDC, 2013,[113] HPS, 2012,[135] PHE, 2013,[233] WHO, 2013[326]		2011	**1,111**	49.1	1,108	103	213	-	1.77	Sur (M)	Strong
DHSSPS,[16] ECDC,2012,[109] EUVAC.NET, 2011,[198] HPS, 2012,[135] PHE, 2013,[233] WHO, 2013[326]		2010	**434**	74.0	396	20	124	-	0.70	Sur (M)	Strong
DHSSPS,[16] ECDC, 2011,[106] EUVAC.NET, 2010,[197] HPS, 2009,[134] PHE, 2013,[233] WHO, 203[326]		2009	**1,258**	135.5	1,161	12	154	-	2.03	Sur (M)	Strong
DHSSPS,[16] ECDC, 2010,[105] EUVAC.NET, 2009,[196] HPS, 2009,[134] PHE, 2010& 2013,[231,233] WHO, 2013[326]		2008	**1,507**	91.4	1,445	20	199	1	2.45	Sur (M)	Strong
DHSSPS,[16] ECDC, 2009,[103] EUVAC.NET, 2009,[195] PHE, 2010& 2013,[231,233] WHO, 2013[326]		2007	**1,019**	10.05	1,024	19	177	-	1.67	Sur (M)	Strong
DHSSPS,[16] EUVAC.NET, 2007,[194] PHE, 2010& 2013,[231,233] WHO, 2013[326]		2006	**779**	11.0	773	22	151	1	1.29	Sur (M)	Strong

Reported Measles Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Imported	Hospit.	Deaths			
	TOTAL	**2006-2013**	**72,592**		**53,487**	**1,615**	**11,643**	**18**	**-**		
		2013	**13,488**		**16,602**	**223**	**551**	**1**	**-**		
		2012	**5,439**		**4,865**	**207**	**1,098**	**1**	**1.17**		
		2011	**26,133**		**13,575**	**593**	**4,043**	**7**	**5.66**		
		2010	**8,700**		**7,866**	**179**	**2,326**	**2**	**1.89**		
		2009	**4,032**		**3,542**	**91**	**874**	**2**	**0.88**		
		2008	**7,561**		**4,638**	**165**	**938**	**1**	**1.66**		
		2007	**2,485**		**2,468**	**54**	**459**	**1**	**0.55**		
		2006	**4,755**		**3,548**	**103**	**1,354**	**3**	**1.06**		

Note: BMG: Bundesministerium für Gesundheit (Austria, Ministry of Health); *DHSSPS*: Department of Health, Social Services and Public Safety (Northern Ireland); *ECDC*: European Center for Disease Prevention and Control; *EpiCentro*: National Centre for Epidemiology, Surveillance and Health Promotion (Italy); *HCDCP*: Hellenic Center for Disease Control & Prevention (Greece); *HPS*: Health Protection Scotland; *HZJZ*: Hrvatski Zavod za Javno Zdravstvo (Croatia, National Institute of Public Health); *InVS*: Institut de Veille Sanitaire (France); *ISCIII*: Instituo de Salud Carlos III (Spain); *NIZP*: Narodowy Instytut Zdrowia Publicznego (Poland, National Institute of Public Health); *PHE*: Public Health England; *RKI*: Robert Koch Institut (Germany); *SMI*: Smittskyddsinstitutet (Sweden, Institute for Infectious Disease Control); *WHO*: World Health Organization, Centralized Information System for Infectious Diseases.

* Case numbers have been average and the standard deviation (SD) calculated where applicable to indicate variance in national reporting.

• Cases either laboratory confirmed (measles-specific antibodies or PCR) or epidemiologically linked to a laboratory-confirmed case. When variance in reporting occurred, the larger of the numbers was included.

† Reporting method: *Lab*: data provided by laboratories; *Sur*: data obtained through surveillance systems; M = mandatory, V = voluntary, R = regional data, A = aggregated data, C = clinical cases only, L = laboratory testing required, E = errors in reporting known or likely.

[a] Italian's national measles surveillance changed in 2007, but continued to be in use until 2009. Large variances in reporting between the old and new system can be observed.

[b] Based on 2006-2012 data only

Table 3.10. Reported Measles Cases by Nation and Year, 2006-2013. Shown are the annually reported measles cases for each country, including the total number of notified cases, confirmed and imported cases, hospitalizations and deaths. Due to variances in reporting by different sources, the mean total case numbers and standard deviations (SD) have been calculated, as indicated. Annual measles incidences have been determined based on the average total number of reported cases per 100,000 population (source of population data: *The World Bank: DataBank: World Development Indicators, 2013*[285]). The quality of the included sources has been assessed as follows: hard data reports by the WHO, ECDC and governmental agencies were assumed to be accurate and assigned a "strong" quality; estimates and sentinel or regional data reports were assigned a "moderate" quality; voluntary data reports were assigned a "weak" quality.

3.3.5. Cases among Travelers and Migrants

Of the included case studies and reports, 20 describe measles outbreaks associated with an international viral transmission. Affected individuals were either tourists who were infected abroad or persons with a recent migratory background. Cases have been reported particularly among traveling ethnic minorities, such as Roma/ Sinti (14 reports) and Irish travellers (3 reports). Through migratory activities, measles has spread predominantly between the various European nations, leading to ongoing importations and re-importations of measles viruses.

Genotypic and phylogenetic analyses of measles strains can provide important information regarding the origin of an outbreak and sources of importation. A total of 33 studies report the identification of various of these genotypes, which are summarized in Table 3.11.

For the years 2006 through 2010, Muscat and Bang[194–198](EUVAC.NET) reported the number of imported measles cases in Europe to have reached nearly 750. This number is likely higher, however, as the importation status was not known for 20-46% of the annually notified cases.[194–198] More recent data are provided by the WHO;[326] the percentages with and without a known importation status are not reported, however. As shown in Table 3.10, the countries that have reported the most imported cases between 2006 and 2013 were France (423 cases), Germany (409 cases), the United Kingdom (300 cases), and Spain (139 cases).[194–198, 200, 326]

Each year, more than half of all international transmissions originated from other European countries. Between 2006 and 2010, the most common source nations included Switzerland (82 cases), the UK (65 cases), France (61 cases), Italy (59 cases), Spain (39 cases) and Germany (32 cases).[194–198, 200] The remaining cases were reported to have been imported predominantly from India (48 cases), Thailand (34 cases), Ukraine (17 cases), South Africa (12 cases), and Ethiopia (11 cases).[194–198, 200]

Reports concerning more recent measles outbreaks with identified genotypes indicate similar results. As shown in Table 3.11, common source nations of imported cases for 2010 and 2011 were European countries, including Italy, France, Greece, Bulgaria, Romania, and the UK, as well as some African and Asian countries.

Measles Genotypes in Europe, 2006-2011

Genotype	Source(s)	Year(s)	Location Discovered Country (Region)		Location(s) Linked to	Outbreak Size	Cases Sequenced	Clusters	Sporadic Cases	Study Quality
A										
	Magurano et al., 2012[171]	2002-2004	Italy		← (Vaccine strains?)	-	3	1	1	Moderate
	Waku-Kouomou et al., 2010[296]	2008	France	(Nice, Haut-Rhin)	← (Vaccine strains?)	604	2	0	2	Strong
	Magurano et al., 2013[170]	2008	Italy	(Piedmont, Emilia Romagna, Lombardy)	← (Vaccine strains?)	4,177	4	1	-	Moderate
	Filia et al., 2013[118]	2010-2011	Italy		-	5,568	1	0	1	Strong
B3										
	Peña-Rey et al., 2009,[216] Santibanez and Mankertz, 2013,[261] Siedler et al., 2011[267]	2006	Germany	(NRW, Baden-Württemberg)	← Africa (Nigeria?, Kenya?)	64	-	2	-	Moderate Moderate Moderate
	Peña-Rey et al., 2009[216]	2006	Italy		-	18	-	-	-	Moderate
	Peña-Rey et al., 2009[216]	2006	Spain	(Madrid, Canary Island)	← UK	188	-	2	-	Moderate
	Peña-Rey et al., 2009[216]	2006	Spain	(Valencia)	← Spain (Madrid)	3	-	1	-	Moderate
	Peña-Rey et al., 2009[216]	2006	Sweden		-	9	-	-	-	Moderate
	Peña-Rey et al., 2009[216]	2006	Sweden		← Thailand	5	-	-	-	Moderate
	Peña-Rey et al., 2009[216]	2006	UK		← Ireland	55	-	-	-	Moderate
	Curtale et al., 2010[83]	2006-2007	Italy	(Lazio)	← UK?, Sub-Saharan Africa? → Italy (Puglia)	449	25	1	0	Strong
	Magurano et al., 2012[171]	2006-2007	Italy		← Albania, UK → Italy	-	51	1	1	Moderate

Measles Genotypes in Europe, 2006-2011

Genotype	Source(s)	Year(s)	Location Discovered Country	(Region)	Location(s) Linked to	Outbreak Size	Cases Sequenced	Clusters	Sporadic Cases	Study Quality
	Waku-Kouomou et al., 2010[296]	2008	France	(Nice, Haut-Rhin)	← Germany? West Africa	604	1	0	1	Strong
	Parent du Châtelet et al., 2010[75]	2008-2010	France		-	4,753	-	-	-	Strong
	Filia et al., 2011[119]	2009-2010	Italy	(Piedmont, Liguria)	← Africa	2,252	4	1	1	Strong
	López Hernández et al., 2010[167]	2010	Spain	(Granada)	-	59	2	1	-	Moderate
	Kalaycioglu et al., 2013[152]	2010-2011	Turkey		← South Africa	-	1	0	1	Moderate
	Filia et al., 2013[118]	2010-2011	Italy		-	5,568	23	-	-	Strong
C2										
	Magurano et al., 2012[171]	2004	Italy		← Morocco? Germany? Luxembourg? Czech Republic? Denmark?	-	3	1	0	Moderate
D4										
	Peña-Rey et al., 2009[216]	2006	Italy	(Bologna, Lazio)	-	178	-	2	-	Moderate
	Peña-Rey et al., 2009[216]	2006	Italy	(Sardinia)	← Italy	9	-	-	-	Moderate
	Peña-Rey et al., 2009[216]	2006	Italy	(Tuscany)	← India	40	-	-	-	Moderate
	Peña-Rey et al., 2009[216]	2006	Spain	(Catalonia)	← Romania	3	-	1	-	Moderate
	Peña-Rey et al., 2009[216]	2006	UK		-	19	-	-	-	Moderate
	Curtale et al., 2010[83]	2006-2007	Italy	(Lazio)	← Italy (South Tirol) ← Romania → Italy (Sardinia), Spain (Barcelona)	449	32	1	0	Strong
	Peña-Rey et al., 2009[216]	2006-2007	Spain	(Catalonia)	← Italy	381	-	1	-	Moderate

Measles Genotypes in Europe, 2006-2011

Genotype	Source(s)	Year(s)	Location Discovered Country	(Region)	Location(s) Linked to	Outbreak Size	Cases Sequenced	Clusters	Sporadic Cases	Study Quality
	Magurano et al., 2012&2013[170,171]	2006-2008	Italy		← Italy, Europe, Asia → USA	-	285	2	-	Moderate Moderate
	Peña-Rey et al., 2009[216]	2007	Spain	(Castile&Leon)	-	16	-	-	-	Moderate
	Peña-Rey et al., 2009,[216] Siedler et al., 2011[267]	2007	Germany	(Bavaria)	← UK	95	-	-	-	Moderate Moderate
	Cohuet et al., 2009[79]	2007	UK	(England)	→ UK (England, Wales), Norway	173	74	1	0	Strong
	Peña-Rey et al., 2009[216]	2007	UK		← Ireland	158	-	2	-	Moderate
	Kaic et al., 2009[149]	2008	Croatia	(Zagreb)	-	49	6	6	0	Strong
	Waku-Kouomou et al., 2010[296]	2008	France	(Nice, Haut-Rhin)	← France (Lyon), Europe (Austria?, Switzerland?, Greece?)	604	21	2	1	Strong
	D'Agaro et al., 2011[96]	2008	Italy	(Friuli Venezia Giulia)	← Italy (Piedmont?), UK, Germany?	46	10	2	0	Strong
	Bassetti et al., 2011[51]	2008-2009	Italy	(Bologna)	← Italy (Liguria) ← France, Spain, Netherlands	83	83	1	0	Moderate
	Rogalska et al., 2010[251]	2008-2009	Poland		← United Kingdom, Poland	163	21	19	-	Strong
	Ghebrehewet et al., 2013[125]	2008-2009	UK	(Cheshire)	← UK	104	3	1	-	Strong
	Parent du Châtelet et al., 2010[75]	2008-2010	France		← UK	4,753	681	-	-	Strong
	Antona et al., 2013[44]	2008-2011	France		-	22,178	1,387	-	-	Moderate
	Filia et al., 2011[119]	2009-2010	Italy		← Italy, Europe	2,252	87	11	-	Strong
	Pfaff et al., 2010,[221] Santibanez and Mankertz, 2013[261]	2010	Germany		← France (Taizé)	13	6	1	1	Strong Moderate
	Roggendorf et al., 2012[255]	2010	Germany	(Essen)	-	15	-	1	-	N/A

Measles Genotypes in Europe, 2006-2011

Genotype	Source(s)	Year(s)	Location Discovered Country (Region)		Location(s) Linked to	Outbreak Size	Cases Sequenced	Clusters	Sporadic Cases	Study Quality
	Filia et al., 2013[118]	2010-2011	Italy		-	5,568	161	-	-	Strong
	Kalaycioglu et al., 2013[152]	2010-2011	Turkey		← Greece, France	-	5	1	3	Moderate
	Cilla et al., 2011[77]	2011	Spain	(Basque Country)	← Europe (France, Spain)	23	17	3	2	Strong
	Mayoral Cortés et al., 2012[178]	2011	Spain	(Andalusia)	← Spain (Madrid)?	1,759	-	-	-	Strong
D4-Hamburg										
	Hegasy et al., 2012,[137] Mankertz, Mihneva et al., 2011,[173] Siedler et al., 2011[267]	2008-2009	Germany	(Hamburg)	→ Europe (Poland, Austria, Greece, Turkey, Romania, Bulgaria, Ireland, etc.)	216	12	1	-	Strong Strong Moderate
	Mankertz, Mihneva et al., 2011,[173] Orlikova et al., 2010[207]	2009	Poland		← Bulgaria, Germany? → Ireland, UK (Northern Ireland)	54	4	3	0	Strong Moderate
	Mankertz, Mihneva et al., 2011[173]	2009	Germany	(Lower Saxony)	← Germany (Hamburg) → UK (London)	72	18	1	-	Strong
	Siedler et al., 2011[267]	2009	Germany	(NRW, Baden-Württemberg)	-	143	-	-	-	Moderate
	Mankertz, Mihneva et al., 2011[173]	2010	Austria	(Graz, Vienna)	← Bulgaria	-	4	1	1	Strong
	Mankertz, Mihneva et al., 2011[173]	2010	Germany	(Mannheim, Munich, etc.)	← Bulgaria	84	47	7	1	Strong
	Mankertz, Mihneva et al., 2011[173]	2010	Turkey		← Bulgaria, Romania	1	1	0	1	Strong

Measles Genotypes in Europe, 2006-2011

Genotype	Source(s)	Year(s)	Location Discovered Country (Region)	Location(s) Linked to	Outbreak Size	Cases Sequenced	Clusters	Sporadic Cases	Study Quality
	Mankertz, Mihneva et al., 2011,[173] Melidou et al., 2012,[179] Pervanidou et al., 2010[218]	2010	Greece	← Bulgaria	126	19	13	-	Strong Strong Strong
	Mankertz, Mihneva et al., 2011[173]	2009-2011	Others* -	← Germany → Germany, Greece, Poland, Turkey, etc.	≥24,800	-	-	-	Strong
D5									
	Waku-Kouomou et al., 2010[296]	2007	France	← Thailand → UK (London)	3	-	1	0	Strong
	Magurano et al., 2012[171]	2007	Italy	← Japan	-	4	1	-	Moderate
	Peña-Rey et al., 2009,[216] Siedler et al., 2011[267]	2007-2008	Germany (Bavaria, Baden-Württemberg)	← Switzerland	795	-	3	-	Moderate Moderate
	Waku-Kouomou et al., 2010[296]	2008	France	← Switzerland, UK	604	72	3	-	Strong
	Schmid et al., 2010,[262] Wadl et al., 2011[295]	2008	Germany (Bavaria)	← Austria (Salzburg) ← Switzerland	217	26	59	-	Strong Weak
	Parent du Châtelet et al., 2010[75]	2008-2010	France	-	4,753	57	-	-	Strong
	Antona et al., 2013[44]	2008-2011	France	← UK?, Canada?	22,178	-	-	-	Moderate
D6									
	Peña-Rey et al., 2009,[216] Santibanez and Mankertz, 2013,[261] Siedler et al., 2011[267]	2006	Germany (NRW)	← Ukraine, Russia	1,452	-	-	-	Moderate Moderate Moderate
	Peña-Rey et al., 2009[216]	2006	Greece	-	171	-	-	-	Moderate

Measles Genotypes in Europe, 2006-2011

Genotype	Source(s)	Year(s)	Location Discovered Country (Region)		Location(s) Linked to	Outbreak Size	Cases Sequenced	Clusters	Sporadic Cases	Study Quality
	Peña-Rey et al., 2009[216]	2006	Poland		← Ukraine?	120	-	-	-	Moderate
	Peña-Rey et al., 2009[216]	2006	Spain	(Canary Island)	← Germany	3	-	1	-	Moderate
	Peña-Rey et al., 2009[216]	2006	Spain	(La Rioja)	← Ukraine?	18	-	-	-	Moderate
D8										
	Santibanez and Mankertz, 2013,[261] Siedler et al., 2011[267]	2007	Germany	(NRW)	← Southeast Asia → USA	251	-	-	-	Moderate Moderate
	Magurano et al., 2012[171]	2007	Italy	Rome	← Russia?, India?	-	1	0	1	Moderate
	Waku-Kouomou et al., 2010[296]	2008	France	(Moulins)	← Netherlands, UK?	604	11	1	0	Strong
	Magurano et al., 2013[170]	2008	Italy	(Emilia Romagna)	← Canada?, India?	4,177	1	0	1	Moderate
	Parent du Châtelet et al., 2010[75]	2008-2010	France		-	4,753	-	-	-	Strong
	Filia et al., 2011,[119] Orsi et al. 2010[208]	2009-2010	Italy		← Italy ← Europe, India	2,252	21	11	-	Strong Strong
	Bätzing-Feigenbaum et al., 2010,[52] Santibanez and Mankertz, 2013,[261] Siedler et al., 2011[267]	2010	Germany	(Berlin)	← India	62	13	1	-	Moderate Moderate Moderate
	Roggendorf et al., 2010[254]	2010	Germany	(Essen)	← Germany (Berlin)?	71	2	1	0	Strong
	Filia et al., 2013[118]	2010-2011	Italy		-	5,568	69	-	-	Strong
D9										
	Waku-Kouomou et al., 2010[296]	2008	France	(Nice, Paris)	← Thailand	604	6	1	1	Strong

Measles Genotypes in Europe, 2006-2011

Genotype	Source(s)	Year(s)	Location Discovered Country (Region)		Location(s) Linked to	Outbreak Size	Cases Sequenced	Clusters	Sporadic Cases	Study Quality
	Magurano et al., 2013[170]	2008	Italy	(Marche)	← Thailand?	4,177	1	0	1	Moderate
	Filia et al., 2013[118]	2010-2011	Italy		-	5,568	2	1	0	Strong
	Kalaycioglu et al., 2013[152]	2011	Turkey		← Malaysia, Russia, Japan, UK	-	20	3	1	Moderate
G3										
	Brown et al., 2011[59]	2010	Multiple†		← Indonesia, Malaysia, Morocco, England	-	25	2	18	Strong
	Antona et al., 2013[44]	2011	France		← Europe?, Southeast Asia?	22,178	40	-	-	Moderate
	Cilla et al., 2011[77]	2011	Spain	(Basque Country)	-	23	3	1	0	Strong
H1										
	Magurano et al., 2013[170]	2008	Italy	(Veneto)	← China?, Russia?	4,177	1	0	1	Moderate
	Kasper et al., 2009[156]	2009	Austria	(Styria)	-	37	2	2	0	Moderate
	Filia et al., 2013[118]	2010-2011	Italy		-	5,568	1	-	1	Strong
H2										
	Parent du Châtelet et al., 2010[75]	2008-2010	France		-	4,753	-	-	-	Strong

Note: NRW: North-Rhine Westphalia, Germany, *UK*: United Kingdom

* The D4-Hamburg strain was also observed in Bulgaria (>24,000 cases reported), Ireland, Northern Ireland, Romania (2 sporadic cases), Serbia (14 cases, 1 sporadic), Macedonia (about 400 cases), Switzerland (1 sporadic case) and Belgium (>40 cases).

† The following European countries are included: Germany, England, France, the Netherlands, Spain, and Switzerland.

Table 3.11. Measles Genotypes in Europe, 2006-2011. Shown are the measles-specific genotypes that have been detected in the selected European countries during the indicated time period. The predominant circling strains belonged to the B3 and D4 genotypes. Measles viral types D5, D6, D8, D9 and G3 occurred less frequently and A, C2, H1 and H2 only sporadically or as part of smaller, confined outbreaks. The country and region of the outbreak as well as likely origin of importation (←) and location of exportation (→), are shown upon availability.

The most prevalent measles genotypes reported in Europe within the last decade were B3 and D4, including the D4-Hamburg subtype originating from Germany. Less frequently occurring genotypes were D5, D6, D8, D9 and G3. Other reported genotypes—A, C2, D7, H1 and H2—appeared only sporadically or were the source of small, confined outbreaks. The following paragraphs provide an overview of the study and report outcomes for these measles genotypes.

A Strains of the A genotype were observed among few cases in Italy and France. Although the exact origin could not be determined, they are likely vaccine-related because their molecular structure closely matches the Schwarz and Edmonston vaccine strains.[170,171,296]

B3 This genotype is endemic in Africa,[257] but has been reported in several European nations in the past years.[119,152,296] Most cases occurred sporadically, but larger outbreaks and transmission within Europe have been reported as well.[83,171,216] As shown in Fig. 3.8, viral outbreaks of this genotype have occurred in Germany, Italy, Spain, Sweden, Turkey and the UK. Curtale et al.[83] and Magurano et al.[171] describe in separate reports that measles cases were imported from the UK, possibly also from Albania or Africa, to central Italy in 2006 and 2007. From there, the disease spread to other parts of the country. Between 2008 and 2011, most reported cases were likely imported directly from Africa.[119,152,296]

D4 The D4 genotype has been circulating in Europe for several years and has been the source of most reported outbreaks (see Table 3.11). Italy, Spain, Germany, the United Kingdom, Croatia, France, Poland and Turkey have all detected measles cases attributed to this genotype. In 2006 and 2007, a large outbreak in the Lazio Region of Italy involving around 450 people was described by Curtale et al.[83] Based on the genotypic analyses of this outbreak, the D4 measles virus could be traced to South Tirol, from where it had been transmitted via a small Roma/Sinti population. This outbreak in Northern Italy, in turn, could be traced back to Romania, where

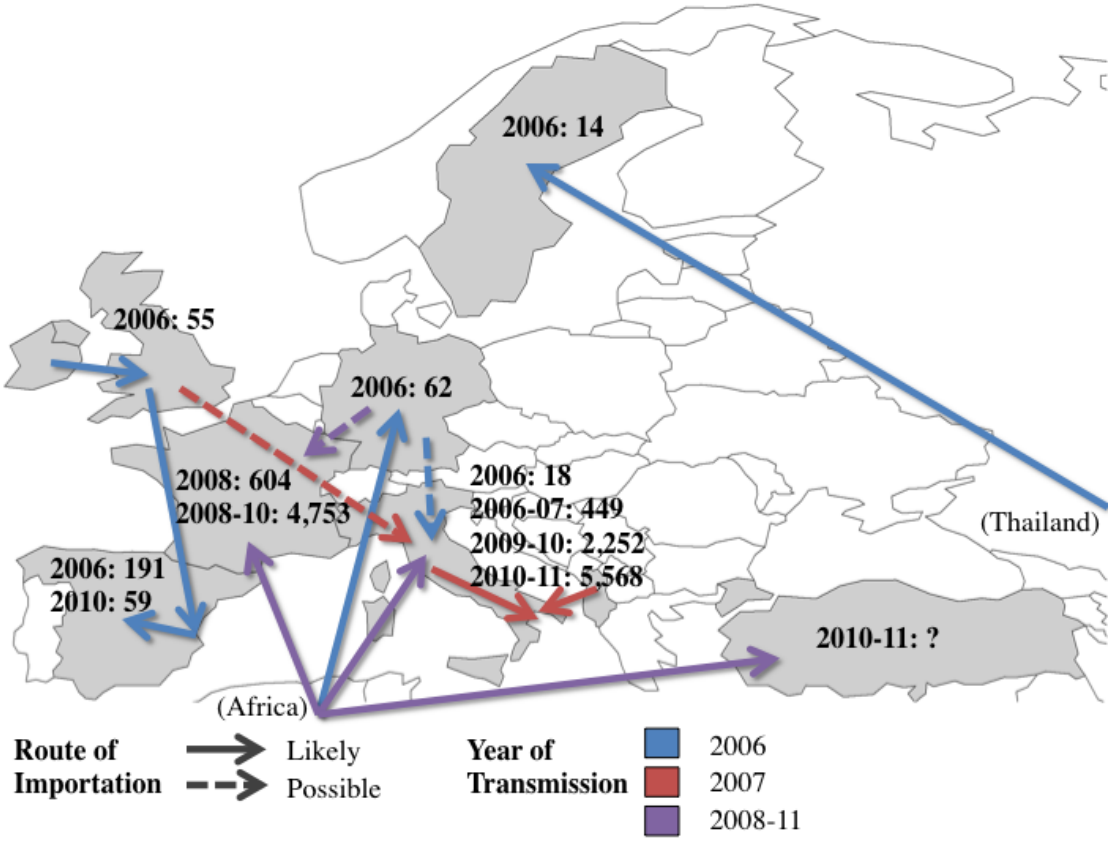

Figure 3.8. Routes of Measles Genotype B3 Transmission, 2006-2011. Measles genotype B3, typically endemic on the African continent, has been the source of several outbreaks in Europe between 2006 and 2011. For each country and year experiencing an outbreak, the number of cases reported has been indicated. Predominantly affected were France and Italy. Likely and possible routes of transmission have been marked as shown. ***Sources***: *Curtale et al., 2010*,[83] *Filia et al., 2011&2013*,[118,119] *Kalaycioglu et al., 2013*,[152] *López Hernández et al., 2010*,[167] *Magurano et al., 2012*,[171] *Parent du Châtelet et al., 2010*,[75] *Peña-Rey et al., 2009*,[216] *Santibanez and Mankertz, 2013*,[261] *Siedler et al., 2011*,[267] *Waku-Kouomou et al., 2010*.[296] Geographic data obtained from www.naturalearthdata.com.

a large outbreak involving over 4,000 people had been taking place since 2004. The virus was described to have been imported by migrant families originating from Romania.[83] From the Lazio region, the virus was later transported to Sardinia, Italy and Barcelona, Spain, also by Roma populations.[83] In Italy, the D4 genotype continued to appear over the course of the following years and was transmitted both endemically and internationally from various European countries. A spread from Italy to the United States of America (USA) was also documented.[171] The maps in Figs. 3.9 and 3.10 show a summary of the transmission patterns between 2006 and 2011.

The D4 genotype was frequently reported in the United Kingdom between 2007 and 2010, being transmitted both locally and internationally. Cohuet et al.[79] describe

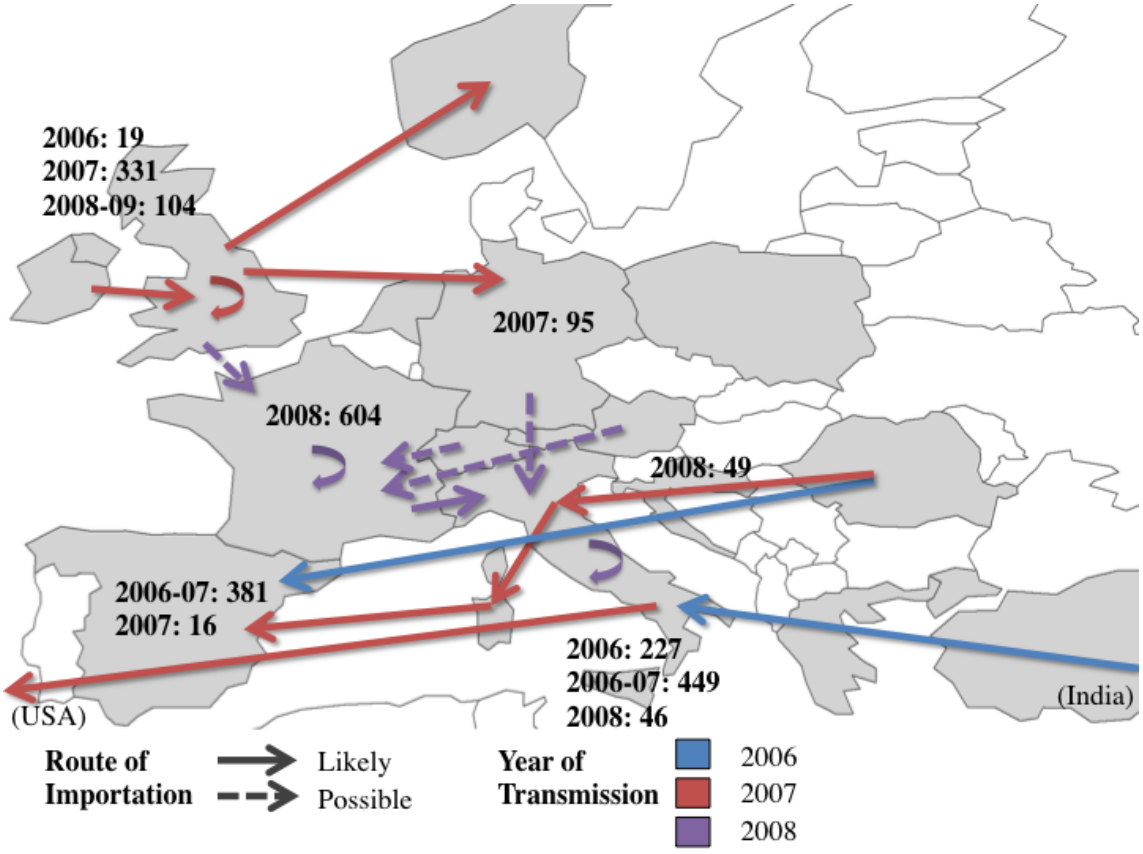

Figure 3.9. Routes of Measles Genotype D4 Transmission, 2006-2008. Viral measles strains belonging to the D4 genotype were commonly found in Europe in the past years. For each country and year experiencing an outbreak, the number of cases reported has been indicated. Predominantly affected were France, Italy, Spain and United Kingdom. Likely and possible routes of transmission have been marked as shown. ***Sources***: *Cohuet et al., 2009*,[79] *Curtale et al., 2010*,[83] *D'Agaro et al., 2011*,[96] *Kaic et al., 2009*,[149] *Magurano et al., 2012&2013*,[170,171] *Peña-Rey et al., 2009*,[216] *Siedler et al., 2011*,[267] *Waku-Kouomou et al., 2010*.[296] Geographic data obtained from www.naturalearthdata.com.

a 2007 outbreak among a community of Irish travellers in the UK. A total of 173 cases were reported throughout the country, 90% of them among members of the Irish traveller community and 10% among persons who had come in contact with an infected individual from this community.[79] An identical D4 genotype was determined for all of the 74 (43%) sequenced cases, confirming the link between them.[79] Although the origin of the infection could not be determined, a spread to other parts of England and Wales as well as Norway was observed. Between 2007 and 2010, outbreaks in Germany, Poland and France could all be traced back to the D4 measles strains circulating in the UK.

In a 2010 report by Pfaff et al.,[221] 13 measles cases among young Germans (aged 9 to 32 years) who had traveled to France to attend a religious mass gathering are

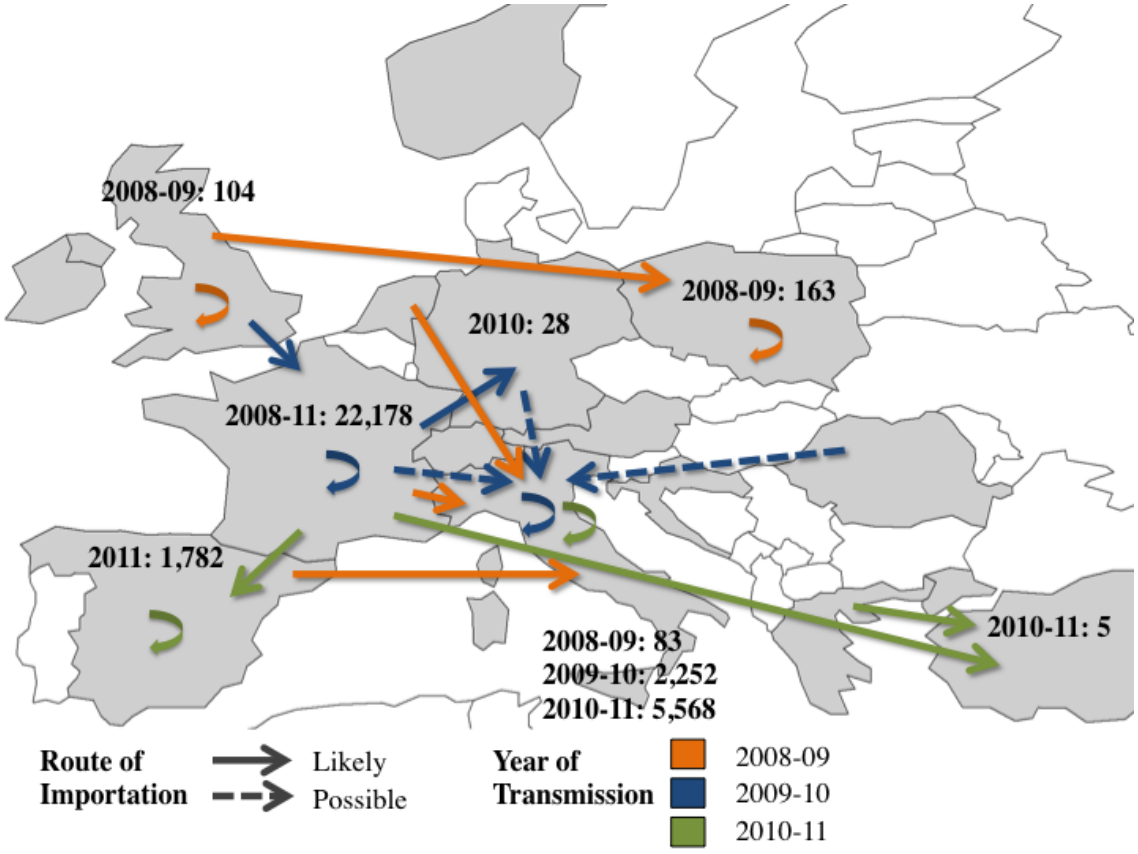

Figure 3.10. Routes of Measles Genotype D4 Transmission, 2009-2011. Between 2009 and 2011, a tremendous increase in measles cases caused by the D4 genotype was reported. For each country and year experiencing an outbreak, the number of notified cases has been indicated. Particularly affected was France, with more than 22,000 cases. Italy and Spain also reported large outbreak numbers. Likely and possible routes of transmission have been marked as shown. ***Sources***: *Antona et al., 2013*,[44] *Bassetti et al., 2011*,[51] *Cilla et al., 2011*,[77] *Filia et al., 2011&2013*,[118,119] *Ghebrehewet et al., 2013*,[125] *Kalaycioglu et al., 2013*,[152] *Mayoral Cortés et al., 2012*,[178] *Parent du Châtelet et al., 2010*,[75] *Pfaff et al., 2010*,[221] *Rogalska et al., 2010*,[251] *Roggendorf et al., 2012*,[255] *Santibanez and Mankertz, 2013*.[261] Geographic data obtained from www.naturalearthdata.com.

described. All cases were linked to each other, as was ascertained in interviews with the patients as well as through the genotypic analyses of clinical samples from the primary and five secondary cases, all of which shared the same D4-Manchester genotypic variant originating from the UK.[221]

In December of 2008, a new D4 viral strain was discovered in Hamburg, Germany.[137] In the consecutive outbreak, a local Roma community was particularly affected.[137] From Hamburg, this strain was spread to other parts of Germany and several European countries, predominantly through Roma communities, but also through other travelers.[173,267] A tremendously large outbreak involving more than 24,000 cases occurred in Bulgaria between 2009 and 2011.[173] From there, the virus was transmitted to Poland, Austria, Greece, Turkey and many other countries.[173,179,207,218]

Various re-importations to Germany were also observed.[173,267] The map in Fig. 3.11 shows the likely routes of transmission (also see Table 3.11 for details). By 2011, over 25,000 people had been affected by the D4-Hamburg viral strain.[137,173]

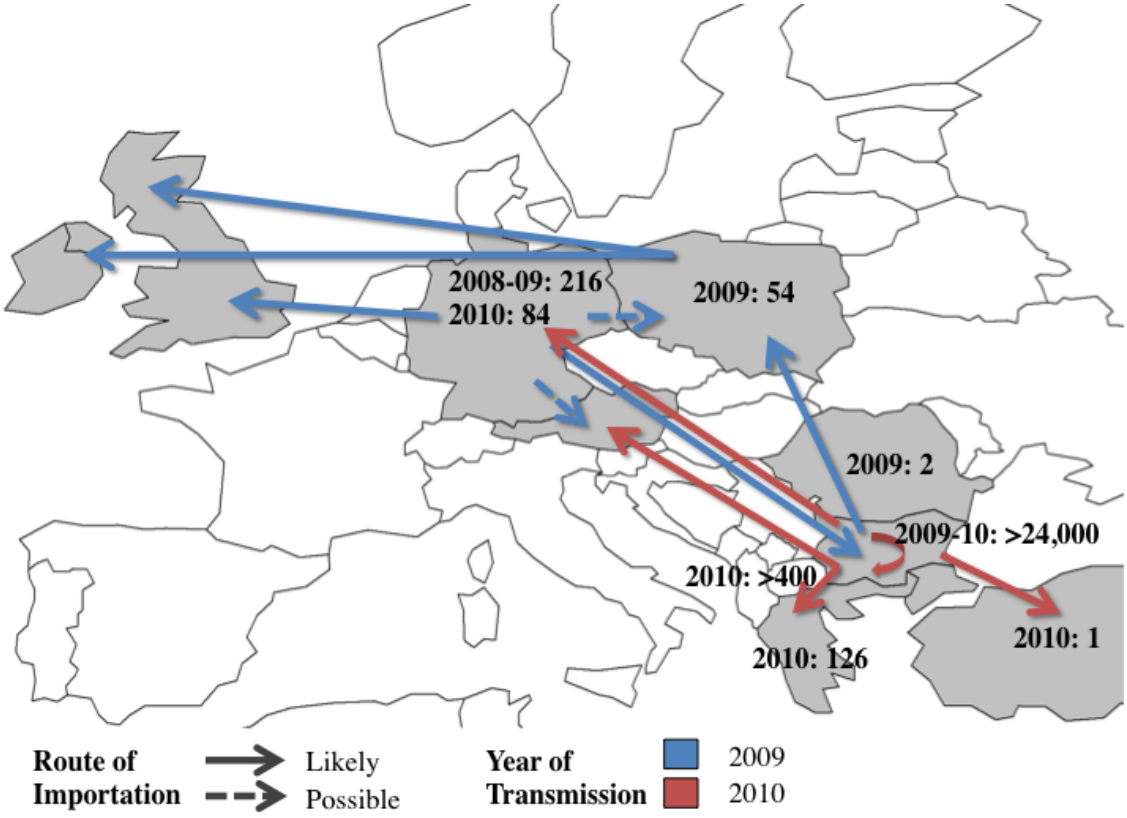

Figure 3.11. Routes of Measles Genotype D4-Hamburg Transmission, 2008-2010. A new measles strain called D4-Hamburg was discovered in Germany at the end of 2008 and spread throughout Europe over the course of the next couple of years. Predominantly affected was Bulgaria with over 24,000 cases. From there, the strain was spread to Poland, Austria, Greece, Turkey, Macedonia, Serbia, and several other nations, including a re-transmission to Germany. The likely and possible routes of transmission have been marked as shown. ***Sources***: *Hegasy et al., 2012*,[137] *Mankertz, Mihneva et al., 2011*,[173] *Melidou et al., 2012*,[179] *Orlikova et al., 2010*,[207] *Pervanidou et al., 2010*,[218] *Siedler et al., 2011*.[267] Geographic data obtained from www.naturalearthdata.com.

D5 Genotype D5 was described among outbreaks in France, Italy, Austria and Germany. Some cases were imported from Thailand and Japan and then transmitted to the UK and Switzerland, where it circled epidemically between 2007 and 2009.[171,257,296] From there, cases were re-imported to the listed central European countries.[216,296] Between 2008 and mid-2009, the D5 genotype likely contributed significantly to the large outbreaks reported in France as well.[44,75] Furthermore, a sizable measles outbreak was described in an anthroposopic school in Salzburg, Austria that was likely initiated by a visiting student from Switzerland and affected

Austrian as well as German children who were attending the school.[262,295] These students imported the disease to Bavaria, Germany, resulting in an outbreak involving 217 people in 59 different school, kindergarten and familial clusters.[295] The disease transmission could be stopped by excluding non-immune children from educational facilities for at least two weeks.[295] After 2009, the D5 genotype was largely replaced by the D4 genotype in central Europe.

D6 In 2006, measles strain D6 was detected in Germany, Poland, Greece and Spain. The virus had likely been imported from the Ukraine or Russia, where it circled endemically until 2007.[257,261] An importation from Germany to Spain was also observed.[216] The transmission of this genotype seems to have been interrupted, as no recent cases have been reported.[257]

D7 This genotype was last detected in Italy in 2002 and 2003, where it may have been responsible for several large outbreaks involving over 20,000 people.[171] It had likely been imported from other European nations and was circling endemically in Italy until it was replaced by the D4 and B3 strains.[171] With the exception of a few sporadic cases in India reported up to 2006, the D7 genotype has not been detected since.[257]

D8 Between 2007 and 2009, genotype D8 was endemic in Southeast Asian countries, including India and Nepal, as well as in Eastern Mediterranean nations, including Morocco and Oman.[257] Imported cases were detected in France, Germany and Italy; several of them could be traced back to India.[52,119,208] In 2010, an outbreak involving 62 people occurred in Berlin, Germany.[52] Genotyped samples from 13 of the cases all carried the same strain, which had been previously detected in India.[52,261,267] As the index case had recently traveled to India, the outbreak could be clearly linked. During the same time, another measles outbreak involving 71 people occurred in Essen, Germany. This outbreak, which predominantly affected students at an anthroposophic school, also involved the D8 strain and was likely imported

from Berlin. In Italy, the D8 genotype also continues to be a frequent source of recent measles infections.[118,119] Between 2008 and 2011, it was detected in at least eleven different regions of the country, likely circling endemically.[118,119,170,208]

D9 Measles D9 strains are endemic in Southeast Asian and Western Pacific regions.[257] The genotype was not detected among the included European nations until 2008, at which time a few cases were reported in France and Italy. The source of infection had likely been Thailand.[118,170,296] In 2011, a first occurrence of the D9 genotype in Turkey was reported by Kalaycioglu et al.[152] Of 26 sequenced samples, 20 belonged to this genotype, which occurred in three small clusters and one sporadic case, suggesting multiple importations. Possible source nations include the United Kingdom, Russia, Malaysia and Japan.[152]

G3 The G3 measles strains are also found predominantly in Southeast Asian and Western Pacific regions.[257] Much like the D9 strains, they had not been detected in Europe until recently. In 2010 and 2011, imported outbreaks involving this genotype were reported in Austria, Germany, England, France, the Netherlands, Spain and Switzerland.[44,60,77,156] Several of these cases could be linked directly to Indonesia, Malaysia and Morocco. Transmission withing Europe from the UK to other nations was also observed.[59]

H1 and H2 Both of the H genotypes occurred in sporadic cases in Italy (H1) and France (H2). In 2009, an outbreak involving 37 people in Styria, Austria, most of them part of an anthroposopic community, was also caused by the H1 genotype. Both genotypes are endemic in Asia and have in recent years been reported predominantly in China and Vietnam.[239,257] Although the origins of the measles infections among the European cases were not identified, they were likely directly imported from the Asian continent.[170]

The genotypic and phenotypic analyses of measles viruses have shown that travel and migration are frequently the cause of outbreaks all across Europe. Although many viral strain importations from non-European countries have been described, the predominant spread occurs within the European continent. Frequent travel among unvaccinated individuals or groups, such as Roma/Sinti and Irish Traveller populations, increases the risk of measles transmission. Pockets of non-immune populations, in anthroposphic communities or schools, for instance, further contribute to the persistence of outbreaks. These and other populations at risk for measles infections due to low vaccination coverage will be addressed in Section 3.3.7 below.

3.3.6. Vaccination Coverages

Each of the included European nations recommends or mandates the vaccination with two MCV dosages, as illustrated in Table 3.8 on Page 65. The national vaccination coverage varies between the nations and inter-European regions, however. According to WHO and UNICEF reports,[312,324] the 2012 vaccination coverage for the MCV-1 dosage ranged from an estimated 76% in Austria to 99% in Greece. Immunization rates for the secondary dosage were lower, ranging from 67% in France to 95% in Sweden and Poland.[312] Recent 2012 data were not available for all nations, however, and official estimates are only published for the primary dosage MCV coverages.[312,324] In Tables 3.12 and 3.13, the available nationally reported coverage data and estimates are shown for the years 2006 through 2012. A general upward trend in immunization rates can be observed for most of the countries, most notably Germany (MCV-1: 3% increase, MCV-2: 15% increase) and the United Kingdom (MCV-1: 8% increase, MCV-2: 12% increase). Exceptions are Poland, Spain and Turkey, for which 4%, 5% and 8% decreases in MCV-2 coverage were reported, respectively.

Country	National Vaccination Coverage Reports and Estimates (%)						
	2012	2011	2010	2009	2008	2007	2006
Austria	76*	76*	76*	76	83	79	80
France	89	89	90	90	87	87	90*
Germany	97	96	96	96	95	94	94
Greece	99	99	99*	99	99	99	98
Italy	90	90	91	90	90	90	88
Spain	97	97	95	98	98	97	97
Sweden	97	96	97	97	96	96	97
UK	93	90	93	86	86	86	85
Croatia	95*	96	96	95	98	96	95
Poland	98	98*	98	98	98*	98	99
Turkey	98*	98	97	97	97	96	98

Table 3.12. Primary Dosage Measles Vaccination Rates, by Year and Country. Shown are the national one-dosage measles immunization rates reported by the WHO and UNICEF, as based by each country's data, indicated through the WHO/UNICEF Joint Reporting Form. When coverage rates were not submited, official WHO/UNICEF estimates were included instead (marked with an *). Data are as of October and July 2013, respectively. ***Sources***: *WHO vaccine-preventable diseases: monitoring system, 2013 global summary: coverage series*,[312] *WHO/UNICEF estimates for 1980-2012*.[324]

When analyzing the vaccination coverages by European subregions, differences between them emerge. Figures 3.12 and 3.13 illustrate the inter-regional trends for the averaged primary and secondary MCV immunization rates since 2000. Although positive trends can be observed for all four subregions, only the Eastern and Southern regions have average MCV-1 coverage rates continually surpassing the WHO-recommended threshold of 95%. The Western European region lags substantially behind, mostly due to the low immunization rates estimated for Austria.[324] Germany is the only country among the three included Western European representatives with an MCV-1 immunization rate surpassing 95% (reached in 2008, see Table 3.12 for details). Regional averages for MCV-2 coverage are considerably lower, however, and the WHO-recommended threshold has been reached only by the Eastern European subregion. The high coverage rates in this region have not been sustained entirely, though, and dropped particularly in Turkey, from 94% in 2007 to 86% in 2011, as noted in Table 3.13. Among the selected countries in the other subregions, Sweden is the only nation that reports a 95% national MCV-2 vaccination rate. The United Kingdom and most of the Southern and Western European nations have not yet reached the 95%-coverage goal.

Country	National Vaccination Coverage Reports (%)						
	2012	2011	2010	2009	2008	2007	2006
Austria	-	-	-	64	62	56	61
France	67	67	-	-	-	-	-
Germany	92	92	90	91	89	83	77
Greece	83	77	-	77	77	77	-
Spain	90	91	92	90	94	95	94
Sweden	95	95	94	95	94	-	95
UK	87	88	87	79	75	74	75
Croatia	-	98	98	-	98	98	98
Poland	95	-	94	95	-	98	99
Turkey	-	86	91	88	92	94	84

Table 3.13. Secondary Dosage Measles Vaccination Rates, by Year and Country. Shown are the national immunization rates with at least two dosages of a measles-containing vaccine, as based on each country's national report using the WHO/UNICEF Joint Reporting Form. No immunization rates were available for Italy. Data are as of October, 2013. ***Source***: *WHO vaccine-preventable diseases: monitoring system, 2013 global summary: coverage series*.[312]

3.3.7. Sociodemographic Factors influencing Measles Susceptibility

As described above, certain populations are particularly at risk for measles infection and transmission, including travelers, immigrants and migrating ethnic populations. According to WHO recommendations for the elimination of measles, all European countries are requested to provide additional immunization opportunities to these and other susceptible populations.[310] The literature review resulted in 49 studies and reports addressing immunization coverage and seroprevalence of measles-specific antibodies. In the following subsections, susceptible populations residing in each nation are described according to the sociodemographic factors age, gender, educational status, socioeconomic status, place of residence and migratory background.

Age Various age groups have different susceptibilities to measles. As such, age is the most commonly reported demographic factor in immunization coverage and seroepidemiology studies. A total of 26 reports on national measles coverage among different age groups have been included and are summarized in Table 3.14. As shown, the annual immunization rates with a primary (D1) and secondary (D2)

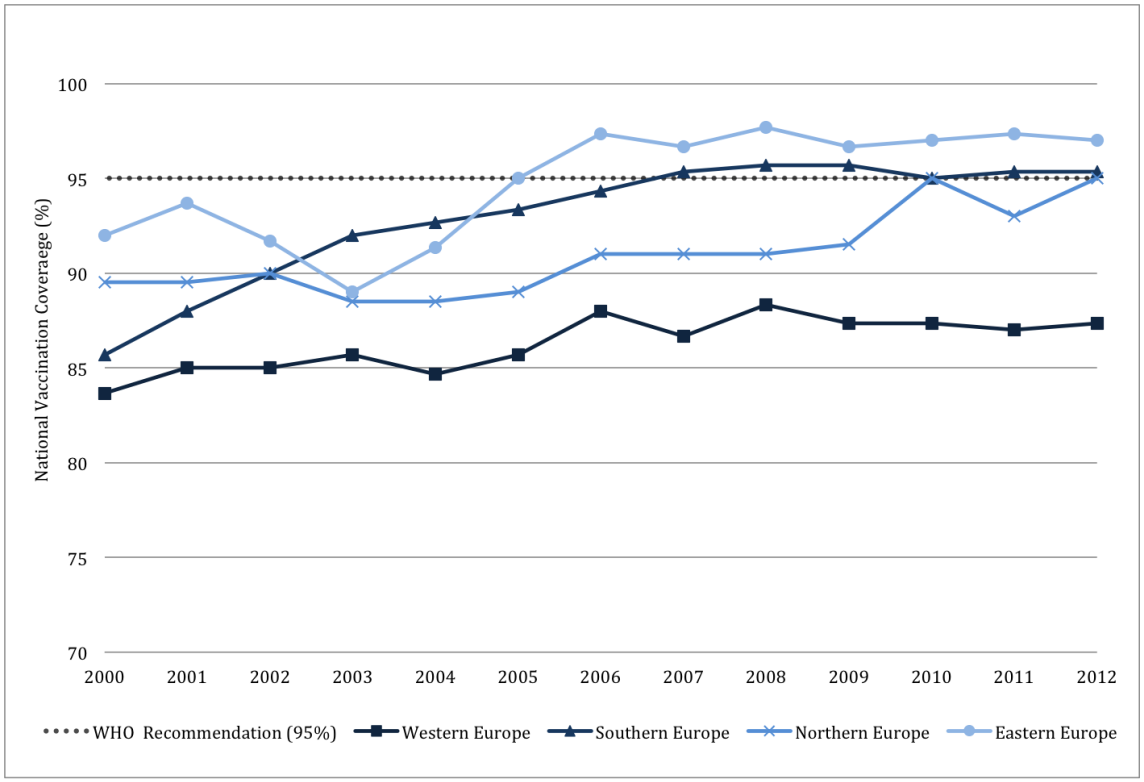

Figure 3.12. Regional Measles Primary Dosage Vaccination Coverage Over Time. Nationally reported immunization rates for the primary dosage of measles-containing vaccines have been averaged for each European subregion for the years 2000 through 2012. Missing data were supplemented by official WHO and UNICEF estimates. Western Europe: Austria, France, Germany; Southern Europe: Greece, Italy, Spain; Northern Europe: Sweden, United Kingdom; Eastern Europe: Croatia, Poland, Turkey. The WHO-recommended 95%-threshold for the elimination of measles has been marked. This threshold has been reached or surpassed by the Southern, Northern and Eastern European regions, but not by the Western European region. Eastern Europe is the only region in which high coverage rates have been sustained for several years in all of the included nations. Modified after *WHO vaccine-preventable diseases: monitoring system, 2013 global summary: coverage series*,[312] *WHO/UNICEF estimates for 1980-2012* (as of July 2013).[324]

MCV dosage are provided for the following age groups: preschool-aged children (1-5 years), school-aged children (6-14 years), and adolescents (15-19 years). Regional differences in vaccination rates (ranges) have been included upon availability. An additional eleven regional studies addressing age in correlation with measles susceptibility are described for the included nations.

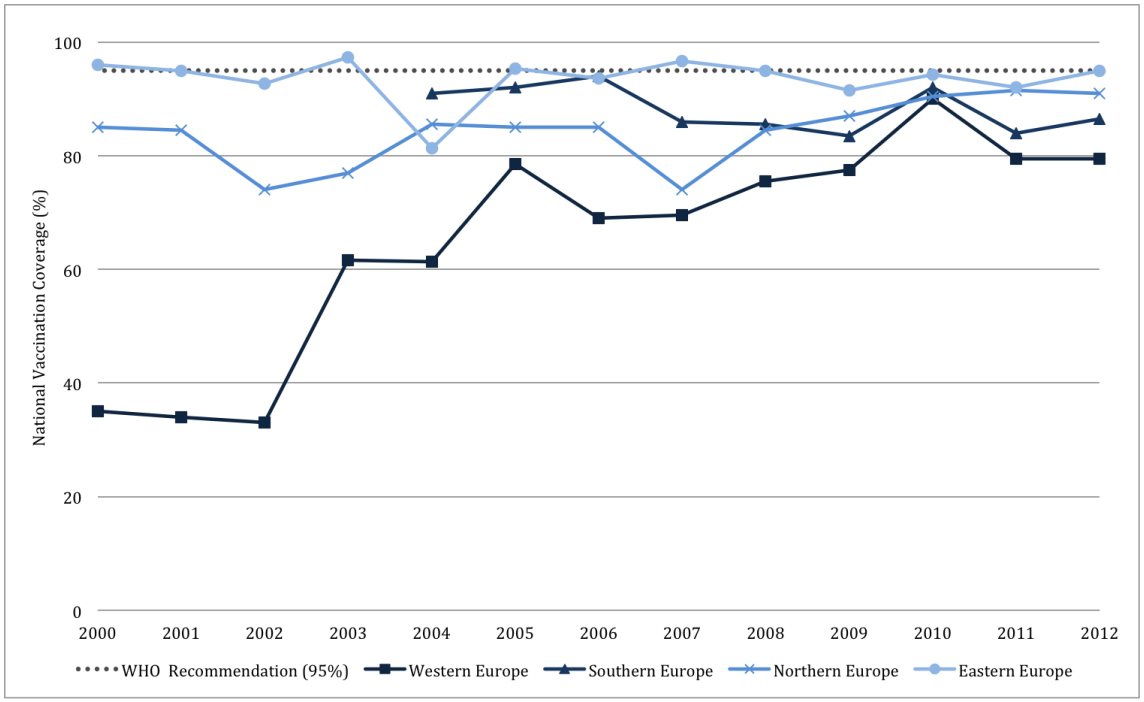

Figure 3.13. Regional Measles Secondary Dosage Vaccination Coverage Over Time. Averages of nationally reported immunization rates for the secondary dosage of measles-containing vaccines are shown by European subregion for the years 2000 through 2012. Western Europe: Austria, France, Germany; Southern Europe: Greece, Italy, Spain; Northern Europe: Sweden, United Kingdom; Eastern Europe: Croatia, Poland, Turkey. The WHO-recommended 95%-threshold for the elimination of measles has been marked. This threshold has been reached only by the Eastern European region. The high coverage rates have not been sustained even in this region, however. The immunization rates within the other three subregions are substantially lower than 95%, as shown. Modified after *WHO vaccine-preventable diseases: monitoring system, 2013 global summary: coverage series*.[312]

Measles Vaccination Coverage, by Age Group and Vaccination Dosage

Source(s)	Country	Age	Vaccination Coverage (%) according to Year and Measles Dosage (Range)														Quality
			2012		2011		2010		2009		2008		2007		2006		
			D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	
	Austria																
ECDC, VENICE II, 2012[180]		1-5 Years	-	-	-	-	-	-	100	89	-	-	-	-	-	-	Strong
ECDC, VENICE II, 2012[180]		6-14 Years	-	-	-	-	-	-	-	84	-	-	-	-	-	-	Strong
	Croatia																
HZJZ, 2011&2012,[22,41] Usonis et al., 2011[289]		1-5 Years	94.8 (85–99)	-	98.6 (91–99)	-	-	-	-	-	97.6*	-	-	-	-	-	Strong N/A
HZJZ, 2011&2012,[22,41] Usonis et al., 2011[289]		6-14 Years	-	97.0 (83–100)	97.9 (94–100)	99.4 (94–100)	-	-	-	-	-	98*	-	-	-	-	Strong N/A
	France																
InVS, 2011[144]		1-5 Years	-	-	89.4* (76–96)	67.3* (46–83)	89.2* (76–96)	60.9* (29–74)	-	-	89.1* (78–95)	-	90.1* (81–95)	-	89.4* (76–96)	-	Moderate
InVS, 2011[144]		6-14 Years	-	-	-	-	-	-	-	-	96.6[a]	85.0[a]	-	-	93.3[b]	44.3[b]	Moderate
InVS, 2011[144]		15-19 Years	-	-	-	-	-	-	95.5	83.9	-	-	-	-	-	-	Moderate
	Germany																
RKI, 2009-2013[240–243,246]		1-5 Years	-	-	96.6[c] (95–98)	92.1[c] (86–96)	96.4[c] (94–98)	91.5[c] (87–95)	96.1[c] (94–98)	90.2[c] (86–95)	95.9[c] (93–98)	89.0[c] (85–94)	95.4 [c] (93–98)	88.4[c] (82–94)	93.2	69.0	Strong
Poethko-Müller et al., 2007&2009& 2013[223,225,226]		6-14 Years	-	-	-	-	-	-	-	-	-	-	-	-	94.3[d]	77.0[d]	Strong Moderate
Poethko-Müller et al., 2007&2009& 2013[223,225,226]		15-19 Years	-	-	-	-	-	-	-	-	-	-	-	-	94.0	77.5	Strong Moderate

Measles Vaccination Coverage, by Age Group and Vaccination Dosage

Source(s)	Country	Age	Vaccination Coverage (%) according to Year and Measles Dosage (Range)														Quality
			2012		2011		2010		2009		2008		2007		2006		
			D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	
	Greece																
Pavlopoulou et al., 2013[215]		1-5 Years	-	-	-	63.7[e]	-	63.7[e]	-	-	-	-	-	-	-	-	Strong
Sakou et al., 2011[259]		6-14 Years	-	-	-	-	-	-	-	95.7	-	-	-	-	-	-	Strong
Sakou et al., 2011[259]		15-19 Years	-	-	-	-	-	-	-	91.5	-	-	-	-	-	-	Strong
	Italy																
Ministero della Salute, 2013[187]		1-5 Years	89.2	-	89.9	-	90.5	-	89.9	-	89.7	-	89.6	-	88.2	-	Strong
	Poland																
NIZP, 2006-2013[88–94]		1-5 Years	96.0 (84–100)	-	96.0 (84–100)	-	96.0 (85–100)	-	95.8 (84–100)	-	96.1 (85–100)	-	95.9 (84–100)	-	96.2 (85–100)	-	Strong
NIZP, 2006-2013[88–94]		6-14 Years	99.7 (100)	95.4[f] (87–100)	99.3 (100)	95.8[f] (85–100)	99.8 (100)	95.3[f] (86–100)	99.7 (100)	96.4[f] (85–100)	99.7 (100)	98.1[f] (91–100)	99.7 (100)	98.8[f] (96–100)	99.8 (100)	99.2[f] (98–100)	Strong
	Spain																
MSPSI, 2013[21]		1-5 Years	97.1	90.3	96.8	91.3	95.5	92.3	97.4	90.4	97.6	94.4	97.2	95.0	96.9	94.1	Strong
	Sweden																
SMI, 2010&2013[10,32]		1-5 Years	97.4	-	97.2	-	96.4	-	96.5	-	96.7	-	96.2	-	96.2	-	Strong
SMI, 2009&2012[7,19]		6-14 Years	97.2	95.1	97.4	95.1	98.3	94.4	98.6	94.9	98.5	94.4	-	-	98.8	94.9	Strong
	Turkey																
Usonis et al., 2011[289]		1-5 Years	-	-	-	-	-	-	97*	-	-	-	-	-	-	-	N/A

Measles Vaccination Coverage, by Age Group and Vaccination Dosage

Source(s)	Country	Age	Vaccination Coverage (%) according to Year and Measles Dosage (Range)													Quality
			2012		2011		2010		2009		2008		2007		2006		
			D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	
Usonis et al., 2011[289]		6-14 Years	-	-	-	-	-	-	-	88*	-	-	-	-	-	-	N/A
	UK																
PHE, 2013[230]		1-5 Years	94.3 (94–97)	88.2 (88–92)	93.4 (93–97)	86.5 (86–92)	92.5 (92–97)	85.0 (84–92)	91.7 (91–96)	83.6 (83–90)	87[g]	74[g]	86[g]	73[g]	87[g]	74[g]	Strong

Note: ECDC: European Center for Disease Prevention and Control; *HZJZ*: Hrvatski Zavod za Javno Zdravstvo (National Institute for Public Health, Croatia) *InVS*: Institut de veille sanitaire (Institute for Public Health Surveillance, France); *MSPSI*: Ministerio de Sanidad, Servicios Sociales e Igualdad (Ministry of Health, Social Services and Equality, Spain); *NIZP*: Narodowy Instytut Zdrowia Publicznego (National Institute of Public Health, Poland); *PHE*: Public Health England; *RKI*: Robert Koch Institute (Germany); *SMI*: Smittskyddsinstitutet (Institute for Infectious Disease Control, Sweden); *VENICE II*: Vaccine European New Integrated Collaboration Effort.

* Estimates

[a] Coverage at age 11 years.

[b] Coverage at age 6 years.

[c] Data collected from vaccination records prior to school entry; children 4-6(7) years of age are included.

[d] Age groups 7-10 and 11-13 years are included (2003-2006).

[e] Data biased towards immunization rates in the city of Athens, Greece.

[f] Coverage among children aged ≥10 years (the mandatory MCV-2 vaccination age in Poland).

[g] Data for England only.

Table 3.14. Measles Vaccination Coverage, by Age Group and Vaccination Dosage. Shown are the annual age-stratified immunization rates with either one (D1) or two (D2) measles dosages, as reported by various studies or governmental agencies. Reporting variances by region or age are shown where applicable. Quality of the included studies has been assessed and is indicated in the table above (see Study Characteristics, Appendix E for details). Verified data reports by governmental agencies were assigned a "strong" quality; estimates were assigned a "moderate" quality.

Based on current vaccination recommendations *infants* below the age of one year have a high susceptibility towards measles because of missing vaccinations and low seroconversion rates (see Section 1.3.1) are the most susceptible to measles, as they have typically not received immunizations yet. Vaccination coverage reports among this age group are rare and have therefore not been included in Table 3.14. A large, randomized cross-sectional study conducted between 2003 and 2006 in Germany did include immunization rates among children 0 to 14 months of age. This *Health of Children and Adolescents in Germany Study* (KiGGS) involved a total of 17,641 participants, of which 935 (5.3%) were less than one year old. The vaccination status was known for 93.3% of all participants and a measles immunization rate of 9.0% (primary dosage) and 1.4% (secondary dosage) was reported for those study participants below the age of 15 months.[223,226] The exact rate among infants below 12 months of age was not reported, however.

Pre-school-aged children have typically been vaccinated with at least one MCV dosage and are better protected against measles than infants are. However, in many of the included countries, the full two-dosage MCV vaccination is not yet recommended for this age group (see Table 3.8). Therefore, limited data of MCV-2 coverage exists.

As shown in Table 3.14, the MCV-1 immunization rates among pre-school-aged children in France,[144] Poland[88–94] and Sweden[10,32] tend to be lower than they are among school-aged children or adolescents. Insufficient comparative data are available to describe such a trend for the other countries. The limited data available for Croatia, Germany and Greece do suggest similar findings, however.

Additional studies analyzing the measles susceptibility among preschool-aged children were found for Greece, Spain, Italy and Germany:

Pavlpoulou et al.[215] assessed the MMR vaccination status among a sample of 731 young children living in Athens, Greece in 2010 and 2011. The authors determined that 90.5% of the children had received at least one MMR vaccination by the

age of 24 months, but that only 35.9% had received the age-appropriate complete two-dosage immunization at age 60 months.[215] The overall complete immunization coverage of all participating children up to the age of 65 months was with 63.7% substantially higher, but still far away from the WHO-recommended threshold.[215]

A similar study conducted in Catalonia, Spain, by Borràs, et al.[55] showed a very high MCV-1 coverage among pre-schoolers. In a random sample of 627 children under the age of 3 years, 98.9% had received at least one MMR dosage.[55] The MCV-2 vaccination rate was not described, but nation-wide coverage reports provided by the *Ministerio de Sanidad, Servicios Sociales e Igualdad* (MSPSI) among 3-to 6-year-old children has been considerably high (>90%) in the past years (see Table 3.14).

A representative seroepidemiological survey in Tuscany, Italy, conducted between 2005 and 2006 revealed that 63.2% of 1-year-old children and 87.7% of 2- to 4-year-old children had positive anti-measles Immunoglobulin G (IgG) antibody titers, indicating a susceptibility of 36.8% and 12.3%, respectively.[53] A nation-wide survey conducted in Italy in 2004 showed even lower seropositive rates, however. In that study, 65.1% of one-year-olds and 25.5% of 2- to 4-year-olds were reported to be at risk for measles infections.[53]

In Frankfurt am Main, Germany, a local seroepidemiological survey conducted in 2009 revealed similar results. 31.9% of children between 1 and 4 years of age were susceptible to measles.[121] This was an improvement from 2005, however, at which time about 60% of 1- to 4-year-olds were at risk.[121]

Anti-measles seroprevalence was also determined as part of the German KiGGS study (described above). Among nearly 14,000 participants (79%), positive seroprevalence rates of 73.3% and 90.1% were determined for children aged 1 to 2 years and 3 to 6 years, respectively. Clearly seronegative (excluding borderline titers) were 26.0% and 8.6% of the participants in the respective age groups. These differences were significant.

Vaccination coverages among children entering the school system in Germany are regularly reported by the *Robert Koch Institut* (RKI). Although the children are between 4 and 7 years old, they have been added to the preschool group in Table 3.14 for easier comparability. An increasing trend in the annually published data[240–243,246] can be observed. While the 2007 immunization rate averaged 95.4% (range: 93%-98%) for the primary MCV dosage, this rate increased to 96.6% (range: 95%-98%) in 2011.[238,240,246] Full two-dosage vaccination rates have been increasing as well, from 88.4% (range: 82%-94%) in 2007 to 92.1% (range: 89%-96%) in 2011.[238,240,246] Although the overall vaccination coverage is near the WHO-recommended threshold, this goal has not been reached quite yet. In addition, the data may be overestimated, as the vaccination status among about 15% of the annually included children is not available due to missing immunization documents. Children without vaccination cards are often not or only insufficiently vaccinated, thus possibly skewing the annual coverage results.[238]

The measles susceptibility among children in Austria is even less clear. Only very few reports have been found, and those that address immunization coverage are inconsistent. While a very high MCV-1 coverage of 100% was reported among 3-year-old children by the VENICE II Consortium[180] in 2009, a coverage of only 76% was published by the WHO for the same year.[312] More recent statistical data are not available, but the Austrian Ministry of Health (BMG) states that the "vaccination rate among children and adolescents is 90% for the first MMR immunization, and far below 80% for the second MMR immunization"[24] [translation].† Due to the discrepancies between these data reports, conclusions regarding measles susceptibility among Austrian children can not be drawn.

Measles immunization rates among *school-aged children*, available for Croatia, France, Poland and Sweden as well as scarcely for Austria, Germany, Greece and Turkey, show a generally high coverage among this age group. MCV-1 coverages ≥95% were reported repeatedly in Croatia,[22,41] France,[144] Poland[88–94] and Sweden[7,19] during

† "die Durchimpfungsrate bei Kindern und Jugendlichen [liegt] für die erste MMR Impfung bei 90%, für die zweite MMR Impfung allerdings weit unter 80%." (translated by author)

the past couple of years. Equally high MCV-2 vaccination rates were observed in these countries, with the exception of France, where the last available coverage rate was reported to have been 85% in 2008.[144] For Poland, only data of children aged 10 years or older have been included, as this is the mandatory vaccination age for the second MCV dosage. The coverage is much lower among younger school-aged children,[88–94] and the in Table 3.14 indicated immunization rates should be interpreted accordingly. In addition, a slightly decreasing trend in the amount of Polish children who are fully vaccinated by the age of 10 years can be observed. Nonetheless, the overall coverage is high and near or above the WHO-recommended threshold in all of the countries that regularly report vaccination rates among school-aged children.

Various local cross-sectional studies and seroepidemiologidal surveys concerning the measles susceptibility among children and adolescents aged 6 to 14 years were conducted during the past years. The results vary greatly between the different nations.

In Styria, Austria, Stronegger and Freidl[281] report the measles coverage among 2,386 students in grades one, four and seven (respective mean ages: 6.5 years, 9.6 years and 13.1 years) from 176 randomly selected classrooms. The vaccination rates with at least one MCV dosage were 88.4% among the first graders, 84.9% among the fourth graders and 76.8% among the seventh graders. The older children were thus shown to be less adequately immunized. Overall, these vaccination rates are far from the 95% threshold for herd immunity.

In Athens, Greece, on the other hand, a high measles coverage was observed in a 2009 cross-sectional study by Sakou et al.[259] As part of the study, which included 1,005 children and adolescents 11 to 19 years of age from all across the country, a 95.7% MCV-2 coverage was reported among those 11 to 14 years old.[259] These rates were higher than those reported among pre-school-aged children living in Athens by Pavlpoulou et al.[215] (see above).

In the city of Essen, Germany, a study was conducted among nearly 3,500 sixth grade students (mean age: 12 years). Roggendorf, Frynik and Hofmann[252] analyzed the second-dosage MMR (MMR-2) coverage among these children before and after an intervention during which students and their parents received information materials and guidance regarding missing vaccinations. Before the intervention, in 2001, the MMR-2 immunization rate was with 43% extremely low.[252] In 2002, the vaccination coverage among the now seventh graders was with 59% significantly higher.[252] Ninth graders at the same schools served as control group: only 34% of these students had received the full two-dosage MMR immunization.[252] Although these data are not representative of the entire nation, they do reflect that the vaccination coverage among older students is likely much lower than among children entering the school system (shown in Table 3.14).

More recent seroepidemiological surveys conducted in Germany revealed a better protection against measles among the school-aged population. The measles antibody seroprevalence among the KiGGS study (2003-2006) participants was 90.6% among those 7 to 10 years old and 88.5% among those 11 to 13 years old.[227] This difference between the two age groups was not significant, however.[227] The 2009 seroepidemiological study conducted in Frankfurt am Main (see above) showed a lower level of protection among children aged 5 to 9 years, with an anti-measles IgG seropositivity rate of 68.1%, than among those aged 10 to 19 years, with a seropositivity rate of 71.1%.[121] Clear conclusions are difficult to draw based on these varying study results. The KiGGS study is more representative of the entire nation, however.

In the 2005-2006 Italian study by Bechini et al.[53] (described above), the measles seroprevalence among school-aged children living in Tuscany was 82.2% among those aged 5 to 9 years and 62.6% among those aged 10 to 14 years. This difference was statistically significant (p=0.002).[53] The protection against measles was also found to be lower among these older age groups than among the pre-schoolers aged 2 to 4 years (87.7%, see above). The difference in seroepidemiology between the 2-to-4-year and 5-to-9-year age groups was not significant, however.[53]

The measles antibody seroprevalence among children attending two different schools in Denizi, Turkey were assessed before and after a mass vaccination campaign in December of 2003.[57] Prior to the campaign, the proportion of students in grades one through eight with a positive anti-measles IgG antibody titer was 74.7%.[57] The with 62.7% and 57.5% lowest seroprevalence rates were among students in the fifth and eighths grades.[57] These rates were significantly lower than those among the other grade levels (1-4, 6 and 7), ranging between 77.4% and 83.0% ($p<0.01$).[57] The low protection against measles among students in the eighths grades of both schools is likely due to an older vaccination policy, under which vaccinations among first grade students were not performed at the time these children were starting school. The mass vaccination campaign at the end of 2003 led to an overall increase in seropositivity of 21.8% in the two schools, reaching an overall protection among 96.5% of the students.

Few literature sources address measles susceptibility among *adolescents*. The nationwide reports available for Germany[223,225,226] (2003-2006), Greece[259] (2009) and France[144] (2009) show a slight drop in the immunization rates among this age group compared to the school-aged children. In the German KiGGS study, this difference was not significant.[223] The data reported for France by the *Institute de Veille Sanitaire* (InVS)[144] did not directly compare different age groups. However, in an older cross-sectional sampling study conducted among French schoolchildren and adolescents between 2001 and 2004, a non-significant difference in measles coverage rate was found among 11-year-old children (94.1%) and 15-year-old adolescents (93.9%).[43] (The second-dosage immunization rates were low, reaching 56.8% and 65.7% among the respective age groups).[43] In Greece, on the other hand, the 2009 study by Sakou et al.[259] found a significantly lower MCV-2 vaccination coverage among adolescents aged 15 to 19 years (91.5%) compared to those aged 11 to 14 years (95.7%, $p<0.001$). Overall, these studies suggest that adolescents are somewhat more susceptible to measles than school-aged children are.

As the various studies and reports show, the risk of measles infection varies greatly between the included European nations and among various age groups. Among the

different countries included in this report, high two-dosage MCV coverages meeting or surpassing the WHO-recommended 95%-threshold have been reported for Croatia, Greece, Poland and Sweden. Insufficient available data for all of the selected countries as well as differences in data reporting make a comparison between the nations difficult, however. The same is true for comparisons among different age groups. Nonetheless, a general patterns can be observed: The measles susceptibility is highest among infants, followed by pre-school-aged children and adolescents. School-aged children have the lowest susceptibility and are best protected against measles.

Gender Eight studies assessed the role of gender as a factor of measles susceptibility. Most of the papers regarded the KiGGS study participants in Germany, addressed in the previous subsection. Among all included children and adolescents aged 2 years and older, 93.7% of girls and 93.6% of boys were vaccinated with at least one MCV dosage; fully vaccinated with two or more MCV dosages were 73.9% and 74.5%, respectively. These differences were not significant.[223,225,226] Gender variances in anti-measles IgG antibody seroprevalence were found, however. Among the children and adolescents with a known vaccination status, 8.8% of girls and 10.2% of boys had negative titers and were thus susceptible to measles. In both a univariate and a multivariate odds ratio analysis, the risk of a male to have a negative measles antibody titer was significantly higher (univariate: OR=1.33, p=0.015; multivariate: OR: 1.33, p=0.004).[224] When all participants with and without known vaccination status were included, the results were similar: Seronegative titers were reported for 9.2% of girls and 10.8% of boys (multivariate OR: 1.13, p=0.008).[227] The seroepidemiological survey conducted in Tuscany, Italy, also found a slightly higher measles susceptibility among males (16.5% vs. 14.9% negative or equivocal titers); this difference was not significant, however.[53] A correlation between gender and measles vaccination coverage could also not be determined in the study conducted by Stronegger and Freidl[281] among Austrian children. The vaccination rate was slightly (0.5%) lower among boys than among girls, but this difference was not significant (p=0.76).[281] Similarly, no gender differences were found in a

representative telephone-based immunization survey conducted between 1999 and 2004 in Germany.[263] The timely MCV-1 vaccinations among 2,116 young children were assessed: 47.2% of girls and 46.3% of boys were vaccinated before the age of 15 months (p=0.281).[263] These studies show that while males may be slightly less often vaccinated, gender only plays a minor role, if any, in affecting measles susceptibility.

Education The influence of parental education on the vaccination status of children was analyzed in eight studies. An association has been found by some of the authors, but the direction of correlation remains unclear. While some studies found that children of parents with a high level of education were better protected against measles, other found that the opposite was true, and yet others that there was no association whatsoever. These study results are summarized below.

Among Austrian schoolchildren in Styria, a correlation between paternal educational level and measles vaccination was determined by Stronegger and Freidl.[281] With increasing paternal education, from basic compulsory education to university level, increasing immunization coverage was observed (range: 74.9%-88.0%); this association was significant ($p<0.001$).[281] A similar trend could be described for the maternal education level, but this positive correlation was not statistically significant ($p=0.042$).[281]

Borrás et al.,[55] on the other hand, report a significant difference in general vaccination coverage among Spanish children below the age of 3 years whose mothers have a university-level educational status (92.0%) and those whose mothers have a lower educational status (86.3%). The authors also found a significant difference in immunization status between those children attending a day-care center (89.4%) and those who did not (81.7%).[55]

In Germany, maternal education was compared to measles antibody seroprevalence among the KiGGS study participants. Children of mothers with a high (university) educational level were with 11.9% seronegative titers *more* suscepti-

ble to measles than children of mothers with a medium (tenth grade completion) or low (eighth/ninth grade completion) educational status were (9.7% and 8.5%, respectively).[224,227] These variations in seroepidemiology were small, but significant (p=0.003).[227]

In the 1999-2004 telephone-based national survey (described above), parental education (defined as having attended school for <10 years or ≥10 years) was not associated with a timely MCV-1 immunization of children. However, the level of maternal education (with or without university graduation) was associated with the measles vaccination rate among the participating children: 47.9% of those with mothers who graduated from a university and 43.3% of those with mothers who did not were vaccinated against measles by the age of 15 months (p=0.003).[263]

A further study conducted in 2007 in the German federal state of North Rhine-Westphalia (NRW) analyzed the general vaccination uptake among 5- and 6-year-old children, assessed as part of the mandatory school-entry health screening examinations.[256] Of 41,697 children for whom the educational status of at least one parent was known, 57.9% did not have a completed vaccination record. Children of parents with a low educational level, defined as not having completed basic schooling or graduating after the eighth, ninth or tenth grade without any additional vocational training,[146,256] were more likely to not be fully immunized than children of parents with a medium or high educational level, defined respectively as completing the 10th grade with vocational training/graduating after at least twelve years of school or graduating from university/technical college,[146,256] were. However, in a multivariate analysis adjusted for the participation in early recognition and prevention examinations, this difference was not statistically significant (p=0.098).[256] The influence of parental education on the vaccination status of children in Germany is thus not clear. The study results above show that both positive and negative associations have been found.

In the cross-sectional studies by Pavlopoulou et al.[215] and Sakou et al.,[259] conducted in Greece, similar results emerged. Pavlopoulou et al.[215] found a slightly negative

association between maternal educational level and the completed, timely vaccination status of children. Sakou et al.,[259] on the other hand, described a positive association between a higher maternal and/or paternal educational level and the likelihood of a completed vaccination status among their children. These differences in immunization between children of parents with a high (>12 years of school) or low (≤12 years of school) educational status were not significant, however.[215,259]

No clear patterns describing the influence of parental education on the vaccination status of children can be observed. As with gender, educational status likely plays only a subordinate role in measles susceptibility.

Socioeconomic Status A correlation between socioeconomic status (SES) and the risk of measles infection was assessed by six recent studies and reports.

The German KiGGS study found a slightly negative association between the SES of children and adolescents and their MMR-coverage.[223,225,226] Of those participants aged 2 to 17 years with a high SES, 91.6% were vaccinated against measles with a primary dosage and 70.9% with a secondary dosage.[226] Those participants of an intermediate or low SES had a 94.2% and 94.9% MCV-1 coverage and a 76.7% and 73.6% MCV-2 coverage, respectively.[226] In a univariate analysis, this difference was significant ($p<0.001$).[223] In a multivariate analysis, adjusted for age, gender, place of residence, migration background and other sociodemographic variables, the odds of not being vaccinated were no longer dependent on the SES, however ($p=0.951$).[223,225]

In the national immunization survey conducted between 1999 and 2004 in Germany, Schönberger et al.[263] observed no difference in the timely MCV-1 vaccination of children whose parents were employed or unemployed. Similarly, neither a high or low SES nor an active or inactive parental occupational status had an impact on the proportion of children with a complete vaccination status in Catalonia, Spain.[55] Stronegger and Freidl[281] also found no clear correlation between the immunization rate of Austrian children and the employment status of their parents, though a

much lower vaccination coverage (74.0%) was observed when only the mother was employed than when both parents (82.9%), only the father (82.4%) or neither parents (81.5%) were employed (γ correlation coefficient: -0.049, p=0.32).

Bozkurt et al.[58] assessed the measles antibody seroprevalence among school-aged children 7 to 14 years old in two schools that were located in a low SES area and a high SES area. Similar positive seroprevalences rates of 74.9% (low SES) and 74.5% (high SES) were found.[58] Stratified by grade level, a notable difference between the schools was only observed among fifths graders (p=0.01).[58] After a mass vaccination campaign, the positive seroprevalence rates increased at both schools to 94.2% (low SES) and 98.7% (high SES).[58] Although a lower susceptibility to measles was observed among the students from the high SES area, this correlation was not significant.

Overall, no clear association between measles susceptibility and socioeconomic status could be determined.

Residence The influence of urban or rural residence on the measles vaccination status of children was analyzed by only three studies. Among Austrian schoolchildren, 86.0% of those living in urban areas and 81.7% of those in rural areas were vaccinated with at least one MCV-dosage.[281] This correlation was not significant (γ correlation coefficient: 0.16, p=0.027).[281] In Greece, a complete vaccination status among children and adolescents 11 to 19 years of age was more frequent among those study participants residing in urban districts (p=0.031). In the German federal state of NRW, those children living in an urban area were also slightly more likely to have a complete immunization status by the time of their school-entry health examination at age 5 or 6 years (42.2% urban vs. 40.3% rural).[256] Nonetheless, clear, significant associations between place of residence and vaccination status were not reported by theses studies.

Migration 15 recent studies and reports assessed the measles susceptibility among immigrants, refugees and traveling ethnic groups within the selected European countries. A generally higher risk of infection was found among these migrating populations. However, the findings were not consistent throughout the literature.

In Greece, a negative association between a complete vaccination status and a foreign paternal nationality was found. Although children with fathers of a Greek nationality were only slightly more likely to be fully vaccinated than those with forgein-born fathers were ($p=0.034$), the age-appropriate immunization coverage at 24 months was significantly higher among the children with native fathers ($p<0.001$).[215] Among adolescents living in Greece, a lower MMR vaccination coverage among immigrants (84.4%) than among native Greeks (93.3%) was observed as well ($p=0.05$).[259] However, in the study population sample, the non-native adolescents were extremely under-represented, possible skewing the results.[259]

The KiGGS study in Germany found a similar vaccination coverage among children with and without a migratory background, defined as either having two forgein-born parents or being an immigrant with at least one forgein-born parent.[226] Among children aged 7 to 10 years, those with a migratory background were significantly better protected against measles than their non-foreign counterparts were.[226] The opposite was true among adolescents aged 14 to 17 years, however; the vaccination coverage was much lower among the migrant population of this age group.[226] The analysis by first and second-generation migrants revealed that among those children and adolescents who had immigrated themselves, the MCV-1 coverage was much lower (87.1%) than among those who had been born in Germany, either to immigrant parents (95.0%) or to native parents (93.7%).[223,225] Similar results were found in the measles antibody seroprevalence study conducted by Poethko-Müller and Mankertz[224] among the KiGGS study participants with a migratory background. The proportion of susceptible children and adolescents (with a negative anti-measles IgG titer) was with 14.5% much higher among the forgein-born group than among the German-born group (8.2%). These difference were statis-

tically significant ($p<0.001$) in both univariate and multivariate (adjusted for age, gender, SES, etc.) analyses.[223,224]

The national, telephone-based immunization survey conducted by Schönberger et al.,[263] on the other hand, revealed no significant association between native or foreign parental nationality and the timely MCV-1 vaccination of young children in Germany. Rosenkötter et al.[256] also reported that children with a migratory background were only slightly more likely to have an incomplete vaccination status at age 5 to 6 years than German-born children were; this difference was not statistically significant ($p=0.872$).

Only one study concerning the measles susceptibility among refugees was found through the literature search. In 2010, a small measles outbreak occurred in a shelter for asylum seekers in Germany, where 427 refugees from 18 different nations, including Afghanistan, Serbia, Macedonia, Iraq and Syria, were staying at the time of the outbreak.[282] The vaccination status of all of the shelter residents was unknown.[282] As part of the outbreak control measures, the measles IgG antibody seroprevalence was determined for 300 (70.3%) of the residents, and an overall susceptibility rate of 13% was calculated.[282] Children and adolescents between the ages of 9 months and 18 years were with a seronegativity rate of 16.3% slightly more susceptible than adults aged 19 to 40 years (14.4% seronegative) were.[282] Among the 41 residents who were older than forty years, all had a positive anti-measles IgG titer.[282] When comparing these data to the KiGGS study results, the susceptibility among the children and adolescent refugees were somewhat higher than among the first-generation immigrants (16.3% vs. 14.5%, see above). The study differences in terms of sample size, location and laboratory testing make such a comparison difficult, however.

MCV immunization coverage among the Roma ethnic group was assessed by three studies conducted in Poland and Germany as a result of measles outbreaks involving predominantly members of the respective Roma communities. The 2009 outbreak in and around Hamburg, Germany, which resulted in the European-wide spread of

the D4-Hamburg genotype (see Section 3.3.5), involved at least 69 members of local Roma settlements (of 216 total cases).[137] The vaccination status was known for 91% of all cases: 75% had not been vaccinated, 25% had been vaccinated with at least one MCV dosage and 2% with two MCV dosages.[137] Unfortunately, the immunization statuses among the cases of the Roma ethnic group were not reported. Later during 2009, a measles outbreak caused by the same D4-Hamburg genotype was reported in Pulawy, Poland.[207] A total of 41 cases were reported, of which 35 (85%) belonged to the local Roma community. The vaccination status was known for 32 cases and among them, only one person had been previously vaccinated with a single MCV dosage.[207] As a result of this outbreak, a mass vaccination campaign targeting specifically the Roma ethnic community was conducted. Prior to the campaign, the vaccination coverage was assessed among 102 children and adolescents below the age of twenty years: 19% were not vaccinated, 35% had been vaccinated with a single MCV dosage, 18% had received at least two MCV dosages and 28% had an unknown immunization status.[279] After the campaign, 56% of the eligible children and adolescents were vaccinated with a single MCV dosage and 37% with a secondary dosage. Although the immunization coverage rates could be improved, they are still very low among this population.

No studies were found regarding the vaccination coverage among the Irish Traveller communities in the United Kingdom. However, the vaccination statuses of affected members of this minority group were assessed during several separate measles outbreaks. Cohuet et al.[79] report that none of the 124 confirmed cases during the 2007 outbreak that involved almost exclusively members of the Irish Traveller population had been vaccinated. The immunization rate during the 2008-2009 outbreak in Central and Eastern Cheshire, of which over 20% of cases belonged to the Traveller community, was also reported as extremely low.[125] Among those eligible for vaccination, only 24% had received a primary MCV dosage and as little as 7% a secondary MCV dosage.[125] During smaller outbreaks in the Thames Valley between 2006 and 2009, a somewhat higher vaccination rate among measles cases from Traveller communities was observed: 49% had received a single MMR dosage.[169] However, none

of the affected individuals had been vaccinated with a second MCV dosage.[169] (See Section 3.3.5 for further details about these outbreaks.)

The studies described here suggest that the measles vaccination coverage among migrants is often low. Recent and first-generation immigrants as well as refugees have an increased risk of measles infections. Although little is known about the overall vaccination coverage among traveling ethnic minorities, such as the Roma and Irish Traveller populations, the outbreak assessments in recent years suggest that a high susceptibility to measles exists.

Among the sociodemographic factors analyzed, migratory background and age are the only two that clearly affect measles susceptibility. The risk of infection is high among recent immigrants, refugees and members of traveling ethnic populations as well as among infants, preschool-aged children and adolescents. Gender, parental education level, socioeconomic status and urban or rural place of residence have no notable impact on the level of susceptibility to measles, however.

3.3.8. Effects of Migration within Europe

Migration plays an important role in the persistence of measles in Europe. As described in Section 3.3.7 above, migrants residing in the studied European nations are often less sufficiently vaccinated than native residents are and consequently have a higher risk of infection. Particularly unimmunized individuals traveling from measles outbreak regions to other nations within the European continent are contributing to the transmission of the disease. Table 3.11 and Figs. 3.8 to 3.11 show that the majority of imported measles cases reported in recent years originated from neighboring countries. As migration within Europe is becoming increasingly relevant, the rate of measles susceptibility among residents of the various European nations is gaining importance as well.

Among the studied nations, the susceptibilities to measles vary greatly. Different disease incidences and vaccination coverages have led to an inhomogeneous protection among the residents of these countries. Using Germany, the nation with the highest migrant population, as an example, the susceptibilities among immigrant children and adolescents have been estimated, as illustrated in Fig. 3.14.

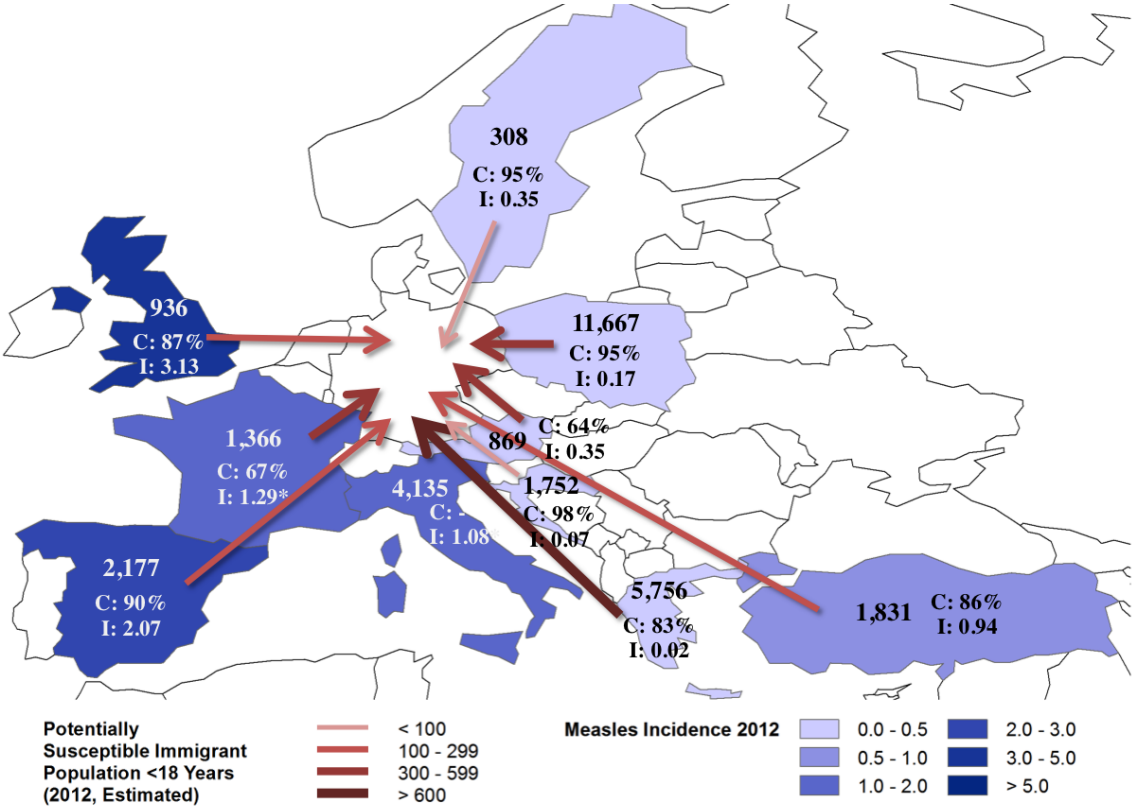

Figure 3.14. Migratory Flows and Potential Measles Susceptibilities Among Immigrant Children and Adolescents in Germany, 2012. Indicated are the child and adolescent (<18 years) populations migrating to Germany in 2012 from the respective European source nations. The national measles second-dosage coverage rates (C) and incidences per 100,000 population (I) are provided for each country, as shown. All data are for 2012 or the most recent year available (2011 coverages for Croatia and Turkey; 2009 coverages for Austria). Nations with uncertain measles incidences due to known or likely errors in reporting have been marked with an asterisk (∗). The estimated numbers of potentially susceptible children and adolescents are represented by arrows of varying strengths, whereby the national coverage rates have been applied to determine the likely numbers of insufficiently immunized individuals. The with <100 lowest populations of susceptible children likely arrived from Croatia and Sweden, the with nearly 1,000 largest population from Greece. ***Source***: *Statistisches Bundesamt Deutschland, 2014*.[33] For measles incidence and coverage sources see Tables 3.10 and 3.13. Geographic data obtained from www.naturalearthdata.com.

In 2012, a total of 30,799 individuals below the age of 18 years immigrated from one of the selected European nations to Germany.[33] Of these, most originated from Poland (38%), Greece (19%) and Italy (13%).[33] Each nation's MCV-2 coverage (see Table 3.13) in 2012 (or most recent year available) was used to determine the approximate numbers of fully immune vs. partially or non-immune individuals

migrating from the selected countries to Germany. Due to lack of exact vaccination rates among the emmigrant populations, the immunization coverages were assumed to be equal to those nationally reported. The estimated numbers of susceptible migrant children and adolescents are shown in Fig. 3.14, represented by arrows of varying strengths. A total of 3,385 young migrants from the selected European nations were potentially non-immune to measles in 2012. The largest populations arrived from Greece (979), Poland (583), France (451), and Italy (414), whereby the later population size is likely underestimated due to lacking MCV-2 coverage data. Of the remaining migrant population potentially susceptible to measles, an estimated 313 arrived from Austria, 256 from Turkey, 218 from Spain, 122 from the UK, 35 from Croatia and 15 from Sweden. Although the data are merely estimates, clear differences in measles contraction and transmission risks between the various European nations are evident and similar trends may be anticipated in the future.

In order to eliminate measles from the entire European continent, the different susceptibilities among residents of various nations should be kept in mind and efforts made to improve the vaccination rates in those countries with low coverages, as will be further discussed in Chapter 4.

3.3.9. Rating of Vaccination Programs

Each of the representative European nations included in this report has a slightly different measles immunization program. As described in the subsections above, the effectiveness of the programs vary as well, not only in vaccination coverage but also in the prevention of measles cases. The grading system delineated in the Materials and Methods Section 2.4 was applied to assess the performance of each national vaccination program.

In Table 3.15, the grading levels as well as pertinent performance indicators are shown. For each nation, the average, minimum and maximum annual measles incidences for the years 2006 to 2012 were calculated based on the nation-wide reported

case numbers (see Table 3.10). Second-dosage measles or MMR immunization rates have been included for preschool- and school-aged children for the year 2012 (or most recent available). In Croatia, Poland, Sweden, and Turkey, vaccination coverages were not available for pre-school-aged children, as the MCV-2 dosage is provided at a later age (see Table 3.8). Furthermore, MCV-2 coverage data was not available for Italy and inconsistent for Austria. As such, these six countries were graded solely based on the annual measles incidences, as described in Section 2.4. For the three Eastern European nations and Sweden, a second grade was determined using the vaccination rates among school-aged children, however. These have been indicated in parentheses, as shown.

Quality indicators of the national measles surveillance systems have been included in Table 3.15 as well. As described in the Section 3.3.3 above, all included nations require the reporting of measles cases, either through physicians and hospitals or laboratories. Nonetheless, under-reporting is known to occur in at least two of the countries—Germany[182] and France.[270] The annual measles incidences of these nations were therefore not included in the grading. Incorrect annual case numbers are also suspected in Italy[118] as well as in Austria and Greece due to low laboratory confirmation rates. In the remaining countries, high laboratory confirmation rates make under-reporting less likely.

Comparison of National Measles Vaccination and Surveillance Programs

Nation	Incidence 2006-2012 (per 100,000)			2-Dose Vaccination Coverage 2012 (%)		Mandatory National Surveillance	Reporting Errors	Grading Level
	Mean	Min	Max	Age 1-5	Age 6-14			
Austria	1.24	0.25	5.24	89[a]	84[a]	Yes	Unknown	4
France	5.05	0.07	22.87	67.3[b]	-	Yes	Yes	5*
Germany	1.21	0.20	2.79	92.1	-	Yes	Yes	3*
Greece	0.90	0.01	4.59	63.7[b]	83[c]	Yes	Unknown	4
Italy	2.90	0.69	7.55	-	-	Yes	Unknown	4
Spain	1.78	0.09	7.70	90.3	-	Yes	No	3
Sweden	0.17	0.01	0.32	-	95.1	Yes	No	3 (2)
UK	1.86	0.70	3.13	88.2	-	Yes	No	4
Croatia	0.26	0.00	1.36	-	97.0	Yes	No	4 (2)
Poland	0.22	0.05	0.36	-	95.4	Yes	No	3 (2)
Turkey	0.17	0.00	0.94	-	86[b,c]	Yes	No	3 (3)

[a] 2009 vaccination coverage data.
[b] 2011 vaccination coverage data.
[c] WHO/UNICEF estimate.
* Grade level refers only to vaccination coverage data due to inadequate disease surveillance or under-reporting of cases.

Table 3.15. Comparison of National Measles Vaccination and Surveillance Programs. Each selected nation's immunization program is summarized in terms of key performance indicators. Recent average annual incidences and ranges for the years 2006-2012 as well as the average vaccination coverages among pre-school- and school-aged children (1-5 years and 6-14 years of age, respectively) for the year 2012, or most recent available, are shown. Surveillance system performance is measured by presence of mandatory surveillance (yes/no) and errors in reporting (yes/know/unknown). The grading levels were determined according to the criteria described in Section 2.4, whereby deviations for countries recommending the secondary dosage vaccination among school-aged children are shown in parentheses. ***Sources***: Bacci, 2010&2011 (EUVAC.NET),[48,49] ECDC, 2009-2013.[103,105,106,109,110] (For incidence and vaccination coverage data sources see Tables 3.10, 3.13 and 3.14.)

According to the grading system, the best performing measles immunizations plans are those of Germany, Poland, Spain, Sweden and Turkey. All five of these nations attain a grading level 3, suggesting that measles control is adequate, but sustained elimination not yet achieved. Taking the vaccination rates among school-aged children into consideration, Sweden, Croatia and Poland receive a level 2 grading due to high MCV-2 coverages of >95% and considerably low annual measles incidences. The temporary elimination of the disease (incidence $\leq$0.10/100,000/year) was accomplished by all three nations: Croatia in 2006, 2007, 2009 and 2012, Poland in 2010 and 2011, and Sweden in 2007, 2009, and 2010. Furthermore, similarly low incidences were observed in France (2006-2007), Greece (2007-2009 and 2012), Spain (2009) and Turkey (2006-2010). Nonetheless, none of the included European nations has been able to eliminate measles entirely as of yet.

The currently least successful measles immunization programs are those of Austria, France, Italy and the United Kingdom. The MCV-2 coverage rates for these nations are below 90%, leaving large portions of the populations unprotected against the disease. The generally high annual measles incidences further support this finding. (See Table 3.15 for details.)

When all performance indicators are taken into consideration, the most successful measles immunization programs are those of Poland and Sweden. Due to Poland's very late MCV-2 immunization age of ten years, however, Sweden's strategy may be superior, as it allows for a wider protection among the child population. Nonetheless, with a maximum measles incidence of $<1/100{,}000$/year and complete vaccination coverage $>95\%$, both nations are close to reaching the WHO elimination goal. The other European countries included in this report require further strategies in order to achieve the sustained elimination of measles.

3.4. Mumps

In accordance with the measles and rubella elimination strategies, a control of mumps may be achieved through the co-vaccination of all three diseases, as recommended by the WHO.[300] Although mumps poses a less critical public health concern than measles and rubella do,[300] its complications, particularly among adolescents and adults, warrant its incorporation into immunization plans. The success of the included nations' mumps vaccination strategies in terms of immunization rates and case numbers are delineated below.

3.4.1. Study and Report Selection

A total of 160 studies and reports were obtained through the mumps literature search. Of these sources, 81 were found using the Pubmed database, 45 using Med-

line and 61 using the SSCI/SCI-Expanded database. An additional 45 reports were obtained through governmental and public health agencies, including the WHO and ECDC. After titles and abstracts were screened, 96 articles were excluded because they were not relevant to the search. Common reasons for exclusion were the focus on different pathogens (predominantly measles and rubella), subjects belonging to specific employment groups and method analyses. Excluded studies grouped as "other" concerned mostly vaccination effectiveness and safety. The remaining 64 sources were screened again based on the full text, and an additional five studies were excluded: two because they were pertinent to measles and three for "other" reasons, including mumps-associated complications and secondary attach rates, without the inclusion of overall case numbers in the respective outbreaks (see Appendix G for a complete list).

Included were a total of 59 studies and reports. They were separated into groups based on their pertinence to mumps case reports (32) or vaccination coverage (25). One mumps-specific seroepidemiological antibody study and three other reports were included as well because they were relevant to the literature search. A flow diagram of the entire study selection process is provided below in Fig. 3.15.

3.4.2. National Immunization Plans

The nations included in this report all recommend or mandate the vaccination against mumps as part of two-dosage MMR immunization schemes. Table 3.8 on Page 65 shows the ages at which children are scheduled to receive both MMR dosages in their respective countries of residency.

As stated in Section 1.3.2, the WHO recommends that both mumps-containing vaccine dosages are provided for children before entry into the school system (at age 5 to 7 years, see Section 3.1.5).[300] This recommendation is not reflected in the immunization plans of all countries, however. Second-dosage immunizations are provided at a later time for children residing in Sweden, Croatia, Turkey and

Poland. Nonetheless, with the exception of Poland, these nations do provide in-school immunizations during the first grade level and allow for an early protection among the respective school-aged populations.[25,39,272] Poland is the only country in which the full vaccination coverage is not scheduled until the age of 10 years.[18] Section 3.3.2 provides further details.

3.4.3. Surveillance Systems

Mumps is a mandatory notifiable disease in most of the European nations included in this report.[49,110] Clinical cases are reported through physicians or hospitals in Croatia, Greece, Italy, Poland, Spain, Sweden, Turkey and the UK.[110] In addition, laboratories in Greece, Sweden and the UK notify local health authorities about the detection of mumps viruses.[110]

Non-mandatory surveillance systems exist in Austria and France. In Austria, only confirmed mumps cases are reported by laboratories on a voluntary basis; clinical cases are not notified.[109,110] In France, a sentinel surveillance system exists, based on which the annual disease occurrences are estimated.[2–4,8,14,15,20,49] The case statistics from these nations are thus difficult to analyze and compare with those of other countries (see Section 3.4.4 below).

Until 2013, mumps cases in Germany were reported by only 5 of 16 federal states, formerly belonging to the German Democratic Republic. As of April 2013, the infection protection act (*Infektionsschutzgesetz, IfSG*) was amended to include the mandatory nation-wide monitoring of mumps cases.[159] For the data analysis in this report, only the regionally reported cases occurring between 2006 and 2012 could be included, however.[49,249]

A further indicator of a well-performing surveillance system is the confirmation of clinical mumps cases. Laboratory or epidemiological verification is lacking in many European countries. In 2011, only about 50% of the European-wide reported

cases had been confirmed.[110] Particularly the here included Eastern and Southern European nations (with the exception of Italy) have very low verification rates, as presented in Table 3.16. In Poland, for instance, less than 0.01% of the reported clinical cases are confirmed through laboratory testing. In Greece and Spain, the rates are somewhat higher, but also reach only 13% and 19%, respectively. These inadequate mumps verification rates diminish the quality of the countries' respective surveillance systems.

Efficient surveillance systems, on the other hand, exist in the Northern European nations, Sweden and the UK, as well as in Italy. These countries require the nation-wide reporting of all cases, and the laboratory confirmation rates are high (see Table 3.16).[98,110] Regular active monitoring of mumps infections in addition to the standard passive notification through health care workers and laboratories is performed only in the UK, however.[109,110] All other included nations collect mumps case data passively.[109,110]

Overall, the mumps surveillance systems are adequate in only some of the studied European nations, and could be improved in others through active monitoring and case confirmations. Particularly in Austria and France, mumps occurrences are insufficiently monitored and case numbers therefore likely underreported.

3.4.4. Case Reports and Incidence

Data on mumps cases was obtained from 32 sources, including the WHO, ECDC, and governmental agencies, as shown in Fig. 3.15. The 2006-2012 annual case numbers and incidences for each included nation are presented in Table 3.16. As described in Section 2.4, averages and standard deviations have been calculated where applicable. Annual confirmed cases and hospitalizations are also indicated upon availability. No mumps-related deaths were reported in the indicated time period.[48,49,103,105,106,109,110,189,190]

A total of 208,146 (averaged) mumps infections were reported by the selected European nations between 2006 and 2012. (The full range, including non-averaged reports and the 95%-confidence intervals for the French estimates,[2–4,8,14,15,20] lies between 170,342 and 241,374 cases.) Although a decreasing trend can be observed, from over 57,000 cases in 2006 to about 20,000 cases in 2012, many countries still indicate large outbreak numbers. Poland, Turkey, the UK and Spain each reported recent annual case numbers surpassing 1,000, whereby the latter indicated the by far highest number with more than 9,500 cases in 2012 (see Table 3.16). France also estimates that over 10,000 residents were infected with mumps in recent years (2010-2012).[15,20]

Data on mumps cases occurring in 2013 was available for only three of the included nations: Germany reported 577 cases,[249] Sweden 47[274] and Greece none.[138] In comparison to the previous year, the case number in Germany had increased more than 10-fold. However, this tremendous increase can be explained by the new regulation requiring a nation-wide mumps surveillance as of 2013 (see Section 3.4.3, above). The number of infections observed in Sweden and Greece were in line with those reported during previous years.

Both Sweden and Greece also had the consecutively lowest annual mumps incidences of <1.00/100,000 between 2006 and 2012.[138,274,326] (Austria and Germany were not included in the analysis, as the correct and nation-wide mumps occurrences are unknown.) Italy and Croatia reported moderately low incidences <5.00/100,000 as well.[22,109,110,186,326] Turkey has seen a sharp decrease in the annual mumps incidences in recent years, from nearly 30/100,000 in 2006 to 2.20/100,000 in 2011. In Spain, on the other hand, an increase from a low of 4.08/100,000 in 2009 to a high of 20.64/100,000 in 2012 was observed. Poland has had a steady mumps incidence of 6-9/100,000 since 2008. Further details are shown in Table 3.16.

The number of mumps-related hospitalizations and complications were reported for Italy, Poland, the UK and, to some extend, Greece. Among these four countries, a total of 1,504 mumps cases required hospitalization in the past years. According to an-

nual reports by the ECDC[103,105,106,109,110] and the former EUVAC.NET,[48,49,189,190] the overall hospitalization rate in Europe has ranged from 4% to 12% and the complication rate from 1% to 13% between 2006 and 2011. The most common complications were orchitis (61%) and meningitis (15%).[110]

Male children and adults are more frequently affected by mumps than females are. The European-wide male-to-female ratio has ranged between 1.2 and 1.4 in recent years.[103,105,109,110] This pattern is generally observed across all age groups.[103,105,106,109,110]

The age distribution of mumps cases has changed over the course of the past decade. Between 2000 and 2007, the predominantly affected age group in Europe was 5 to 9 years old (39.1%), followed by the 10- to 14-year-old age group (25.5%).[190] Since 2008, a general shift to older age groups has been documented. In 2009-2011, most cases were seen among the 15- to 24-year-old population.[106,109,110] The currently higher susceptibility among adolescents and adults is further addressed below in the Section 3.4.6.

Unlike studies regarding measles and rubella, no recent reports on mumps cases among migrant populations were found in the literature search. However, the susceptibility among immigrants and travelers is delineated below.

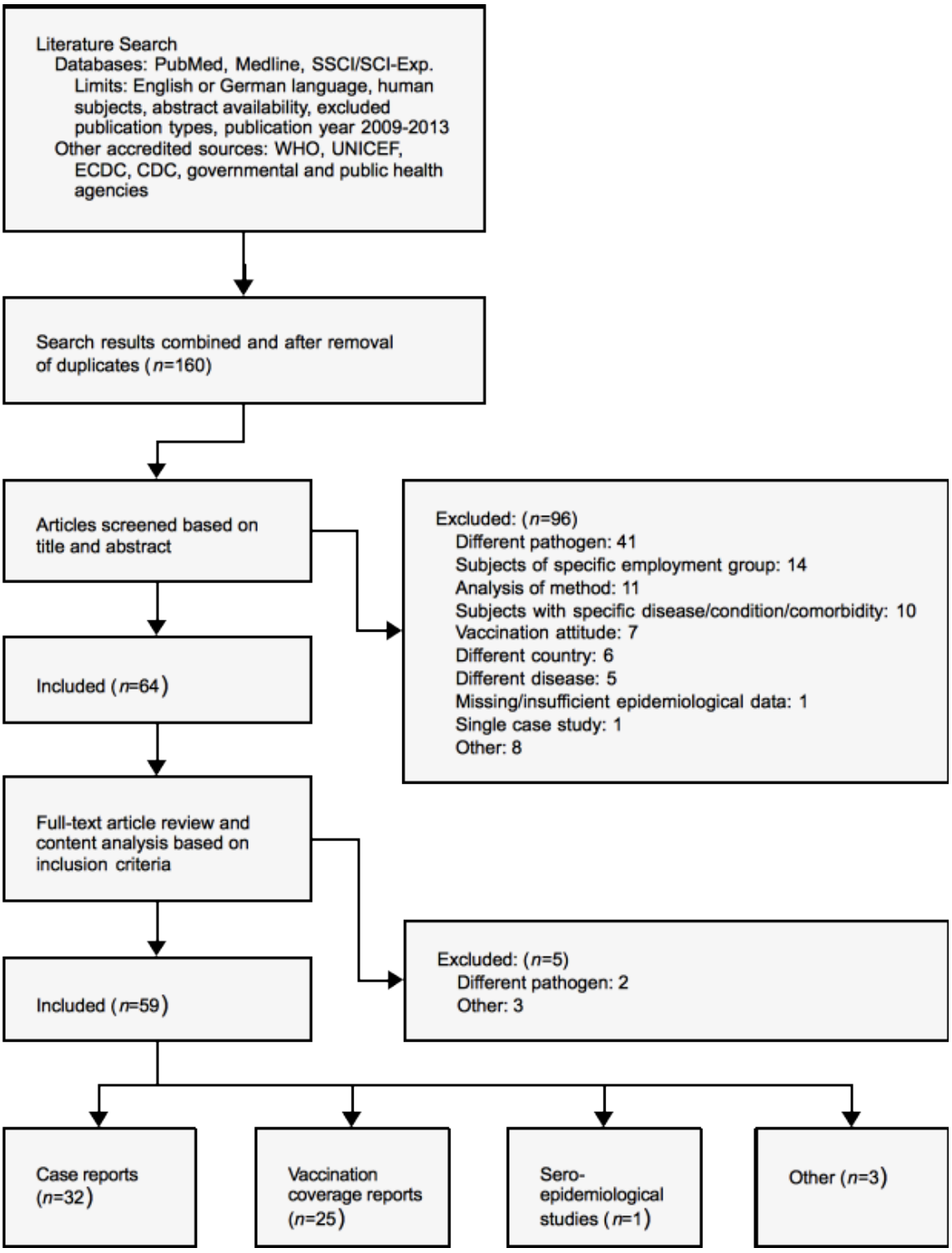

Figure 3.15. Publication Selection Flow Diagram: Mumps. The mumps-specific literature search selection process is shown. The inclusion and exclusion criteria described in Appendix A were employed. Figure adapted from Liberati et al., *The Prisma Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration*, Figure 1.[164]

Reported Mumps Cases by Nation and Year, 2006-2012

Source(s)	Country	Year(s)	Number of Cases Reported				Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Hospitalized			
	Austria	**2006-2013**	**310**		**310** (100%)	**-**			
		2012	-	-	-	-	-	Lab (V, E)	Weak
ECDC, 2013[110]		2011	25	-	25	-	0.30	Lab (V, E)	Weak
ECDC, 2012[109]		2010	15	-	15	-	0.18	Lab (V, E)	Weak
ECDC, 2011[106]		2009	14	-	14	-	0.17	Lab (V, E)	Weak
ECDC, 2010[105]		2008	22	-	22	-	0.26	Lab (V, E)	Weak
ECDC, 2009[103]		2007	7	-	7	-	0.08	Lab (V, E)	Weak
ECDC, 2012[109]		2006	227	-	227	-	2.75	Lab (V, E)	Weak
	Croatia	**2006-2013**	**519**		**6** (1%)	**-**			
HZJZ, 2012,[22] WHO, 2013[326]		2012	95	-	-	-	2.23	Sur (M)	Strong
HZJZ, 2012,[22] WHO, 2013[326]		2011	86	-	-	-	2.01	Sur (M)	Strong
EUVAC.NET, 2011,[49] HZJZ, 2012,[22] WHO, 2013[326]		2010	39	2.1	0	-	0.87	Sur (M)	Strong
EUVAC.NET, 2010,[48] HZJZ, 2012,[22] WHO, 2013[326]		2009	57	0.7	0	-	1.28	Sur (M)	Strong
EUVAC.NET, 2009,[189] HZJZ, 2012,[22] WHO, 2013[326]		2008	102	12.0	6	-	2.29	Sur (M)	Strong
EUVAC.NET, 2008,[190] HZJZ, 2012[22]		2007	75	1.4	0	-	1.69	Sur (M)	Strong
EUVAC.NET, 2007,[190] HZJZ, 2012[22]		2006	66	0.0	0	-	1.49	Sur (M)	Strong
	France	**2006-2013**	**47,195**		**-**	**-**			
Réseau Sentinelles, 2012[20]		2012	3,729[a]	-	-	-	5.68	Sur (S, E)	Moderate
Réseau Sentinelles, 2011[15]		2011	5,841[a]	-	-	-	8.94	Sur (S, E)	Moderate

Reported Mumps Cases by Nation and Year, 2006-2012

Source(s)	Country	Year(s)	Number of Cases Reported				Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Hospitalized			
Réseau Sentinelles, 2010[14]		2010	6,144[a]	-	-	-	9.45	Sur (S, E)	Moderate
Réseau Sentinelles, 2009[8]		2009	11,106[a]	-	-	-	17.16	Sur (S, E)	Moderate
Réseau Sentinelles, 2008[4]		2008	4,876[a]	-	-	-	7.57	Sur (S, E)	Moderate
Réseau Sentinelles, 2007,[3] WHO, 2013[326]		2007	7,999[a]	1.4	-	-	12.50	Sur (S, E)	Moderate
Réseau Sentinelles, 2006[2]		2006	7,500[a]	-	-	-	11.79	Sur (S, E)	Moderate
	Germany	**2006-2013**	**906**		**-**	**-**			
RKI, 2013[249]		2012	48	-	-	-	0.06	Sur (R, E)	Weak
RKI, 2013[249]		2011	197	-	-	-	0.24	Sur (R, E)	Weak
RKI, 2013[249]		2010	195	-	-	-	0.24	Sur (R, E)	Weak
RKI, 2013[249]		2009	99	-	-	-	0.12	Sur (R, E)	Weak
RKI, 2013[249]		2008	215	-	-	-	0.26	Sur (R, E)	Weak
RKI, 2013[249]		2007	78	-	-	-	0.09	Sur (R, E)	Weak
RKI, 2013[249]		2006	74	-	-	-	0.09	Sur (R, E)	Weak
	Greece	**2006-2013**	**101**		**13** (13%)	**22**			
HCDCP, 2013,[138] WHO,2013[326]		2012	2	0.0	-	-	0.02	Sur (M)	Strong
ECDC, 2013,[110] HCDCP,[138] WHO, 2013[326]		2011	1	0.0	0	-	0.01	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2011,[49] WHO, 2013[326]		2010	2	0.0	2	0	0.02	Sur (M)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[48] WHO, 2013[326]		2009	21	0.6	3	20	0.18	Sur (M)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[189] WHO, 2013[326]		2008	5	0.0	2	2	0.04	Sur (M)	Strong
ECDC, 2009,[103] EUVAC.NET, 2008[190]		2007	23	0.0	3	-	0.21	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2007[190]		2006	47	-	3	-	0.42	Sur (M)	Strong

Reported Mumps Cases by Nation and Year, 2006-2012

Source(s)	Country	Year(s)	Number of Cases Reported				Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Hospitalized			
	Italy	**2006-2013**	**6,512**		**6,736** (100%)	**197**			
WHO, 2013[326]		2012	322	-	-	-	0.53	Sur (M)	Strong
ECDC, 2013,[110] WHO, 2013[326]		2011	761	48.8	758	-	1.25	Sur (M)	Strong
ECDC, 2012,[109] Ministero della Salute, 2013,[186] EUVAC.NET, 2011,[49] WHO, 2013[326]		2010	579[b]	94.9	721	14	0.96	Sur (M)	Strong
ECDC, 2011,[106] Ministero della Salute, 2013,[186] EUVAC.NET, 2010,[48] WHO, 2013[326]		2009	999	158.1	1,103	47	1.66	Sur (M)	Strong
ECDC, 2010,[105] Ministero della Salute, 2013,[186] EUVAC.NET, 2009,[189] WHO, 2013[326]		2008	1,167	257.6	1,387	21	1.95	Sur (M)	Strong
ECDC, 2009,[103] Ministero della Salute, 2013,[186] EUVAC.NET, 2008[190]		2007	1,312	0.0	1,312	52	2.21	Sur (M)	Strong
ECDC, 2012,[109] Ministero della Salute, 2013,[186] EUVAC.NET, 2007,[190] WHO, 2013[326]		2006	1,373	142.6	1,455	63	2.33	Sur (M)	Strong
	Poland	**2006-2013**	**33,605**		**24** (<1%)	**893**			
WHO, 2013[326]		2012	2,779	-	-	-	7.21	Sur (M)	Strong
ECDC, 2013,[110] NIZP, 2012[87]		2011	2,585	0	0.0	24	6.71	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2011,[49] NIZP, 2012,[87] WHO, 2013[326]		2010	2,754	0.0	3	32	7.21	Sur (M)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[48] NIZP, 2010,[86] WHO, 2013[326]		2009	2,954	0.0	1	35	7.74	Sur (M)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[189] NIZP, 2010[86]		2008	3,271	0	0.0	37	8.58	Sur (M)	Strong
ECDC, 2009,[103] EUVAC.NET, 2008,[190] NIZP, 2008,[85] WHO, 2013[326]		2007	4,147	0.0	0	109	10.88	Sur (M)	Strong

Reported Mumps Cases by Nation and Year, 2006-2012

Source(s)	Country	Year(s)	Number of Cases Reported				Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Hospitalized			
ECDC, 2012,[109] EUVAC.NET, 2007,[190] NIZP, 2008,[85] WHO, 2013[326]		2006	15,115	0.0	20	656	39.63	Sur (M)	Strong
	Spain	**2006-2013**	**36,269**		**6,893** (19%)	**-**			
ISCIII,[142] WHO, 2013[326]		2012	9,539	0.7	-	-	20.64	Sur (M)	Strong
ECDC, 2013,[110] ISCIII,[142] WHO, 2013[326]		2011	3,686	1,440.2	794	-	7.98	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2011,[49] ISCIII,[142] WHO, 2013[326]		2010	2,272	620.4	315	-	4.93	Sur (M)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[48] ISCIII,[142] WHO, 2013[326]		2009	1,874	510.8	185	-	4.08	Sur (M)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[189] ISCIII,[142] WHO, 2013[326]		2008	3,501	597.5	1012	-	7.68	Sur (M)	Strong
ECDC, 2009,[103] EUVAC.NET, 2008,[190] ISCIII,[142] WHO, 2013[326]		2007	8,543	3,597.0	3147	-	19.03	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2007,[190] ISCIII,[142] WHO, 2013[326]		2006	6,856	50.8	1440	-	15.54	Sur (M)	Strong
	Sweden	**2006-2013**	**284**		**225** (79%)	**-**			
SMI, 2013,[274] WHO, 2013[326]		2012	33	0.0	-	-	0.35	Sur (M)	Strong
ECDC, 2013,[110] SMI, 2013,[274] WHO, 2013[326]		2011	38	0.0	30	-	0.40	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2011,[49] SMI, 2013,[274] WHO, 2013[326]		2010	24	0.0	16	-	0.26	Sur (M)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[48] SMI, 2013,[274] WHO, 2013[326]		2009	33	1.0	21	-	0.35	Sur (M)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[189] SMI, 2013,[274] WHO, 2013[326]		2008	52	0.6	51	-	0.56	Sur (M)	Strong
ECDC, 2009,[103] EUVAC.NET, 2008,[190] SMI, 2013,[274] WHO, 2013[326]		2007	47	0.5	47	-	0.51	Sur (M)	Strong

Reported Mumps Cases by Nation and Year, 2006-2012

Source(s)	Country	Year(s)	Number of Cases Reported				Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Hospitalized			
ECDC, 2013,[110] EUVAC.NET, 2007,[190] SMI, 2013,[274] WHO, 2013[326]		2006	58	1.7	60	-	0.64	Sur (M)	Strong
	Turkey	**2006-2013**	**51,166**		**-**	**-**			
WHO, 2013[326]		2012	-	-	-	-	-		
WHO, 2013[326]		2011	1,609	-	-	-	2.20	Sur (M)	Strong
EUVAC.NET, 2011,[49] WHO, 2013[326]		2010	1,525	0.0	-	-	2.11	Sur (M)	Strong
EUVAC.NET, 2010,[49] WHO, 2013[326]		2009	2,268	123.7	-	-	3.18	Sur (M)	Strong
WHO, 2013[326]		2008	9,514	-	-	-	13.52	Sur (M)	Strong
WHO, 2013[326]		2007	16,524	-	-	-	23.78	Sur (M)	Strong
WHO, 2013[326]		2006	19,726	-	-	-	28.74	Sur (M)	Strong
	UK	**2006-2013**	**31,280**		**27,235** (98%)	**392**			
HPS, 2013,[135,136] PHE, 2013,[233] WHO, 2013[326]		2012	3,282[b]	147.1	-	-	5.19	Sur (M)	Strong
HPS, 2013,[135,136] PHE, 2013,[233] ECDC, 2013,[110] WHO, 2013[326]		2011	2,834	206.1	2,714	-	4.52	Sur (M)	Strong
DHSSPS, 2013,[16] HPS, 2013,[135,136] PHE, 2013,[233] ECDC, 2012,[109] EUVAC.NET,[49] WHO, 2013[326]		2010	4,537	258.3	4,383	78	7.29	Sur (M)	Strong
DHSSPS, 2013,[16] HPS, 2013,[135,136] PHE, 2013,[233] ECDC, 2011,[106] EUVAC.NET,[48] WHO, 2013[326]		2009	8,676	603.1	8,663	152	14.04	Sur (M)	Strong
DHSSPS, 2013,[16] HPS, 2013,[135,136] PHE, 2013,[233] ECDC, 2010,[105] EUVAC.NET,[189] WHO, 2013[326]		2008	2,743	356.4	2,644	36	4.47	Sur (M)	Strong
DHSSPS, 2013,[16] HPS, 2013,[135,136] PHE, 2013,[233] ECDC, 2009,[103] EUVAC.NET,[190] WHO, 2013[326]		2007	3,086	865.8	2,702	35	5.06	Sur (M)	Strong

Reported Mumps Cases by Nation and Year, 2006-2012

Source(s)	Country	Year(s)	Number of Cases Reported				Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Hospitalized			
DHSSPS, 2013,[16] HPS, 2013,[135,136] PHE, 2013,[233] ECDC, 2009,[103] EUVAC.NET,[190] WHO, 2013[326]		2006	6,124	1,259.0	6,129	91	10.11	Sur (M)	Strong
	TOTAL	**2006-2012**	**208,146**		**41,442**	**1,504**	**-**		
		2012	**19,829**		**-**	**-**	**4.27**		
		2011	**17,663**		**4,321**	**24**	**3.82**		
		2010	**18,085**		**5,455**	**124**	**3.94**		
		2009	**28,099**		**9,990**	**254**	**6.14**		
		2008	**25,466**		**5,124**	**96**	**5.60**		
		2007	**41,840**		**7,218**	**196**	**9.25**		
		2006	**57,165**		**9,334**	**810**	**12.72**		

* Case numbers have been average and the standard deviation (SD) calculated where applicable to indicate variance in national reporting.

• Cases either laboratory confirmed (mumps-specific antibodies or PCR) or epidemiologically linked to a laboratory-confirmed case. When variance in reporting occurred, the larger of the numbers was included.

† Reporting method: *Lab*: data provided by laboratories; *Sur*: data obtained through surveillance systems; M = mandatory, V = voluntary, R = regional data, S = sentinel surveillance data, E = errors in reporting known or likely.

[a] Estimates

[b] Provisional data

Abbreviations: *DHSSPS*: Department of Health, Social Services and Public Safety (Northern Ireland); *ECDC*: European Center for Disease Prevention and Control; *HCDCP*: Hellenic Center for Disease Control & Prevention (Greece); *HPS*: Health Protection Scotland; *HZJZ*: Hrvatski Zavod za Javno Zdravstvo (Croatia, National Institute of Public Health); *ISCIII*: Instituo de Salud Carlos III (Spain); *NIZP*: Narodowy Instytut Zdrowia Publicznego (Poland, National Institute of Public Health); *PHE*: Public Health England; *RKI*: Robert Koch Institut (Germany); *SMI*: Smittskyddsinstitutet (Sweden, Institute for Infectious Disease Control); *WHO*: World Health Organization (Centralized Information System for Infectious Diseases).

Table 3.16. Reported Mumps Cases by Nation and Year, 2006-2012. The annually reported mumps cases for each selected nation are shown, including the total number of notified cases, confirmed cases, and hospitalizations. Due to variances in reporting by different sources, the mean total case number and standard deviations (SD) have been calculated, as indicated. Annual mumps incidences have been calculated based on the average total number of reported cases per 100,000 population (source of population data: *The World Bank: DataBank: World Development Indicators, 2013*[285]). The quality of the included sources has been assessed as follows: case-based data reports by the WHO, ECDC and governmental agencies were assumed to be accurate and assigned a "strong" quality; estimates and sentinel data reports were assigned a "moderate" quality; voluntary data reports and non-national data were assigned a "weak" quality.

3.4.5. Vaccination Coverage

As for measles, two dosages of a mumps-containing vaccine are necessary for an adequate immunity against the disease and its complications.[300] In order to reach a sufficient population immunity to eliminate the disease entirely, a second-dosage MMR vaccination coverage of $\geq$95% is recommended.[300,301]

The national mumps immunization rates closely match those for measles, as both diseases are co-vaccinated in all the included countries. Tables 3.12 and 3.13 on Pages 97 and 98 show each nation's primary and secondary dosage immunization coverages for the years 2006-2012. When the vaccination rate was unknown for a specific year, official WHO and UNICEF estimates were indicated instead, as shown.[312,324] Regional trends in immunization coverage over time are illustrated in Figs. 3.12 and 3.13. Further details are provided in the measles subsection *Vaccination Coverage* (Section 3.3.6).

3.4.6. Sociodemographic Factors Influencing Mumps Susceptibility

The literature search revealed 26 studies regarding mumps immunization coverage and antibody seroprevalence in the selected European countries. Various population indicators are analyzed below in terms of mumps susceptibility: age, gender, educational status, socioeconomic status, and migratory background. (No mumps-specific studies assessing the influence of urban or rural residency were found through the literature search.)

Age As noted above, a change in age-related mumps susceptibility has been observed over the course of the past ten years. Whereas young school-aged children typically have the highest risk of infection in unvaccinated populations, adolescents

and young adults are more likely to develop a mumps infections in insufficiently vaccinated populations, as is the case in most of the included European nations.[110,159]

Table 3.17 shows the mumps-specific vaccination coverages among children and adolescents of different age groups (1-5 years, 6-14 years, and 15-19 years) in France, Germany and Poland. All other countries report combined MMR coverages, which are included in Table 3.14 in Section 3.3.7.

Due to the limited amount of data, no clear trends suggesting lower vaccination rates among older children and adolescents can be observed. In the German KiGGS study (see Section 3.3.7 for details), a lower mumps vaccination rate was reported among adolescents 14 to 17 years of age compared to children 7 to 13 years of age.[226] However, no such differences could be observed in Poland (see Table 3.17).[94]

The vaccination coverages among school-aged children in Poland do suggest that older birth cohorts were not vaccinated sufficiently, however. In 2006, as little as 44.6% of children aged 6 to 14 years had been vaccinated with a mumps-containing vaccine.[88] In some regions, the immunization rate was a low as 2%.[88] Complete two-dosage vaccinations were received by only 14.6% (regional range: 0%-54%).[88] A high susceptibility among these former students (now young adults) is likely, should catch-up immunizations have been missed.

Other studies regarding the susceptibility among adolescents have been addressed in Section 3.3.7. Among them, the Greek study by Sakou et al.[259] revealed a significant difference in MMR-2 immunization coverage among adolescents aged 15 to 19 years compared to those aged 11 to 14 years. Similar differences described by the authors of other studies were not significant, however (see Section 3.3.7 for details).

Mumps seroprevalence, assessed as part of the German KiGGS study, found similar results among 13,930 participants between the ages of 1 and 17 years. The highest susceptibility was discovered among young children aged 1 to 2 years (26.4% seronegative), as expected due to low vaccination coverage among this age group, followed by 11 to 13 year-old children (15.1% seronegative).[227] Adolescents, aged 14

to 17 years, also had a considerably high susceptibility (14.8% seronegative).[227] Pre-school-aged children (3 to 6 years old) and young school-aged children (7 to 10 years old), on the other hand, were the least susceptible (13.5% and 13.3% seronegative, respectively).[227] In spite of this age-related trend, the differences in seroprevalence among participants older than 3 years were not significant. Nonetheless, the recently described increases in cases among adolescents do suggest a higher risk of infection among this age group.[106,109,110,159]

Mumps Vaccination Coverage, by Age Group and Vaccination Dosage

Source(s)	Country	Age	Vaccination Coverage (%) according to Year and Mumps Dosage (Range, if available)												Quality
			2012		2011		2010		2009		2008		2007		2006		
			D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	
	France																
InVS, 2011[144]		1-5 Years	-	-	89.4* (76–96)	67.3* (46–83)	89.2* (76–96)	60.9* (29–74)	-	-	88.1* (78–95)	-	89.3* (81–95)	-	87.8* (76–95)	-	Moderate
InVS, 2011[144]		6-14 Years	-	-	-	-	-	-	-	-	-	-	-	-	91.2 (85–97)	-	Moderate
	Germany																
Poethko-Müller et al., 2007,[226] RKI, 2009-2013[240–243, 246]		1-5 Years	-	-	96.3[a] (94–98)	91.9[a] (86–96)	96.1[a] (94–98)	91.2[a] (87–95)	95.8[a] (94–98)	90.0[a] (85–95)	95.6[a] (93–98)	88.8[a] (84–94)	95.1 [a] (93–98)	88.1[a] (82–94)	93.4	68.8	Strong Strong
Poethko-Müller et al., 2007&2009[223, 226]		6-14 Years	-	-	-	-	-	-	-	-	-	-	-	-	94.1[b]	76.3[b]	Strong
Poethko-Müller et al., 2007[226]		15-19 Years	-	-	-	-	-	-	-	-	-	-	-	-	92.3	70.8	Strong
	Poland																
NIZP, 2006-2013[88–94]		1-5 Years	95.9 (82–100)	-	96.0 (79–100)	-	96.0 (83–100)	-	95.8 (79–100)	-	95.1 (80–100)	-	85.7 (79–100)	-	74.0 (31–100)	-	Strong
NIZP, 2006-2013[88–94]		6-14 Years	99.4 (99–100)	73.1[c] (42–100)	98.3 (98–100)	64.5[c] (32–100)	92.5 (40–100)	55.4[c] (28–100)	80.2 (33–100)	44.6[c] (9–100)	68.1 (30–100)	35.2[c] (5–99)	59.3 (30–100)	25.8[c] (3–99)	44.6 (2–99)	14.6[c] (0–54)	Strong
NIZP, 2006-2013[88–94]		15-19 Years	99.4 (99–100)	77.0 (52–100)	-	-	-	-	-	-	-	-	-	-	-	-	Strong

Note: InVS: Institut de Veille Sanitaire (Institute for Public Health Surveillance, France); *NIZP*: Narodowy Instytut Zdrowia Publicznego (National Institute of Public Health, Poland); *RKI*: Robert Koch Institute (Germany).

* Estimates

[a] Data collected from vaccination records prior to school entry, children 4-7 years of age are included.

[b] Age groups 7-10 and 11-13 years are included (2003-2006).

[c] Coverage among children aged ≥10 years (the mandatory MMR-2 vaccination age in Poland).

Table 3.17. Mumps Vaccination Coverage, by Age Group and Vaccination Dosage. Available annual immunization rates with either one or two mumps dosages are provided for France, Germany and Poland. The coverage rates are shown for pre-school-aged (1 to 5 years old) and school-aged (6 to 14 years old) children as well as adolescents (15 to 19 years old). Reporting variances by region are shown upon availability. The quality of included studies and reports has been assessed according to the criteria described in Chapter 2 and Appendix D. Official data reports by governmental agencies were assumed to be accurate and assigned a "strong" quality; estimates were assigned a "moderate" quality.

Gender The role of gender in influencing mumps susceptibility was addressed only by the German KiGGS study.[226,227] A non-significant difference in primary dosage mumps vaccination was observed among very young children <15 months of age: 10.1% of girls and 7.9% of boys were immunized.[226] Children and adolescents between the ages of 2 and 17 years had equal mumps coverage rates, however: 93.0% among females and 93.1% among males.[226] The secondary dosage coverage was also very similar, with respective vaccination rates of 71.8% and 72.2%.[226]

The mumps IgG titers determined as part of the KiGGS study revealed slightly larger gender differences. The susceptibility among males was with a 16% seronegativity rate somewhat higher than among females, with a 14.6% seronegativity rate.[227] More males also had borderline mumps IgG titers than their female counterparts did (6.9% vs. 5.5%).[227] These differences were not significant, however (p=0.037).[227]

In spite of the higher mumps occurrence among males residing in Europe (see Section 3.4.4 above), no recent studies describing a clear gender difference in vaccination rates or susceptibility were found.

Education The effect of parental education on mumps susceptibility was also analyzed solely by the KiGGS study.[227] A 2% lower mumps susceptibility (IgG seronegativity) was found among children of mothers with a medium educational level (10^{th} grade completion) compared to those with mothers of a high (university) or low ($8^{th}/9^{th}$ grade completion) educational status.[227] In a multivariate analysis, the impact of maternal education was not found to be significant, however (p=0.055).[227]

Other studies that have assessed either MMR or general vaccination coverage in terms of parental education are described in Section 3.3.6. No clear trend could be observed, suggesting that education has little to no effect on the mumps infection risk.

Socioeconomic Status A slight but significant correlation between SES and mumps susceptibility was described for the KiGGS study participants by Poetko-Müller et al.[226] Children and adolescents of families with a high SES had a significantly lower vaccination coverage than children of families with a low or medium SES had (91.0% vs. 94.3% and 93.7%, respectively; $p<0.05$).[226] Studies conducted in other countries in regard to measles-containing vaccines or general immunization coverage found no such associations with the parental SES, however. Due to the limited availability of mumps-specific studies, a clear correlation between SES and mumps susceptibility can not be determined.

Migration Three studies analyzed the mumps susceptibility among migrants living in the selected European countries. Two of these studies were conducted in Greece regarding the overall vaccination status of migrants;[215,259] they are described in Section 3.3.6. A slightly higher risk of infection among study participants with a migratory background was determined by the authors of both articles.

The German KiGGS study, on the other hand, found no significant difference between the vaccination coverage of children and adolescents with or without a migratory background.[226] A higher mumps susceptibility among migrants due to lower secondary dosage vaccination coverage was only observed among the adolescent age group (14 to 17 years old).[226] The mumps IgG seroprevalence study revealed that both first-generation (foreign-born) and second-generation (German-born) migrants were slightly more susceptible to measles than non-immigrant children and adolescents were (respective seronegativity rates: 18.7%, 16.0%, 14.8%).[227] These differences were not significant in a multivariate analysis, though ($p=0.152$).[227]

As for the sociodemographic factors gender, education and socioeconomic status, no definite correlation between immigration and mumps infection risk can be determined. Age is the only factor that clearly influences the level of mumps susceptibility.

3.4.7. Effects of Migration within Europe

Insufficient studies regarding the mumps susceptibilities of migrants in Europe exist. The small number of studies described above suggest that the infection risks between native and foreign residents do not differ significantly, but exact reports have not been made. Nonetheless, mumps, like measles, is a communicable disease that may be transmitted within Europe through travel and migration.

In Fig. 3.14, the estimated measles susceptibilities of children and adolescents migrating from selected European nations to Germany are depicted. The same values have been determined for mumps susceptibilities, as the MMR-2 coverage rates for both diseases are equal (see Section 3.3.8 for details). However, the much higher mumps incidences in several of the included nations increase the probability of international disease transmission. Compared to measles incidences, the mumps incidences are substantially higher in Croatia (32-fold), France (4-fold), Poland (42-fold) and Spain (10-fold). In Fig. 3.16, each nation's 2012 incidences and coverage rates among immigrants below the age of 18 years are shown.

In order to effectively prevent the transmission of mumps within Europe, efforts must be made to better control the disease in all European nations. Particularly those countries with large outbreak numbers could reduce the disease burden through consequent measles, mumps and rubella vaccinations, as will be further addressed in Chapter 4 below.

3.4.8. Rating of Vaccination Programs

The selected European nations have different mumps immunization programs that vary in effectiveness. They have been objectively graded based on the criteria described in the Materials and Methods Section 2.4. Program performance indicators include the annual disease incidences and vaccination coverage rates as well as the

quality of national surveillance systems. Table 3.18 provides and overview of these indicators.

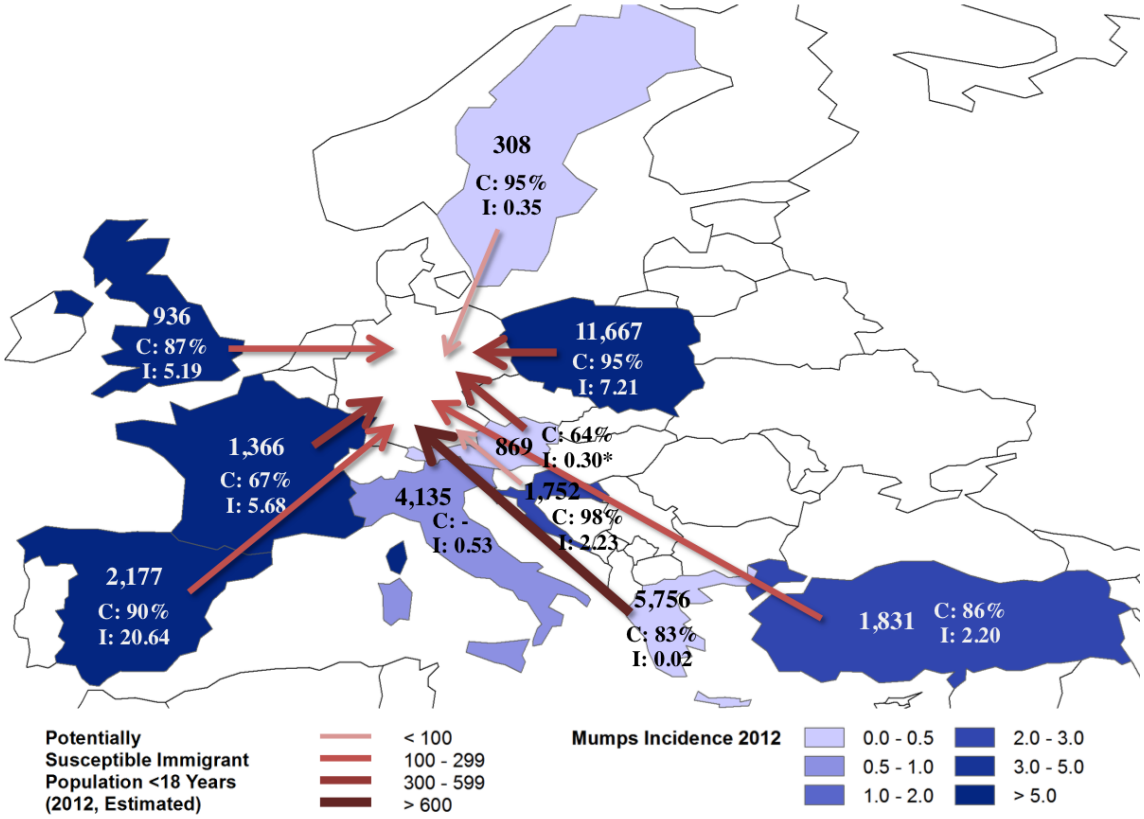

Figure 3.16. Migratory Flows and Potential Mumps Susceptibilities Among Immigrant Children and Adolescents in Germany, 2012. In 2012, a total of 30,799 children and adolescents (<18 years) immigrated to Germany from the indicated European nations. The migrant population size of each country is shown, along with the respective national mumps second-dosage vaccination coverage (C) and incidence per 100,000 population (I). All data are for 2012 or the most recent year available (2011 coverages for Croatia and Turkey; 2009 coverages for Austria). Nations with uncertain mumps incidences due to known or likely errors in reporting have been marked with an asterisk (∗). The estimated numbers of susceptible children and adolescents are represented by arrows of varying strengths, whereby the national coverage rates have been applied to determine the likely numbers of insufficiently immunized individuals. The lowest populations of susceptible children likely arrived from Croatia and Sweden, the highest from Greece. Mumps transmission rates are anticipated to be highest from nations with high incidences, including France, Poland, Spain, and the United Kingdom. ***Source***: *Statistisches Bundesamt Deutschland, 2014*.[33] For mumps incidence and coverage sources see Tables 3.13 and 3.16. Geographic data obtained from www.naturalearthdata.com.

Comparison of National Mumps Vaccination and Surveillance Programs

Nation	Incidence 2006-2012 (per 100,000)			2-Dose Vaccination Coverage 2012 (%)		Mandatory National Surveillance	Reporting Errors	Grading Level
	Mean	Min	Max	Age 1-5	Age 6-14			
Austria	0.62	0.08	2.75	89[a]	84[a]	No	Yes	4*
France	10.44[b]	5.68[b]	17.16[b]	67.3[c]	-	No	Yes	5*
Germany	1.03[d]	0.38[d]	1.72[d]	91.9[c]	-	Yes[e]	Yes[e]	3*
Greece	0.13	0.01	0.42	63.7[c]	-	Yes	No	3
Italy	1.56	0.53	2.33	-	-	Yes	No	4
Spain	11.41	4.08	20.64	90.3	-	Yes	Unknown	3
Sweden	0.44	0.26	0.64	-	95.1	Yes	No	3 (2)
UK	7.24	4.47	14.04	88.2	-	Yes	No	4
Croatia	1.69	0.87	2.29	-	97.0	Yes	Unknown	4 (2)
Poland	12.57	6.71	39.63	-	73.1	Yes	Unknown	5 (5)
Turkey	12.26	2.11	28.74	-	86[c,f]	Yes	Unknown	5 (4)

[a] 2009 vaccination coverage data.
[b] Incidence based on sentinel surveillance estimates.
[c] 2011 vaccination coverage data.
[d] Incidence based on 2012 regional population of those German federal states reporting mumps cases 2006-2012. Source: Federal Statistical Office, Wiesbaden, Germany (Statistisches Bundesamt).[278]
[e] Sub-national surveillance until April of 2013.
[f] WHO/UNICEF estimate.
* Grade level refers only to vaccination coverage data due to inadequate disease surveillance or under-reporting of cases.

Table 3.18. Comparison of National Mumps Vaccination and Surveillance Programs. The included nations' immunization programs are summarized in terms of key performance indicators. Recent average annual incidences and ranges (2006-2012) as well as the average vaccination coverages among 1-5 year and 6-14 year age groups (2012 or most recent available) are shown. Surveillance system performance is indicated by presence of mandatory surveillance (yes/no) and errors in reporting (yes/know/unknown). Grading level was determined according to the criteria described in Section 2.4, whereby deviations for countries recommending the secondary dosage vaccination among school-aged children (6-14 years of age) are shown in parentheses. ***Sources***: *Bacci, 2010&2011 (EUVAC.NET)*,[48,49] *ECDC Annual epidemiological reports on communicable diseases in Europe, 2009-2013*.[103,105,106,109,110] (For incidence and vaccination coverage data sources see Tables 3.13, 3.14, 3.16 and 3.17.)

For each nation, the average, minimum and maximum annual incidences for the years 2006-2012 have been calculated (see Table 3.16 for details). As only regional data were available for Germany, the total 2012 population of the five federal states reporting mumps cases as of 2012 was used to estimate the incidence.[278] For France, the number of mumps cases estimated through the sentinel surveillance system were used for the incidence calculations.

Nation-wide second-dosage mumps or MMR immunization rates are shown for pre-school-aged and school-aged children. In Croatia, Poland and Sweden, data were available for school-aged children only, as the secondary dosage is provided at later vaccination ages (see Section 3.4.2). For Turkey, only the WHO/UNICEF-estimated

second-dosage vaccination coverage was available. No data was obtained for Italy. As such, the vaccination program grading of all five countries did not include the immunization coverage criteria, as described in Section 2.4. For the three Eastern European nations and Sweden, a second grade was determined using the vaccination rates among school-aged children. These have been indicated in parentheses in Table 3.18.

As described earlier, all nations with the exception of Austria and France have mandatory mumps surveillance systems. The case numbers of both nations are likely under-reported and can not be compared with those of other included countries. The sub-national mumps surveillance in Germany up to the year 2013 also prohibits an adequate comparison with the case numbers reported by the other nations. Mumps vaccination programs in all three countries were therefore graded solely based on the secondary dosage immunization coverage among pre-school-aged children. In Greece, Sweden, Italy and the UK, laboratory surveillance and high case confirmation rates make under-reporting unlikely, though it can not be ruled out entirely. Unknown is whether cases in Spain, Croatia, Poland and Turkey are under-reported. The mumps incidences calculated for these nations have nonetheless been considered in the vaccination program grading, as shown in Table 3.18.

The performance of mumps immunization plans is highest in Germany, Greece, Spain and Sweden. All four nations receive a level 3 grade, suggesting that mumps control in these nations is adequate, but elimination is not yet attained. The national vaccination programs with the least success in recent years were those of France, Poland and Turkey. These three nations receive a level 5 grade due to considerably low immunization rates and high mumps incidences. Although the maximum incidences in Spain and the UK were high as well, both nations have immunization rates that raise their grade to a 4 and 3, respectively.

When vaccination coverage among school-aged children is considered, both Sweden and Croatia receive a level 2 grading, as the immunization rates surpass the 95%-threshold. Turkey's grade is also raised from a 5 to a 4 in this case. In Poland, the

level 5 grade remains, however, due to the low second-dosage immunization coverage below 80%. Additional details are provided in Table 3.18.

Taking all of the performance indicators into consideration, the mumps vaccination program in Sweden was determined to be the most successful. With a 95.1% two-dosage coverage rate and maximum disease incidences of <1/100,000, measured on the basis of a well-performing surveillance system, it most closely matches the WHO disease elimination goals. Although these objectives apply to measles and rubella elimination,[307] they have been adapted here for mumps as well.

3.5. Rubella

As described in the Introduction, the WHO European Region has established the goal of eliminating rubella by the end 2015. A country or region is defined as rubella-free by the WHO if no endemic cases of rubella or congenital rubella syndrome (CRS) have occurred in a period of at least 3 years.[307] A well-established surveillance system is also necessary to meet the elimination criteria.[307] In order to reach this goal, high vaccination coverage is necessary in the entire European region. In this section, studies and reports have been analyzed to determine which of the here included nations has reached the elimination goals and which methods may be best to establish nation-wide rubella and CRS control.

3.5.1. Study and Report Selection

A total of 230 studies and reports on rubella were analyzed regarding vaccination and epidemiological statistics for the countries included in this report. Of these, 131 were found through Pubmed, 57 through Medline, 82 through SSCI/SCI-Expanded and 43 through other sources, such as government agencies. Of all search results, 143 (62%) were excluded because they were not relevant to the search (135 based on title

and abstract and 8 based on the full-text articles). Common reasons for exclusion were studies regarding other pathogens or method analyses. A list of all omitted articles and the respective reasons for exclusion are shown in Appendix G. The 87 remaining studies and reports were split into groups based on their pertinence to either case report data, vaccination coverage, or seroepidemiological susceptibility studies, whereby some studies were selected to be included in multiple groups.

Figure 3.17 shows a flow diagram of the study selection process. The most common reasons for exclusion were studies regarding different pathogens (predominantly measles, n=54), analyses of methods (such as screening or intervention methods, n=19) and studies focusing on specific employment groups (such as health care workers, n=15). Excluded studies classified as "other" pertain to genetic variations in immune response to vaccines (n=11) and vaccination safety (n=2), among others. Of the included literature search results, 35 were rubella or CRS case reports, 35 vaccination coverage reports and 19 seroepidemiological studies. In the following sections, the results of these studies and reports are presented along with other pertinent information regarding the vaccine preventable disease rubella.

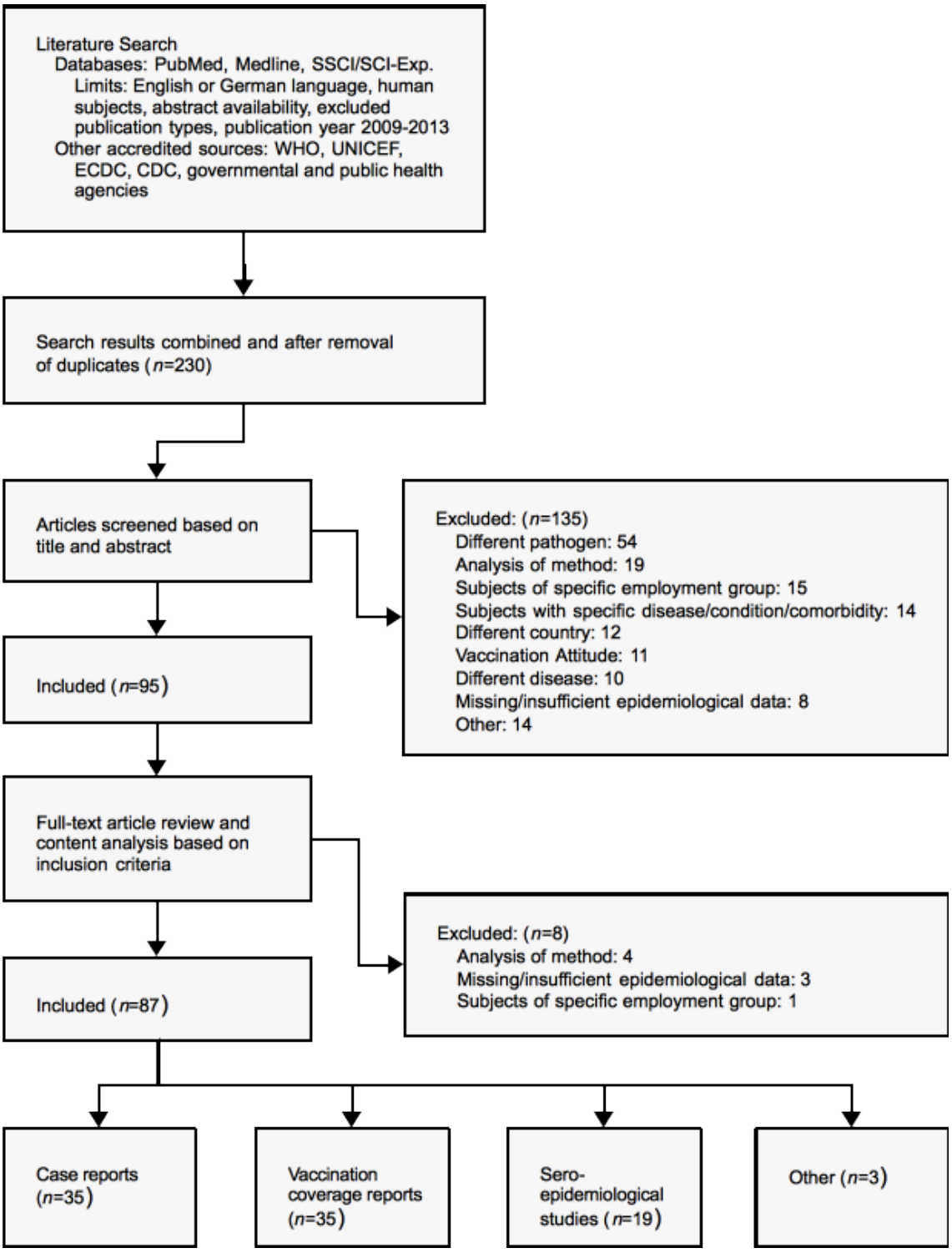

Figure 3.17. Publication Selection Flow Diagram: Rubella. The study and report selection process for publications on rubella is shown. The inclusion and exclusion criteria described in Appendix A were employed. Figure adapted from Liberati et al., *The Prisma Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration*, Figure 1.[164]

3.5.2. National Immunization Plans

Vaccinations against rubella are typically administered in combination with those against measles and mumps. The national immunization schedules for rubella are therefore included in Table 3.8 (*MMR Immunization Schedules for Children (Ages 0-18 Years)*) on Page 65.

As addressed in the Section 1.3.3, most European countries historically vaccinated only girls and young women in order to prevent congenital rubella infections. Over the course of the past decades, the immunization strategy was changed to include children of both sexes, thus attempting to control rubella infections altogether. Most of the included European nations adapted this strategy in the 1980's and 1990's. However, in two countries—Poland and Turkey—rubella vaccines were not commonly available for all children until recent years. In Poland, only 13-year-old girls were vaccinated against rubella until 2003, when a single-dosage MMR vaccine was introduced for boys and girls at the age of 13-15 months; the second MMR dosage, at age 10 years, was not added to the schedule until 2005.[289,328] While rubella inoculants have been accessible in Turkey since 1989, they were only available through the private health sector until 2006, and many Turkish residents did not receive the vaccine prior to its addition to the national vaccination program.[97] Since 2006, recommendations and campaigns for nation-wide MMR vaccinations, particularly among those under the age of 18 years, have been in effect.[39,97] Currently, two-dosage MMR (or MMRV) immunizations for children of both sexes are included in all the national immunization plans studied within the frame of this report.

In addition, some of the European countries recommend the vaccination of susceptible adults, particularly women of child-bearing age, to reduce the prevalence of CRS. In Germany and the UK, for example, a rubella immunization is strongly recommended for all unvaccinated, only single-dosage vaccinated or seronegative women of reproductive age, preferably with a combined MMR inoculant, so that an adequate protection against the disease exists during a potential pregnancy.[98,158] In Sweden and Greece, on the other hand, post-partum vaccinations of women discovered to

be susceptible during pregnancy are recommended.[115,151] This method is employed to reduce the chances of rubella infection during subsequent pregnancies.

3.5.3. Surveillance Systems

The WHO definition of rubella elimination calls for "well performing surveillance systems," including the case-based reporting and confirmation of all rubella cases.[307] The current (as of 2013) target for laboratory confirmation of suspected cases is 80%.[307]

Most European countries, including many of the nations described in this report, have national mandatory surveillance systems in place for monitoring the occurrence of rubella and CRS cases (see Table 3.25 on page Page 198).[30,329] In these nations, physicians, hospitals and laboratories are typically responsible for the reporting of clinical and confirmed cases.[30] Some countries, such as Italy and Austria, did not start mandatory rubella or CRS surveillance until fairly recently (2005 and 2007, respectively), but have nonetheless been contributing to the European-wide monitoring of the disease.[30,109,201]

Germany, while requiring the national reporting of CRS cases since 1961, did not mandate nation-wide post-natal rubella surveillance until April of 2013.[30,177] Prior to this change in the infection protection act (*Infektionsschutzgesetz, IfSG*), only the former East German federal states regularly reported rubella cases.[201,249] Thus, only few case data from the former West German regions are available and comparative data analyses are difficult.

As shown in Table 3.25, mandatory rubella or CRS surveillance does not occur in France, Turkey and the UK.[329] In France, laboratory-based reporting of rubella cases, particularly among pregnant women and newborns, is encouraged, but voluntary.[201] A nation-wide surveillance system is not in effect.[109,329] Turkey, while requiring the reporting of post-natal rubella infections, does not have a particular

surveillance system for CRS cases in place.[289] In the UK, a combined congenital rubella surveillance program for England, Scotland and Wales exists, but the reporting of cases is not mandatory.[130,329]

With the exception of Poland, all national rubella and CRS reports are case-based and additional data, such as demographic variables or maternal vaccination status, are often known. Poland reports aggregated data at a national level, but case-based data is available at a sub-national level.[329]

While most nations report clinical rubella cases on a regular annual or monthly basis,[30] the laboratory confirmation of these cases is often lacking. According to the ECDC 2012 *Annual epidemiological report*,[109] only about 2% of all rubella cases in Europe are confirmed, far below the WHO target of 80%. Table 3.20 gives an indication of the annual laboratory confirmed or epidemically linked cases as a proportion of the total cases reported by each nation. Particularly of note are the tremendous discrepancies between reported and confirmed cases in Poland and parts of the UK (England and Wales). Case confirmation data are also largely unavailable for Turkey. Austria, Germany, Italy and Sweden, on the other hand, have high confirmation rates.

An additional problem reported by several of the included countries is the under-reporting of cases at the national level. Germany, Greece and Italy all state that under-reporting occurs and Austria and Poland state that the occurrence of under-reporting is unknown.[30]

Overall, rubella surveillance is adequate in Europe; however, full mandatory reporting systems are still lacking in France, Turkey and the UK. Furthermore, data for parts of Germany are not available for the years prior to 2013. Laboratory or epidemiologically-linked confirmation of reported cases are lacking in several countries as well and under-reporting is a problem in many of the included nations. These factors limit the comparability of rubella cases between the nations (see below).

3.5.4. Case Reports and Incidence

Predominantly government and public health agencies have been referenced regarding nation-wide rubella case reports. Table 3.20 shows the total number of cases reported by each nation for the years 2006 through 2012 (and 2013, as available). The number of confirmed, hospitalized and mortality cases are indicated as well, though these data were largely unavailable. Annual incidences have been calculated based on the total cases and national population of that year. The number of congenital rubella infections are reported separately in Table 3.19. Data are shown for the years 2001 through 2012 in four-year intervals.

Due to variances in reporting of the total rubella case numbers, averages and standard deviations have been calculated where applicable and are shown in Table 3.20. While no or only few differences in reporting were observed for some countries (i.e. Croatia, Greece, Poland, Sweden and Turkey), substantial variances were found for Spain and Italy, the later with a standard deviation as high as 654.5 for the year 2008.

Among the European nations included in the analysis, a general downward trend in the number of reported rubella cases and incidences could be observed between 2006 and 2012, with a high of 25,477 cases (incidence: 5.63/100,000) in 2007 and a low of 5,040 cases (incidence: 1.10) in 2010. However, due to an extremely large outbreak in Poland during 2013, the total case number has once again risen. According to Paradowska-Stankiewicz et al.,[212] more than 21,000 cases were reported during the first four month of 2013 alone. By the end of the year, a total of 38,585 people had been affected.[116] As Fig. 3.18 shows, the outbreak in Poland has significantly contributed to the persistence or rubella viruses in the European region.

Other countries with high rubella case numbers and large incidences during the past years were Italy, Turkey and the United Kingdom. In Italy, a particularly large outbreak involving more than 5,600 people (some sources report even higher numbers), occurred in 2008. Since then, the incidence of rubella has decreased

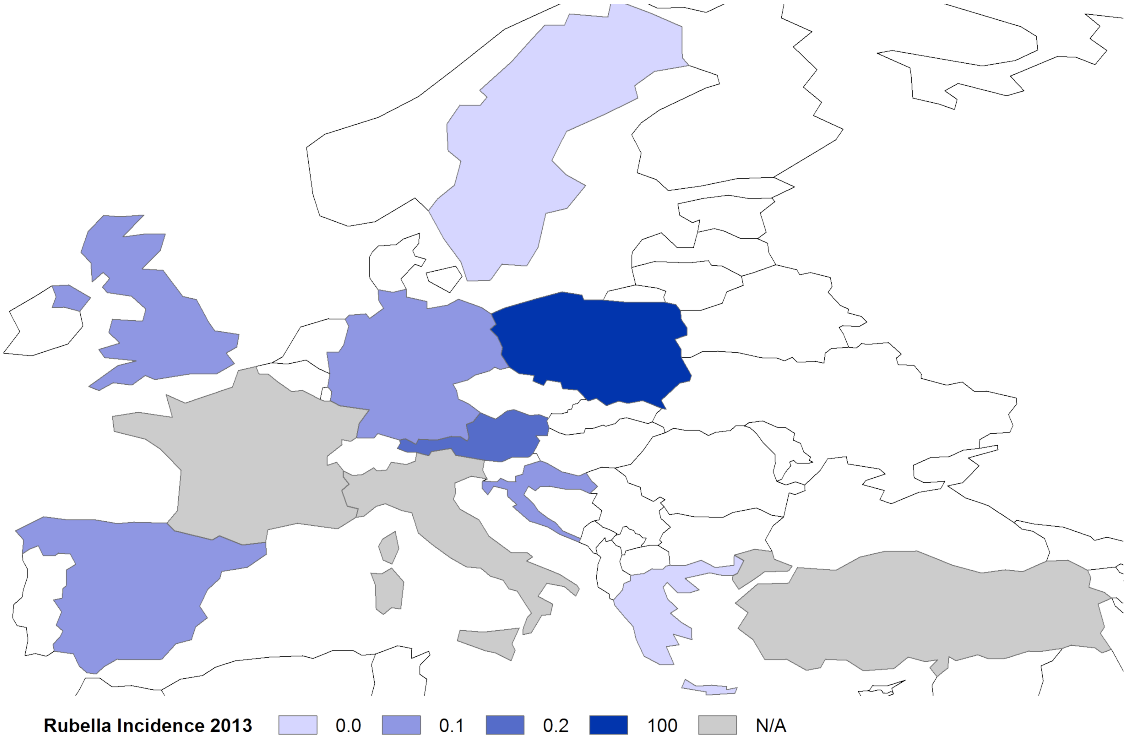

Figure 3.18. 2013 Rubella Incidences Among Selected European Nations. Shown are the 2013 total incidences of rubella (per 100,000 population). While few cases were notified in most of the selected nations, Poland reported a total of 38,585 cases, corresponding to an incidence of 100.13. ***Sources***: *ECDC Surveillance Report, Measles and Rubella Monitoring*,[116] *Robert Koch Institut, 2014*,[250] *Eurostat Statistics Database, 2014*.[34] Geographic data obtained from www.naturalearthdata.com.

considerably, however. Turkey reported an outbreak involving 1,734 people in 2011, after the rates had been successfully decreasing in the previous years due to mass vaccination campaigns. Unfortunately, more recent data for 2012 and 2013 are not currently available. In the UK, outbreaks ranging in size between about 500 cases and 1,300 cases annually have been reported. Most of these stem from England and Wales. The number of laboratory or epidemiologically confirmed cases in Turkey and the UK are extremely low, however (2% and 3%, respectively).

Smaller rubella outbreaks occurred in Spain, Sweden, Austria, Germany and France, whereby data from the later two are difficult to compare due to lack of national, mandatory surveillance during the 2006-2012 time period. The small 2012 outbreak in Sweden involving 50 people was the only significant outbreak in an otherwise nearly rubella-free country. Similarly, the 268 cases reported in Austria during 2009

were part of the only larger outbreak occurring during the 2006-2012 time frame. The overall incidences in all of these nations are low.

The countries meeting the rubella elimination definition set by the WHO[307] are Greece and Croatia. In Greece, no rubella cases have been notified since 2009, at which time only 4 cases were reported. Croatia has also reported only one or two annual cases in the past decade, with the exception of 2007, when a small outbreak involving less than 40 people occurred.[148] Both nations have observed no CRS cases in the past 10 years (see Table 3.19).

Most cases of congenital rubella infections during the past decade were observed in Italy and France. In Italy, 28 cases were reported between 2001 and 2012, whereby the number is likely higher due to lacking national reports during the 2001-2004 time period (data are for southern Italy only).[61] The 18 cases observed in France may also be under-reported due to non-mandatory surveillance. In Poland, two new cases have been reported for 2013 (data not shown in Table 3.19); however, more cases likely occurred at a later time due to potential infections among pregnant women during the large 2013 outbreak.[212]

Although only few data regarding hospitalizations and deaths are available (see Table 3.20), the considerably low number of reported hospitalized patients and no reported mortalities reflect the usually mild disease progression or rubella. Nonetheless, complications warranting hospitalized care, though rare, do occur. Between 2006 and 2012, a total of 363 hospitalized cases were reported. In addition, CRS cases are typically associated with severe complications and disabilities. Though the number of these cases has decreased, 24 cases were still reported by the included nations between 2009 and 2012.

The overall age distribution among rubella cases in Europe has been described by Muscat et al.[201] In 2008, of 21,399 (99.6%) cases for which age was known, 5% were less than 12 months old, 10% were between the ages of 1 and 4 years, 24% between 5 and 9 years, 21% between 10 and 14 years, 23% between 15 and 19

years and 18% 20 years and older.[201] In Poland, more than 80,000 rubella cases were reported between 2003 and 2008. Of these, nearly all (>90%) occurred among children and youths under the age of 20 years.[328] Particularly children under the age of 10 years were affected; this young age-group made up 53% of all cases reported for the 2003-2008 time period.[328] The overall data for Europe between 2007 and 2011, as published by the ECDC, reflect that a large proportion of rubella cases occurred among young children below the age of 5 years and among the 15- to 24-year-old age group.[106] Particularly in the past years, an increased number of affected adolescents and young adults has been observed. This trend has been described for Italy,[95,105] Austria[106,155] and Poland.[110,212]

In terms of gender, males tend to be more frequently affected by rubella than females are, particularly among older children and adolescents.[103,105,106,110] In 2008, 73% of all rubella cases in Poland were boys and men.[328] During the large 2013 outbreak, 81% of the cases were among male adolescents and young men between the ages of 15 and 29 years.[212] Similar results were found in Italy and Austria. In a 2008 outbreak involving 133 people (111 confirmed cases) in North-Eastern Italy, 73.8% were among males.[95] In this particular outbreak, the young-adult age group of 20- to 29-year-olds was predominantly affected, with more than half of all cases belonging to this age group.[95] Among 333 rubella cases in Austria in 2009, 198 (59.5%) were males and, again, mostly adolescents and young adults were affected.[155] Rubella susceptibility as a factor of various sociodemographic variables is further addressed in the subsections below.

Country	Reported CRS Cases			
	2001-2004	2005-2008	2009-2012	Total
Austria[a]	-	-	-	**-**
Croatia	0	0	0	**0**
France[b]	11	2	5	**18**[*]
Germany	6	2	3	**11**
Greece	0	0	0	**0**
Italy	9[c]	18	6	**28**[*]
Poland	5	2	3	**10**
Spain	2	6	3	**11**
Sweden	0	0	1	**1**
Turkey[d]	-	2	2	**4**
UK	4	5	1	**10**

[*] Limited comparability
[a] A national CRS surveillance system was not in effect until 2007.
[b] Voluntary CRS surveillance; laboratory confirmed cases only.
[c] Regional data for southern Italy only.
[d] No CRS surveillance system is in effect.

Table 3.19. Reported Congenital Rubella Syndrome Cases by Country, 2001-2012. The number of congenital rubella syndrome (CRS) cases, as reported through national surveillance systems, are shown for the years 2001-2012 in four-year intervals. The overall numbers are fairly low and a slightly decreasing trend can be observed. Successful CRS-elimination (no cases in >3 years) has been reached by Croatia and Greece. Sweden reported one case in 2011. ***Sources***: *Buffolano et al., 2011*;[61] *Centralized Information System for Infectious Diseases (CISID), WHO European Region, 2013*;[326] *Muscat et al., 2012*;[201] *Zimmerman, Muscat et al., 2011*.[329]

Reported Post-natal Rubella Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	**Confirmed•**	**Imported**	**Hospital.**	**Deaths**			
	Austria	**2006-2013**	**327**	-	**307** (94%)	**4** (1%)	**23** (7%)	**0** (0%)			
ECDC, 2014,[116] WHO, 2013[326]		2013	**11**	1.4	8	1	-	-	0.13	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2013,[114] WHO, 2013[326]		2012	**18**	6.6	21	2	3	0	0.21	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2013,[114] WHO, 2013[326]		2011	**2**	0.5	2	1	-	0	0.02	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2013,[114] EUVAC.NET, 2011,[199] Kasper et al., 2010,[155] WHO, 2013[326]		2010	**3**[a]	0.5	3	0	-	0	0.04	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2013,[114] EUVAC.NET, 2010,[193] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2009	**268**	23.5	247	-	-	0	3.20	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2013,[114] EUVAC.NET, 2009,[192] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2008	**12**	0.0	12	-	7	0	0.14	Sur (M)	Strong
BMG, 2013,[62] ECDC, 2013,[114] EUVAC.NET, 2009,[192] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2007	**14**	0.0	14	-	13	0	0.17	Sur (M)	Strong
		2006	**-**	-	-	-	-	-	-		
	Croatia	**2006-2013**	**40**	-	**33** (82%)	**2** (5%)	**1** (2%)	**-**			
ECDC, 2014,[116] WHO, 2013[326]		2013	**1**	0.0	1	1	1	-	0.02	Sur (M)	Strong
HZJZ, 2012,[22]WHO, 2013[326]		2012	**1**	-	0	0	-	-	0.02	Sur (M)	Strong
WHO, 2013[326]		2011	**0**	-	0	0	-	-	0.00	Sur (M)	Strong
EUVAC.NET, 2011,[199] WHO, 2013[326]		2010	**1**	-	1	0	-	-	0.02	Sur (M)	Strong

Reported Post-natal Rubella Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Imported	Hospital.	Deaths			
EUVAC.NET, 2010,[193] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2009	**0**	0.0	0	0	-	-	0.00	Sur (M)	Strong
EUVAC.NET, 2009,[192] WHO, 2013,[326] Muscat et al., 2012,[201] Zimmerman, Muscat et al., 2011[329]		2008	**1**	0.0	1	0	-	-	0.02	Sur (M)	Strong
EUVAC.NET, 2009,[191] WHO, 2013,[326] Kaic et al., 2012,[148] Muscat et al., 2012,[201] Zimmerman, Muscat et al., 2011[329]		2007	**34**	2.6	29	0	-	-	0.77	Sur (M)	Strong
EUVAC.NET, 2009,[191] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2006	**2**	0.0	1	1	-	-	0.05	Sur (M)	Strong
	France	**2006-2013**	**33**	-	**11** (33%)	**-**	**-**	**-**			
		2013	**-**	-	-	-	-	-	-		
		2012	**-**	-	-	-	-	-	-		
InVS, 2013[145]		2011	**8**[a,b]	-	2	-	-	-	0.01	Lab (V, E)	Weak
InVS, 2013[145]		2010	**4**[a,b]	-	1	-	-	-	0.01	Lab (V, E)	Weak
InVS, 2013[145]		2009	**7**[a,b]	-	2	-	-	-	0.01	Lab (V, E)	Weak
InVS, 2013[145]		2008	**2**[a,b]	-	2	-	-	-	0.00	Lab (V, E)	Weak
InVS, 2013[145]		2007	**5**[a,b]	-	2	-	-	-	0.01	Lab (V, E)	Weak
InVS, 2013[145]		2006	**7**[a,b]	-	2	-	-	-	0.01	Lab (V, E)	Weak
	Germany	**2006-2013**	**292**	-	**292** (100%)	**-**	**-**	**-**			
RKI, 2013[249]		2013	**55**[c]	-	55	-	-	-	0.07	Sur (V, R, E)	Weak
RKI, 2013[249]		2012	**33**[c]	-	33	-	-	-	0.04	Sur (V, R, E)	Weak

Reported Post-natal Rubella Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	**Confirmed•**	**Imported**	**Hospital.**	**Deaths**			
RKI, 2013[249]		2011	**9**[c]	-	9	-	-	-	0.01	Sur (V, R, E)	Weak
RKI, 2013[249]		2010	**14**[c]	-	14	-	-	-	0.02	Sur (V, R, E)	Weak
RKI, 2013[249]		2009	**31**[c]	-	31	-	-	-	0.04	Sur (V, R, E)	Weak
RKI, 2013[249]		2008	**26**[c]	-	26	-	-	-	0.03	Sur (V, R, E)	Weak
RKI, 2013[249]		2007	**13**[c]	-	13	-	-	-	0.02	Sur (V, R, E)	Weak
RKI, 2013[249]		2006	**111**[c]	-	111	-	-	-	0.13	Sur (V, R, E)	Weak
	Greece	**2006-2013**	**5**	-	**3** (60%)	**-**	**-**	**-**			
ECDC, 2014,[116] HCDCP, 2013[138]		2013	**0**	0.0	0	-	-	-	0.00	Sur (M, E)	Weak
HCDCP, 2013,[138] ECDC, 2013,[114] WHO, 2013[326]		2012	**0**	0.0	0	-	-	-	0.00	Sur (M, E)	Weak
HCDCP, 2013,[138] ECDC, 2013,[114] WHO, 2013[326]		2011	**0**	0.0	0	-	-	-	0.00	Sur (M, E)	Weak
ECDC, 2012,[109] EUVAC.NET, 2011,[199] WHO, 2013[326]		2010	**0**	0.0	0	-	-	-	0.00	Sur (M, E)	Weak
ECDC, 2011,[106] EUVAC.NET, 2010,[193] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2009	**4**	0.0	3	-	-	-	0.04	Sur (M, E)	Weak
ECDC, 2010,[105] EUVAC.NET, 2009,[192] Muscat et al., 2012,[201] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2008	**0**	0.0	0	-	-	-	0.00	Sur (M, E)	Weak
ECDC, 2009,[103] EUVAC.NET, 2009,[191] Muscat et al., 2012,[201] Zimmerman, Muscat et al., 2011[329]		2007	**0**	0.0	0	-	-	-	0.00	Sur (M, E)	Weak
ECDC, 2012,[109] EUVAC.NET, 2009,[191] Muscat et al., 2012[201]		2006	**1**	0.0	0	-	-	-	0.01	Sur (M, E)	Weak

Reported Post-natal Rubella Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Imported	Hospital.	Deaths			
	Italy	**2006-2013**	**7,142**	-	**7,854** (100%)	**-**	**-**	**-**			
		2013	**-**	-	-	-	-	-	-		
WHO, 2013[326]		2012	**246**	-	246	-	-	-	0.40	Sur (M, E)	Weak
ECDC, 2013,[110] WHO, 2013[326]		2011	**105**	0.5	105	-	-	-	0.17	Sur (M, E)	Weak
ECDC, 2012,[109] EUVAC.NET, 2011,[199] WHO, 2013[326]		2010	**58**	18.5	84	-	-	-	0.10	Sur (M, E)	Weak
ECDC, 2012,[109] EUVAC.NET, 2010,[193] Ministero della Salute, 2013,[186] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2009	**160**	53.8	221	-	-	-	0.27	Sur (M, E)	Weak
ECDC, 2010,[105] EUVAC.NET, 2009,[192] Ministero della Salute, 2013,[186] Muscat et al., 2012,[201] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2008	**5,649**	654.5	6,183	-	-	-	9.44	Sur (M, E)	Weak
ECDC, 2009,[103] EpiCentro, 2013,[101] EUVAC.NET, 2009,[191] Ministero della Salute, 2013,[186] Muscat et al., 2012,[201] Zimmerman, Muscat et al., 2011[329]		2007	**692**	131.6	758	-	-	-	1.17	Sur (M, E)	Weak
ECDC, 2012,[109] EpiCentro, 2013,[101] EUVAC.NET, 2009,[191] Ministero della Salute, 2013,[186] Muscat et al., 2012,[201] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2006	**232**	24.5	257	-	-	-	0.39	Sur (M, E)	Weak
	Poland	**2006-2013**	**117,625**	-	**1,571** (<1%)	**-**	**338** (<1%)	**-**			
ECDC, 2014[116]		2013	**38,585**	-	1,001	-	-	-	100.13	Sur (M, A)	Strong

Reported Post-natal Rubella Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	**Confirmed•**	**Imported**	**Hospital.**	**Deaths**			
ECDC, 2013,[114] WHO, 2013[326]		2012	**6,261**	2.0	-	-	-	-	16.24	Sur (M, A)	Strong
ECDC, 2013,[110] NIZP, 2012,[87] Karasek and Paradowska-Stankiewicz,2013[154]		2011	**4,290**	0.0	-	-	12	-	11.13	Sur (M, A)	Strong
ECDC, 2012,[109] EUVAC.NET, 2011,[199] NIZP, 2012,[87] WHO, 2013[326]		2010	**4,197**	0.0	1	-	13	-	10.99	Sur (M, A)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[193] NIZP, 2010,[86] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2009	**7,587**	0.0	8	-	34	-	19.89	Sur (M, A)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[192] NIZP, 2010,[86] Muscat et al., 2012,[201] Zimmerman, Muscat et al., 2011[329]		2008	**13,146**	0.0	305	-	124	-	34.48	Sur (M, A)	Strong
ECDC, 2009,[103] EUVAC.NET, 2009,[191] NIZP, 2010,[86] Muscat et al., 2012,[201] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2007	**22,891**	0.0	153	-	155	-	60.05	Sur (M, A)	Strong
ECDC, 2012,[109] EUVAC.NET, 2009,[191] NIZP, 2008,[85] Muscat et al., 2012,[201] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2006	**20,668**	0.0	103	-	-	-	54.19	Sur (M, A)	Strong
	Spain	**2006-2013**	**314**	-	**166** (53%)	**15** (5%)	**5** (2%)	**-**			
ECDC, 2014,[116] ISCIII, 2013,[142] WHO, 2013[326]		2013	**3**	0.0	3	3	-	-	0.01	Sur (M)	Strong
ECDC, 2013,[114] ISCIII, 2013,[142] WHO, 2013[326]		2012	**64**	2.9	12	59	2	-	0.14	Sur (M)	Strong

Reported Post-natal Rubella Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	**Confirmed•**	**Imported**	**Hospital.**	**Deaths**			
ECDC, 2013,[114] ISCIII, 2013,[142] WHO, 2013[326]		2011	**10**	6.8	8	-	3	-	0.02	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2011,[199] ISCIII, 2013,[142] WHO, 2013[326]		2010	**10**	1.4	4	-	-	-	0.02	Sur (M)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[193] ISCIII, 2013,[142] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2009	**22**	4.3	7	-	-	-	0.05	Sur (M)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[192] ISCIII, 2013,[142] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2008	**61**	9.0	44	-	-	-	0.13	Sur (M)	Strong
ECDC, 2009,[103] EUVAC.NET, 2009,[191] ISCIII, 2013,[142] Muscat et al., 2012,[201] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2007	**56**	21.3	14	-	-	-	0.12	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2009,[191] ISCIII, 2013,[142] Muscat et al., 2012,[201] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2006	**88**	1.0	27	-	-	-	0.20	Sur (M)	Strong
	Sweden	**2006-2013**	**64**	-	**62** (97%)	**1** (2%)	**-**				
ECDC, 2014,[116] SMI, 2013,[275] WHO, 2013[326]		2013	**0**	0.0	-	-	-	-	0.00	Sur (M)	Strong
ECDC, 2013,[114] SMI, 2013,[275] WHO, 2013[326]		2012	**50**	0.0	50	1	-	-	0.53	Sur (M)	Strong
ECDC, 2013,[114] SMI, 2013,[275] WHO, 2013[326]		2011	**5**	0.5	5	2	1	-	0.05	Sur (M)	Strong

Reported Post-natal Rubella Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	**Confirmed•**	**Imported**	**Hospital.**	**Deaths**			
ECDC, 2012,[109] EUVAC.NET, 2011,[199] SMI, 2013,[275] WHO, 2013[326]		2010	**3**	0.0	1	2	-	-	0.03	Sur (M)	Strong
ECDC, 2011,[106] EUVAC.NET, 2010,[193] SMI, 2013,[275] Zimmerman, Muscat et al., 2011[329]		2009	**1**	0.0	1	-	-	-	0.01	Sur (M)	Strong
ECDC, 2010,[105] EUVAC.NET, 2009,[192] Muscat et al., 2012,[201] SMI, 2013,[275] Zimmerman, Muscat et al., 2011[329]		2008	**0**	0.0	0	-	-	-	0.00	Sur (M)	Strong
ECDC, 2009,[103] EUVAC.NET, 2009,[191] Muscat et al., 2012,[201] SMI, 2013,[275] Zimmerman, Muscat et al., 2011[329]		2007	**2**	0.0	2	-	-	-	0.02	Sur (M)	Strong
ECDC, 2012,[109] EUVAC.NET, 2009,[191] Muscat et al., 2012,[201] SMI, 2013,[275] Zimmerman, Muscat et al., 2011[329]		2006	**3**	0.5	3	-	-	-	0.03	Sur (M)	Strong
	Turkey	**2006-2013**	**3,749**	-	**85** (2%)	**-**	**-**	**-**			
		2013	**-**	-	-	-	-	-	-		
		2012	**-**	-	-	-	-	-	-		
WHO, 2013[326]		2011	**1,734**	-	-	-	-	-	2.37	Sur (M)	Strong
EUVAC.NET, 2011,[199] WHO, 2013[326]		2010	**64**	-	64	-	-	-	0.09	Sur (M)	Strong
EUVAC.NET, 2010,[193] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2009	**97**	0.0	21	-	-	-	0.14	Sur (M)	Strong
EUVAC.NET, 2009,[192] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2008	**152**	11.5	-	-	-	-	0.23	Sur (M)	Strong

Reported Post-natal Rubella Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	**Confirmed•**	**Imported**	**Hospital.**	**Deaths**			
EUVAC.NET, 2009,[192] WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2007	**644**	0.0	-	-	-	-	0.93	Sur (M)	Strong
WHO, 2013,[326] Zimmerman, Muscat et al., 2011[329]		2006	**1,058**	0.0	-	-	-	-	1.54	Sur (M)	Strong
	UK	**2006-2013**	**7,100**	-	**240** (3%)	**17** (<1%)	**-**	**-**			
ECDC, 2014,[116] PHE, 2010,[234] WHO, 2013[326]		2013	**369**[d]	-	14	4	-	-	0.58	Sur (M, C, E)	Weak
HPS, 2012,[135] PHE, 2010& 2013,[233,234] WHO, 2013[326]		2012	**858**	-	74	10	-	-	1.36	Sur (M, C, E)	Weak
HPS, 2012,[135] PHE, 2010& 2013,[233,234] WHO, 2013[326]		2011	**490**	-	6	-	-	-	0.78	Sur (M, C, E)	Weak
DHSSPS, 2013,[16] EUVAC.NET, 2011,[199] HPS, 2012,[135] PHE, 2010&2013,[233,234] WHO, 2013[326]		2010	**686**	-	13	3	-	-	1.10	Sur (M, C, E)	Weak
DHSSPS, 2013,[16] EUVAC.NET, 2010,[193] HPS, 2009,[134] PHE, 2010&2013,[233,234] WHO, 2013[326]		2009	**1,253**		22	-	-	-	2.03	Sur (M, C, E)	Weak
DHSSPS, 2013,[16] EUVAC.NET, 2009,[192] HPS, 2009,[134] PHE, 2010&2013[233,234]		2008	**1,051**	-	40	-	-	-	1.17	Sur (M, C, E)	Weak
DHSSPS, 2013,[16] EUVAC.NET, 2009,[191] PHE, 2010& 2013[233,234]		2007	**1,126**	-	35	-	-	-	1.85	Sur (M, C, E)	Weak
DHSSPS, 2013,[16] EUVAC.NET, 2009,[191] PHE, 2010& 2013[233,234]		2006	**1,267**	-	36	-	-	-	2.09	Sur (M, C, E)	

Reported Post-natal Rubella Cases by Nation and Year, 2006-2013

Source(s)	Country	Year(s)	Number of Cases Reported						Incidence (per 100,000)	Reporting Method†	Report Quality
			Total	(SD)*	Confirmed•	Imported	Hospital.	Deaths			
	TOTAL	**2006-2013**	**136,543**		**10,624**	**43**	**363**	**-**	**-**		
		2013	**38,968**		**167**	**9**	**1**	**-**	**-**		
		2012	**7,531**		**483**	**25**	**5**	**-**	**1.62**		
		2011	**6,653**		**137**	**3**	**16**	**-**	**1.44**		
		2010	**5,040**		**186**	**5**	**13**	**-**	**1.10**		
		2009	**9,423**		**563**	**0**	**34**	**-**	**2.06**		
		2008	**20,100**		**6,613**	**0**	**131**	**-**	**4.42**		
		2007	**25,477**		**1,020**	**0**	**163**	**-**	**5.63**		
		2006	**23,437**		**540**	**1**	**-**	**-**	**5.22**		

Note: BMG: Bundesministerium für Gesundheit (Austrian Ministry of Health); *DHSSPS*: Department of Health, Social Services and Public Safety (Northern Ireland) *ECDC*: European Center for Disease Prevention and Control; *EpiCentro*: National Centre for Epidemiology, Surveillance and Health Promotion (Italy); *HCDCP*: Hellenic Center for Disease Control & Prevention (Greece); *HPS*: Health Protection Scotland; *HZJZ*: Hrvatski Zavod za Javno Zdravstvo (Croatia, National Institute of Public Health); *InVS*: Institut de Veille Sanitaire (France); *ISCIII*: Instituo de Salud Carlos III (Spain); *NIZP*: Narodowy Instytut Zdrowia Publicznego (Poland, National Institute of Public Health); *PHE*: Public Health England; *RKI*: Robert Koch Institut (Germany); *SMI*: Smittskyddsinstitutet (Sweden, Institute for Infectious Disease Control); *WHO*: World Health Organization.

* Case numbers have been average and the standard deviation (SD) calculated where applicable to indicate variance in national reporting.

• Cases either laboratory confirmed (rubella-specific antibodies or PCR) or epidemiologically linked to a laboratory-confirmed case. When variance in reporting occurred, the larger of the numbers was included.

† Reporting method: *Lab*: data provided by laboratories; *Sur*: data obtained through surveillance systems; M = mandatory, V = voluntary, R = regional data, A = aggregated data, C = clinical cases only, E = errors in reporting known or likely.

[a] Laboratory confirmed cases only.

[b] Maternal rubella cases.

[c] Data only available from former East German regions.

[d] Preliminary Data, as of June 2013.

Table 3.20. Reported Post-natal Rubella Cases by Nation and Year, 2006-2013. Shown are the annually reported rubella cases for each country. Congenital rubella syndrome cases have not been included. Due to variances in reporting by different sources, the mean total case number and standard deviations (SD) have been calculated, as indicated. The annual numbers of laboratory and epidemiologically confirmed cases, hospitalizations and death are also provided. Annual incidences have been calculated based on the total number of reported cases (source of population data: *The World Bank: DataBank: World Development Indicators, 2013*[285]). The Quality of the included reports has been assessed as follows: Hard data reports by the WHO, ECDC and governmental agencies were assumed to be accurate and assigned a "strong" quality; estimates and sentinel or regional data reports were assigned a "moderate" quality; voluntary data reports and underreported data were assigned a "weak" quality.

3.5.5. Vaccination Coverage

As described above in Section 3.5.2, all nations included in this report currently follow the WHO-recommended two-dosage MMR immunization scheme. National rubella vaccination rates are therefore similar to those of measles and mumps (see Sections 3.3.6 and 3.4.5.) To better monitor the rubella elimination progress, however, the WHO and UNICEF report rubella coverage estimates separately based on immunization statistics provided by each nation.[312] Table 3.21 provides an overview of these coverage reports for the years 2006 through 2012 (data as of Oct. 2013).

In this time period, the overall vaccination rates have shown little fluctuation in each country, with the exception of Austria and the United Kingdom. In Austria, the immunization coverage peaked at 83% in 2008, and then dropped again to 77% during the following year.[312] Likewise, in the UK, a large 7% increase in vaccination coverage from 86% to 93% could be observed between 2009 and 2010, which then decreased again to 90% during the following year.[312]

For easier comparability between the nations, the average vaccination rates among each European subregion over time are depicted in Fig. 3.19. Particularly the Eastern European nations have high vaccination coverage rates, as shown. Of note is the large increase in rubella coverage among these nations between the years 2004 and 2006, predominantly due to the recent introduction of rubella containing vaccines (RCV) for all children in Poland (2003) and Turkey (2006).

According to the current rubella elimination goals set by the WHO, high coverage rates of at least 95% for one or more RCV-dosages are necessary.[310] This threshold has been surpassed by Germany, Greece, Spain, Sweden, Croatia, Poland and Turkey; the remaining countries do not have high enough national immunization rates to meet the WHO elimination target as of yet (2012 data for France, Italy, and the UK and 2009 data for Austria).[312] In order to meet the rubella elimination target by 2015, particularly those nations with vaccination rates below 95% are encouraged to address poorly vaccinated population subgroups.[310]

Country	National Vaccination Coverage Estimates (%)						
	2012	2011	2010	2009	2008	2007	2006
Austria	-	-	-	76	83	77	80
France	89	-	90	90	87	87	-
Germany	96	96	96	94	95	94	93
Greece	-	98	-	98	98	98	-
Italy	90	90	91	90	90	90	88
Spain	-	97	95	98	-	-	-
Sweden	97	96	97	97	96	96	95
UK	92	90	93	86	86	86	85
Croatia	95	96	96	-	96	96	95
Poland	98	-	98	98	-	98	98
Turkey	-	98	97	97	97	96	98

Table 3.21. Primary Dosage Rubella Vaccination Rates, by Year and Country. Shown are vaccination coverage estimates reported by the WHO and UNICEF, based on each country's national immunization information using the WHO/UNICEF Joint Reporting Form. Data are as of October, 2013. ***Source***: *WHO vaccine-preventable diseases: Monitoring system, 2013 global summary: Coverage series.*[312]

3.5.6. Sociodemographic Factors influencing Rubella Susceptibility

Certain population groups are especially at risk of rubella infections, and all European countries are requested to provide additional immunization opportunities to these susceptible populations as part of the WHO rubella elimination goal.[310] Due to the high complication rate and disease burden associated with congenital rubella infections, women of childbearing age constitute a particular risk group, for instance. In the following subsections, studies analyzing susceptibility based on rubella vaccination coverage and seroprevalence of anti-rubella antibodies are described according to the sociodemographic factors age, gender, pregnancy, education, socioeconomic status, residence and migration.

Age Rubella susceptibility can vary substantially among different age groups. A total of 35 studies and reports provided vaccination coverage data for children and adolescents living in the nations included in this report between 2006 and 2012. Only limited age-based data exist for Austria, Croatia, Greece and Turkey. Table 3.22

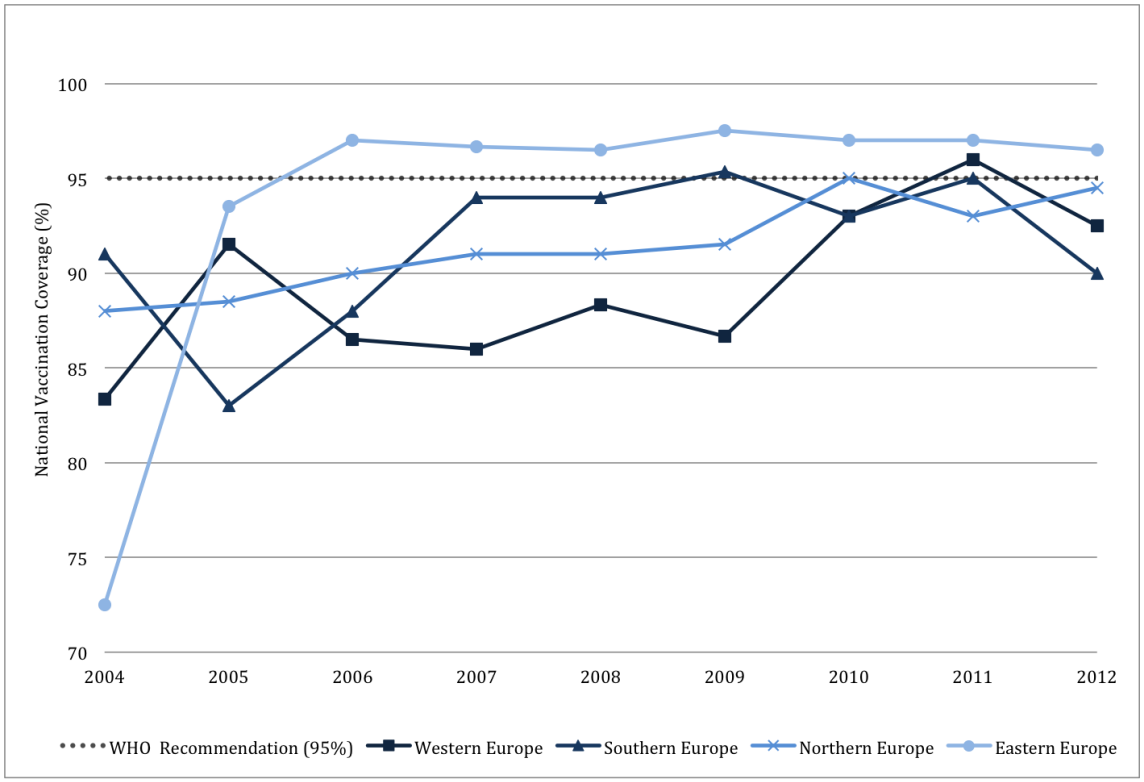

Figure 3.19. Regional Rubella Vaccination Coverage Over Time. Averages of nationally reported immunization rates for the primary dosage of rubella-containing vaccines are shown by European subregion for the years 2004 through 2012. Western Europe: Austria, France, Germany; Southern Europe: Greece, Italy, Spain; Northern Europe: Sweden, United Kingdom; Eastern Europe: Croatia, Poland, Turkey. The WHO-recommended 95%-threshold for the elimination of rubella has been marked. This threshold has been reached or surpassed by all European regions, but high coverage rates have only been sustained in the Eastern European subregion, as shown. Modified after *WHO vaccine-preventable diseases: Monitoring system, 2013 global summary: Coverage series*.[312]

provides an overview of the immunization rates with one or two RCV dosage among children and adolescents in the following age groups: pre-school age (1-5 years), school age (6-14 years), and adolescents (15-19 years). 19 studies measured anti-rubella IgG seroprevalence at various ages, 8 of them among children up to 14 years of age and 17 among adolescents and adults 15 years of age and older. The results of these studies are summarized in Table 3.23 and Table 3.24.

In most countries, a general upward trend in vaccination coverage can be observed over time and with increasing age. The same is true for seroepidemiological studies, though waning immunity with time has also been described by some authors.[227] In the following paragraphs, the rubella susceptibility among various age-groups is analyzed.

Rubella Vaccination Coverage, by Age Group and Vaccination Dosage

Source(s)	Country	Age	Vaccination Coverage (%) according to Year and Rubella Dosage (Range, if available)													Quality
			2012		2011		2010		2009		2008		2007		2006		
			D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	
	Austria																
ECDC, VENICE II, 2012[180]		1-5 Years	-	-	-	-	-	-	100	89	-	-	-	-	-	-	Strong
ECDC, VENICE II, 2012[180]		6-14 Years	-	-	-	-	-	-	-	84	-	-	-	-	-	-	Strong
	Croatia																
HZJZ, 2011&2012,[22,41] Usonis et al., 2011[289]		1-5 Years	94.8 (85–99)	-	98.6 (91–99)	-	-	-	-	-	97.6*	-	-	-	-	-	Strong
HZJZ, 2011&2012,[22,41] Usonis et al., 2011[289]		6-14 Years	-	97.0 (83–100)	97.9 (94–100)	99.4 (94–100)	-	-	-	-	-	98*	-	-	-	-	Strong
	France																
InVS, 2011[144]		1-5 Years	-	-	89.4* (76–96)	67.3* (46–83)	89.2* (76–96)	60.9* (29–74)	-	-	88.9* (78–95)	-	89.5* (80–95)	-	89.1* (76–95)	-	Moderate
InVS, 2011[144]		6-14 Years	-	-	-	-	-	-	-	-	-	-	-	-	91.3* (85–97)	-	Moderate
	Germany																
RKI, 2013[246]		1-5 Years	-	-	96.3[a] (94–98)	91.8[a] (86–96)	96.1[a] (94–98)	91.2[a] (87–95)	95.7[a] (94–98)	90.1[a] (86–95)	95.5[a] (93–98)	88.7[a] (84–94)	94.9 [a] (92–98)	87.9[a] (79–94)	-	-	Strong
Poethko-Müller et al., 2007[226]		6-14 Years	-	-		-	-	-	-	-	-	-	-	-	91.2[b]	69.8[b]	Strong
Poethko-Müller et al., 2007[226]		15-19 Years	-	-		-	-	-	-	-	-	-	-	-	86.6	59.2	Strong
	Greece																
Pavlopoulou et al., 2013[215]		1-5 Years	-	-	-	63.7	-	63.7	-	-	-	-	-	-	-	-	Strong

Rubella Vaccination Coverage, by Age Group and Vaccination Dosage

Source(s)	Country	Age	Vaccination Coverage (%) according to Year and Rubella Dosage (Range, if available)													Quality
			2012		2011		2010		2009		2008		2007		2006		
			D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	
Sakou et al., 2011[259]		6-14 Years	-	-	-	-	-	-	-	95.7	-	-	-	-	-	-	Strong
Sakou et al., 2011[259]		15-19 Years	-	-	-	-	-	-	-	91.5	-	-	-	-	-	-	Strong
	Italy																
Ministero della Salute, 2013[187]		1-5 Years	89.2	-	89.9	-	90.5	-	89.9	-	89.7	-	89.6	-	88.2	-	Strong
Lo Giudice et al., 2009[165]		6-14 Years	-	-	-	-	-	-	-	-	82.1[c]	24.1[c]	-	-	-	-	Strong
Lo Giudice et al., 2009[165]		15-19 Years	-	-	-	-	-	-	-	-	61.8[c]	21.6[c]	-	-	-	-	Strong
	Poland																
NIZP, 2006-2013[88–94]		1-5 Years	95.9 (82–100)	-	96.0 (79–100)	-	96.0 (83–100)	-	95.8 (79–100)	-	95.1 (80–100)	-	85.7 (79–100)	-	74.0 (31–100)	-	Strong
NIZP, 2006-2013[88–94]		6-14 Years	99.4 (99–100)	73.1[d] (42–100)	98.3 (98–100)	64.5[d] (32–100)	92.5 (40–100)	55.4[d] (28–100)	80.2 (33–100)	44.6[d] (9–100)	68.1 (30–100)	35.2[d] (5–99)	59.3 (30–100)	25.8[d] (3–99)	44.6 (2–99)	14.6[d] (0–54)	Strong
NIZP, 2006-2013[88–94]		15-19 Years[e]	99.7	-	99.6	-	99.5	-	99.1	-	99.3	-	99.4	-	99.5	-	Strong
	Spain																
MSPSI, 2013[21]		1-5 Years	97.1 (92–100)	90.3 (71–100)	96.8	91.3	95.5	92.3	97.4	90.4	97.6	94.4	97.2	95.0	96.9	94.1	Strong
	Sweden																
SMI, 2010& 2013[10, 32]		1-5 Years	97.4	-	97.2	-	96.4	-	96.5	-	96.7	-	96.2	-	96.2	-	Strong
SMI, 2009& 2012[7, 19]		6-14 Years	97.2	95.1	97.4	95.1	98.3	94.4	98.6	94.9	98.5	94.4	-	-	98.8	94.9	Strong

Rubella Vaccination Coverage, by Age Group and Vaccination Dosage

Source(s)	Country	Age	Vaccination Coverage (%) according to Year and Rubella Dosage (Range, if available)														Quality
			2012		2011		2010		2009		2008		2007		2006		
			D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	
	Turkey																
Usonis et al., 2011[289]		1-5 Years	-	-	-	-	-	-	97*	-	-	-	-	-	-	-	N/A
Usonis et al., 2011[289]		6-14 Years	-	-	-	-	-	-	-	88*	-	-	-	-	-	-	N/A
	UK																
PHE, 2013[230]		1-5 Years	94.3 (94–97)	88.2 (88–92)	93.4 (93–97)	86.5 (86–92)	92.5 (92–97)	85.0 (84–92)	91.7 (91–96)	83.6 (83–90)	87[f]	74[f]	86[f]	73[f]	87[f]	74[f]	Strong

Note: ECDC: European Center for Disease Prevention and Control; *HZJZ*: Hrvatski Zavod za Javno Zdravstvo (Croatia, National Institute for Public Health); *InVS*: Institut de veille sanitaire (French Institute for Public Health Surveillance); *MSPSI*: Ministerio de Sanidad, Servicios Sociales e Igualdad (Spanish Ministry of Health, Social Services and Equality); *NIZP*: Narodowy Instytut Zdrowia Publicznego (Polish National Institute of Public Health); *PHE*: Public Health England; *RKI*: Robert Koch Institute (Germany); *SMI*: Smittskyddsinstitutet (Swedish Institute for Infectious Disease Control); *VENICE II*: Vaccine European New Integrated Collaboration Effort.

* Estimates

[a] Data collected from vaccination records prior to school entry, children 4-6(7) years of age are included.

[b] Age groups 7-10 and 11-13 years are included (2003-2006).

[c] Data is reported solely from the Messina province of Italy.

[d] Coverage among children aged ≥10 years (the mandatory MMR-2 vaccination age in Poland).

[e] The vaccination coverage is reported for girls only.

[f] Data is reported solely for England.

Table 3.22. Rubella Vaccination Coverage, by Age Group and Vaccination Dosage. Shown are the age-stratified vaccination rates for either one or two rubella or MMR dosages (D1 and D2), as reported by various studies or governmental agencies. Regional variances are shown where applicable. The quality of the included studies has been assessed as indicated (see Appendix E (Study Characteristics) for details). Verified data reports by governmental agencies were assigned a "strong" quality; estimates were assigned a "moderate" quality.

Anti-Rubella IgG Antibody Seroprevalence Rates, by County and Age Group (0-14 Years)

Source	Country	Time Period	*n*	Method	Pos. Titer Definition	Positive Seroprevalence Rate by Age Group							Study Quality
						0-2 years	3-4 years	5-6 years	7-8 years	9-10 years	11-12 years	13-14 years	
Poethko-Müller & Mankertz, 2012[227]	Germany	2003-2006	13,968	ELISA	≥11 IU/ml	77.7%	← 89.9% →		← 89.5% →		← 87.0% →		Strong
Bechini et al., 2012[53]	Italy	2005-2006	1,110	ELISA	>0.200 ΔA	68.4%[b]	89.2%[c]	← 88.3%[d]→			← 87.0%[e]→		Strong
Akkoyunlu et al., 2013[40]	Turkey	2010	206	ELISA	-				← 78.1%[f]→				Weak
Koksaldi-Motor et al., 2012[160]	Turkey	2009	331[a]	CLIA	>4.99 IU/ml				← 73.3%[g]→				Moderate
Kurugöl et al., 2011[161]	Turkey	2008	597	EIA	>15 IU/ml	51.9%	47.1%	48.3%	67.2%		← 88.7%[e]→		Strong
Demirdal et al., 2012[97]	Turkey	2005-2006	1,409[a]	ELISA	-	18.5%[b]	← 28.6%[h]→			← 36.8%[i]→			Strong
Aytac et al., 2009[47]	Turkey	2005	331	ELISA	>0.283 ΔA	9.0%	18.0%	22.5%[j]	-	-	-	-	Strong
Bozkurt et al., 2010[58]	Turkey	2003	235[a]	ELISA	≥15 IU/ml	-	-	-	← 54.3% →		← 93.2% →		Strong

Note: ΔA: Change in absorbency; *CLIA*: Chemiluminescence immunoassay; *EIA*: Enzyme immunoassay; *ELFA*: Enzyme-linked fluorescent assay; *ELISA*: Enzyme-linked immunosorbent assay.

[a] Girls only
[b] Ages 0-1 years
[c] Ages 2-4 years
[d] Ages 5-9 years
[e] Ages 10-14 years
[f] Ages 0-18 years
[g] Ages 0-14 years
[h] Ages 2-6 years
[i] Ages 7-17 years
[j] Age 5 years

Table 3.23. Anti-Rubella IgG Antibody Seroprevalence Rates, by County and Age Group (0-14 Years). Shown are the positive seroprevalence rates of anti-rubella IgG antibodies among age-stratified populations of the indicated nations. The methods used to determine the antibody titers as well as the definition for a positive titer are indicated for each included study. The quality (strong, moderate, or weak) has been assessed for each study according to the criteria outlined in Appendix D (also see Appendix E for further details about each study).

Anti-Rubella IgG Antibody Seroprevalence Rates, by County and Age Group (≥15 Years)

Source	Country	Time Period	*n*	Method	Pos. Titer Definition	Positive Seroprevalence Rate by Age Group					Study Quality
						15-17 years	18-19 years	20-25 years	26-45 years	≥46 years	
Vilibic-Cavlek et al., 2011[294]	Croatia	2005-2009	502[a]	ELISA	-	← 94.6% →				-	Moderate
Poethko-Müller & Mankertz, 2012[227]	Germany	2003-2006	13,968	ELISA	≥11 IU/ml	88.1%	-	-	-	-	Strong
Lo Giudice et al., 2009[165]	Italy	2006-2007	1000[a]	MEIA	>10 IU/ml	← 81.0% →			80.3%	-	Strong
Calimeri et al., 2012[64]	Italy	2006-2007	500[a]	MEIA	>10 IU/ml	← 75.3% →			87.7%	-	Strong
D'Agaro et al., 2010[95]	Italy	2006	1,416[a]	ELISA	>10 IU/ml	← 92.9% →		93.5%	94.6%	-	Strong
Bechini et al., 2012[53]	Italy	2005-2006	1,110	ELISA	>0.200 ΔA	← 84.1% →		92.7%	93.7 →		Strong
Ramos et al., 2012[236]	Spain	2006-2010	2,844[a,b]	ELISA	>10 IU/ml	← 94.8% →				-	Strong
Kakoulidou et al., 2010[151]	Sweden	2004-2006	40,482[a]	MEIA	>10 IU/ml	← 96.0%[e,f,g] →					Weak
Kakoulidou et al., 2010[151]	Sweden	2004-2006	1,155[a,c]	MEIA	>10 IU/ml	← 89.8%[e,f,g] →					Weak
Akkoyunlu et al., 2013[40]	Turkey	2010	1,189	ELISA	-	-		← 73.2% →			Weak
Koksaldi-Motor et al., 2012[160]	Turkey	2009	331[a]	CLIA	>4.99 IU/ml	← 92.8% →			95.4% →		Moderate
Karabulut et al., 2011[153]	Turkey	2008	1,268	ELISA	>10 IU/ml	-		← 95.1%[e,f,g] →		-	Strong
Kurugöl et al., 2011[161]	Turkey	2008	597	EIA	>15 IU/ml	← 98.2% →		98.5%[f]	95.6[g]	95.8[h]	Strong
Uysal et al., 2012[290]	Turkey	2001-2008	5,959[a]	ELFA	-	← 98.1% →				-	Moderate
Tamer et al., 2008[283]	Turkey	2005-2007	1,972[a]	ELISA	>10 IU/ml	← 96.1% →				-	Strong

Demirdal et al., 2009[97]	Turkey	2005-2006	1,409[a]	ELISA	-	36.8%[d]	80.0%[e]	80.9%[f]	78.5%[g]	76.4%[h]	Strong
Byrne et al., 2012[63]	UK	2004-2009	436,054[a,i]	ELISA	>10 IU/ml	← 86.0%[j] →		92.5%[k]	98.2[l]	98.6[m]	Moderate
Hardelid et al., 2009[130]	UK	2004	12,813[a]	ELISA	-[n]	← 94.8% →		96.5%	97.8%[o]	-	Weak

Note: ΔA: Change in absorbency; *CLIA*: Chemiluminescence immunoassay; *EIA*: Enzyme immunoassay; *ELFA*: Enzyme-linked fluorescent assay; *ELISA*: Enzyme-linked immunosorbent assay; *MEIA*: Microparticle enzyme immunoassay.

[a] Women/girls only

[b] 50% of the sample were immigrants.

[c] Sample of recent immigrants and refugees (ages unknown).

[d] Ages 7-17 years

[e] Ages 18-20 years

[f] Ages 20-30 years

[g] Ages 30-40 years

[h] Ages ≥41 years

[i] Number of samples of antenatal women only; individuals may have been included more than once if multiple pregnancies occurred during the study period.

[j] Birth cohorts 1991-1996 (data as of 2009)

[k] Birth cohorts 1986-1990 (data as of 2009)

[l] Birth cohorts 1971-1985 (data as of 2009)

[m] Birth cohorts before 1971 (data as of 2009)

[n] Samples were obtained from newborn screening blood spots and latent class regression finite mixture models were used to determine the cut-off between seronegative and seropositive rubella IgG antibody levels.

[o] Mothers 25 years and older

Table 3.24. Anti-Rubella IgG Antibody Seroprevalence Rates, by County and Age Group (≥15 Years). Positive anti-rubella IgG antibody seroprevalence rates are shown for age-stratified populations of the indicated nations. The methods used to determine the antibody titers as well as the definition for a positive titer are indicated for each study. The study quality has been assessed as strong, moderate or weak according to predefined criteria (see Appendices D and E for details).

Infants have a considerably high risk of rubella infection, as the immunization recommendations do not include children below the age of 12 months. Nonetheless, maternal antibodies may protect infants from a rubella infection during the first months of life. In a seroprevalence study by Aytac et al.[47] conducted in Turkey, infants had a 5.7% lower susceptibility to rubella than 1-year-old children did (87.5% vs. 93.2%), likely indicating the presence of maternal antibodies. Another study conducted in Turkey by Demirdal et al.[97] found a higher susceptibility among this young age group, however: 81.5% of infants were susceptible to rubella, whereas 71.4% of 2- to 6-year-olds were at risk of infection. Other seroprevalence studies did not include children below the age of 1 year, thus limiting the extend to which the rubella susceptibility among this age group can be determined.

Pre-school-aged children between the ages of 1 and 5 years are typically better protected against rubella than infants are, as they are scheduled to receive at least one rubella immunization dosage. Nonetheless, the vaccination coverage varies between the countries, as shown in Table 3.22. High primary dosage RCV immunization rates >95% have been reported by Croatia, Germany, Poland, Spain, Sweden and Turkey. Lower rates were reported by the other countries, as shown. Unclear are the exact single dosage RCV rates in Austria, however. An extremely high 2009 coverage of 100% was reported among 3-year-old children by the ECDC.[180] During the same year, the vaccination rate estimate published by the WHO and UNICEF was much lower, at 76%[312](see Table 3.21). These inconsistent reports make a comparison between Austria and the other included countries difficult.

Next to the nationally reported vaccination rates among pre-school-aged children, various representative studies have assessed the susceptibility among this age group:

As a part of the German KiGGS study, the vaccination status of 16,460 (93.3%) of the 17,641 total participants and the seroprevalence of rubella antibodies among nearly 14,000 (79.2%) participants (excluding children below the age of 1 year) could be determined. In an article published by Poethko-Müller, Kuhnert and Schlaud,[226] increasing vaccination rates were described for children from 9% among those below

the age of 15 months to 92,2% among those aged 3 to 6 years, whereby 89.2% were vaccinated during their second year of life. The vaccination rates with two RCV dosages were considerably low among the populations eligible for the vaccine, ranging from 27.7% among those below the age of 2 years to 67.7% among those 3 to 6 years of age.[226]

In a 2012 paper by Poethko-Müller and Mankertz,[227] the seroprevalence of anti-rubella IgG antibodies according to age was reported for the KiGGS study participants. A positive rubella IgG titer of ≥11 IU/ml was found in 87.6% of the children, whereby a positive or negative history of infection had surprisingly little impact on the seroprevalence (positive history: 87.3%, negative history: 87.9%, unknown: 85.5%).[227] The rubella seroprevalence among various age groups is indicated in Tables 3.23 and 3.24 along with those of other studies. According to this study, young children 1 to 2 years of age had the highest susceptibility for a rubella infection, with 22.0% of them being seronegative for rubella antibodies (IgG titer <8 IU/ml).[227] This finding reflects the non-vaccinated population of 25.7% among this age group,[226] whereby a positive history of rubella infection as well as the proportion of children with a borderline antibody titer (0.4%) may explain the slight difference in susceptibility.

In Greece, the two-dosage RCV rate was measured in a study conducted in 2010 and 2011 in Athens. Pavlpoulou et al.[215] determined in a sample of 731 young children aged 10-65 months that 90.5% had received a at least one MMR vaccination by the age of 24 months and that 35.9% had received the age-appropriate complete two-dosage immunization at age 60 months. The overall complete immunization rate for all children up to the age of 65 months was 63.7%.[215]

Very high primary-dosage MMR vaccination rates were observed by Borràs, et al.[55] among children under the age of 3 years in Catalonia, Spain. In a random sample of 627 children, 98.9% had received at least one MMR dosage.[55] The full two-dosage immunization coverage among children 3 to 6 years old was with >90% also considerably high in the past years, though a decreasing trend can be observed

between 2007 (95.0%) and 2012 (90.3%).[21] Overall, children in Spain have a low rubella susceptibility even at an early age, as is further indicated by the low nationwide incidence of the disease, shown in Table 3.20.

Decreasing susceptibility rates with age were found among Italian children in a study by Bechini et al.[53] Between 2005 and 2006, the sera samples of 1,110 people between the ages of 1 and 50 years were analyzed and revealed a significant age-related seroprevalence trend.[53] While children at the age of 1 year were susceptible to rubella in 31.6% of cases, 12% of children between the ages of 2 and 14 years were anti-rubella IgG seronegative.[53] These data are consistent with the 88%-90% vaccination rates among 2-year-old children.

In Turkey, a 2005 study by Aytac et al.[47] among children below the age of 5 years also revealed that the rubella susceptibility decreased with increasing age, from 93.2% IgG seronegativity among young children aged 1 to 2 years to 68.7% among children aged 4 to 5 years; this age distribution was not statistically significant, however. Similar finding were made by Demirdal et al.[97] in a study with 1,409 girls and women living in the middle Anatolia region of Turkey. Rubella seronegativity decreased with age from 81.5% among the infants to 63.2% among older children.[97] These differences were also not statistically significant. In a 2008 study in Izmir, Kurugöl et al.[161] measured the rubella susceptibility among 600 participants between the ages of 1 and 70 years. As in prior studies, a decrease in susceptibility was found with increasing age, from 48.1% among 1- and 2-year-olds to 1.5% among adults.[161] In this study, the differences in seroprevalence were significant.

According to the reported vaccination rates by government agencies and the study authors, pre-school-aged children are adequately protected against rubella in most of the included nations. However, seroprevalence rates indicate that an increased susceptibility remains among this age group, particularly in comparison to older children and adults.

Recent vaccination coverage among *school-aged children* (6 to 14 years of age) has been reported for Croatia, Poland and Sweden. In addition, limited immunization rate data are available for Austria, France, Germany, Greece, Italy and Turkey. The primary dosage rates among this age group are similar to those among pre-school-aged children. The secondary dosage rates vary greatly, however. In Croatia, Greece and Sweden, the second-dosage RCV coverages are very high and surpass the WHO-recommended 95%-threshold. The two-dosage immunization rates among the other countries are much lower, however, ranging between 24% in Italy (2008 data) to 88% in Turkey (2009 data). The limited availability of age-stratified vaccination rates make a clear comparison difficult, however.

The following studies on vaccination rates and anti-rubella antibody seroprevalence were conducted among school-aged children:

In Germany, the KiGGS study reported a 92.2% primary RCV coverage among 7- to 10-year-old children and a 89.7% coverage among 11- to 13-year-old children.[226] The secondary RCV coverage was much lower, reaching 72.2% among children 7 to 10 years old and 66.6% among those 11 to 13 years old.[226] These rates are comparable to those among pre-schoolers, whereby the second-dosage vaccination rates are slightly higher among the 7- to 10-year age group.

The rubella IgG seroprevalence study conducted among the KiGGS participants by Poethko-Müller and Mankertz[227] revealed that school-aged children were better protected against the disease than their younger counterparts were. While 22% of young pre-school-aged children were seronegative for rubella antibodies, only 9% to 11% of older children were susceptible.[227] Among them, the highest susceptibility was observed for the study participants aged 11 to 13 years.[227] Table 3.23 provides further details regarding the rubella antibody seroprevalence rates among children in Germany and other European countries.

In France, a slightly positive correlation between increasing age and primary RCV coverage was reported in 2005 and 2006, as shown in Table 3.22.[144] Similar results

were found in an earlier study conducted among school-aged children between 2001 and 2004.[43] At that time, 93.1% of 5- to 7-year-old children, 93.9% of 11-year-old children and 93.7% of 15-year-old adolescents were vaccinated against rubella.[43] The second-dosage immunization rates were low, reaching 28.0%, 56.6% and 65.5% among the respective age groups.[43] Unfortunately, no recent data on the vaccination rates of older children have been published to date, so that the current age-related susceptibility is difficult to determine.

In Greece, the previously introduced study by Sakou et al.[259] (see Section 3.3.7) revealed a high two-dosage MMR vaccination rate of 95.7% among school-aged children 11 to 14 years old. This rate was significantly higher than the 91.5% coverage among adolescents aged 15 to 19 years.[259]

Immunization coverage data for Italy is available for children living in the Messina province in 2008, as reported by Lo Giudice, et al.[165] While a continuous increase in MMR primary dosage coverage from 62% to 95% was found among those study participants born between 1993 (age 14 to 15 years in 2008) and 2001 (age 6 to 7 years in 2008), respectively, a decrease in vaccination rate was reported for the subsequent birth cohorts, sinking back down to 82% among those born in 2005 (age 2 to 3 years in 2008).[165] Reported rates for the secondary MMR vaccination dosage were extremely low, averaging 24% (range: 2%-38%) among the 1993 to 2002 birth cohorts.[165] Though these data are only for one province in Italy and nationwide trends can not be determined, they do suggest that the complete two-dosage vaccination coverage may be low in other regions as well. The considerably high number of rubella cases in Italy support this suspicion (see Table 3.20).

Various seroepidemiological studies in Turkey, such as those by Kurugöl et al.,[161] Demirdal et al.,[97] and Bozkurt et al.,[58] suggest that rubella susceptibility decreases with age. Kurugöl et al.[161] describe a seropositivity rate of 88.7% among 10- to 14-year-old children, compared to a 67.2% rate among the 7- to 8-year-old study participants and a 48.3% rate among the 5- to 6-year-old participants. Bozkurt et al.[58] analyzed the rubella susceptibility among school-aged girls in 2003 and found a

significant decreasing trend with increasing age. While 45.7% of girls in grade levels 1 through 4 (7 to 10 years old) were IgG seronegative, only 6.7% among those in grade levels 5 through 8 (11 to 14 years) were susceptible to rubella ($p<0.001$).[58] Similar finding were made by Demirdal et al.[97] in 2009. Rubella susceptibility decreased with age from 71.4% among pre-schoolers (2 to 6 years old) to 63.2% among school-aged children and adolescents (7 to 17 years old).[97] These differences were not statistically significant, however.

Overall, the vaccination coverage and seroprevalence studies show that school-aged children typically have a lower susceptibility to rubella than pre-school-aged children do. Within this age group, some studied found a higher protection among younger children (6 to 10 years old), whereas others found older children (10 to 14 years old) to be better protected against rubella. A clear trend can therefore not be determined.

The rubella susceptibility among *adolescents and adults* was addressed by 3 vaccination coverage and 18 seroprevalence studies. Although the immunization rates were found to be lower among the older age groups, a generally high level of protection was reported by most of the seroprevalence studies, as further described below.

Poethko-Müller, Kuhnert and Schlaud[226] report an 86.8% primary RCV and 59.2% secondary RCV coverage among the German KiGGS study participants aged 14 to 17 years. These rates are significantly lower than among the school-aged children 7 to 13 years old (see above).[226] Similarly, Sakou et al.[259] and Lo Giudice, et al.[165] report lower vaccination rates among adolescents than among school-aged children, as described above.

Five of the rubella antibody seroprevalence studies also found a slightly increasing susceptibility with age. Among the KiGGS study participants, about 12% of adolescents had negative or borderline IgG titers, compared to about 10% among younger children.[227] The Italian study by Lo Giudice, et al.[165] also showed that adults >25 years of age were slightly (0.7%) more susceptible to rubella than their younger

counterparts were. Likewise, the Turkish study by Akkoyunlu et al.[40] discovered a higher susceptibility of 4.9% among adults compared to children and adolescents. Demirdal et al.[97] and Kurugöl et al.[161] both describe decreasing rubella susceptibilities with age up to 30 years, but slight increases among older age groups, as shown in Table 3.24. None of these age-related differences in susceptibility were statistically significant, however.

With the exception of two studies,[40,64] considerably high positive anti-rubella IgG titers >80% were observed among adults. Very high rates near or above 95% were reported for Croatia,[294] Spain,[236] Sweden,[151] Turkey,[153,160,161,283,290] and the UK,[63,130] as delineated below.

The study by Vilibic-Cavlek et al.[294] among 502 Croatian women between the ages of 16 and 45 years revealed that 94.6% of the participants had positive anti-rubella IgG titers. Though slight variantions in seroprevalence were found among different age groups, the lowest among adults aged 21 to 25 years, these were not significant. Overall, the rubella susceptibility in Croatia is very low, as is further supported by the extremely low annual case numbers (see Table 3.20).

In Spain, Ramos et al.[236] report the rubella susceptibility among nearly 3,000 pregnant women to be 5.2%. Kakoulidou et al.[151] also describe a very low 2.2% to 4.2% rubella susceptibility in a sample of over 41,600 pregnant women living in Sweden. Further details about studies regarding rubella susceptibility among women of child-bearing age will be provided below.

Seven of the included studies assessed the rubella antibody seroprevalence among adolescents and adults in Turkey, as shown in Table 3.24. Several of these studies, including those by Demirdal et al.,[97] Tamer et al.[283] and Uysal et al.,[290] focused on rubella susceptibility prior to the nationwide vaccination recommendation in 2006. Since most people were not vaccinated against rubella at the time, antibody seropositivity reflects a history of infection. The high seroprevalence rates reported among the study participants suggest that a large proportion of the general pop-

ulation has been exposed to rubella. Positive seroepidemiological results found in studies conducted after 2006, on the other hand, reflect both rubella vaccinations and prior infections. Most of these studies, including those by Koksaldi-Motor et al.,[160] Karabulut et al.[153] and Kurugöl et al.[161]report very high seroprevalence rates among adolescents and adults. Although these findings may also be reflective of past rubella infections, the high vaccination rates among children (see Table 3.22) suggest a low nation-wide susceptibility.

Studies conducted in the UK by Byrne et al.[63] and Hardelid et al.[130] among adolescents and women above the age of 13 years also report a decreasing susceptibility to rubella with increasing age. While 14.0% of adolescent girls born between 1991 and 1996 (13-18 years old at the time of study) were found to be anti-rubella IgG seronegative, only 7.5% and 1.8% of women born 1986-1990 (19-23 years old) and 1971-1985 (24-38 years old) were susceptible to rubella, respectively.[63] Even lower proportions of seronegative women were observed among residents of the North Thames Valley in England, whereby 5.2% of women <20 years, 3.5% of women 20-24 years and 2.2% of women >25 years were found to be susceptible to rubella. Adolescents and adults in the UK therefore have a lower risk of rubella infection than younger children do.

Furthermore, decreasing rubella susceptibility with age was found among Italian children and adults in the study by Bechini et al.[53] Among children 2 to 14 years old, 12% were seronegative, whereas only about 5% to 7.5% of adults were susceptible to rubella.[53] Differences between adolescents and adults of various age groups were small and not significant, however. The decreased rubella susceptibility among the older age groups suggests that a large percentage of this population has either been vaccinated or has a positive infection history. Similar study results were found among girls and women of childbearing age, as reported in the subsection *Pregnancy* below.

Taking all study results and national vaccination coverage reports into consideration, a general trend in age-related rubella susceptibility can be described. Infants have

the highest risk of infection, followed by pre-school-aged children and school-aged children. Adolescents and adults have the lowest rubella susceptibility. Although the vaccination rates are typically lower among the older age groups, the seroprevalence studies reveal that the immunity against rubella is nonetheless adequate. A positive history of infection among adolescents and adults may partially be responsible for these results, as will be further analyzed in the Discussion.

Gender Eight studies examined whether gender influences the susceptibility to rubella, and found that mostly boys and men are vulnerable to the disease. Due to the considerably late introduction of rubella-containing vaccines for males in several of the European countries studied, certain birth cohorts of the male populations are particularly at risk for infection because of insufficient vaccinations. However, in countries where rubella vaccines were introduced for both males and females at the same time, no significant gender differences in susceptibility have been observed. Below, the study results regarding gender are detailed for Poland, Germany, Italy and Turkey.

In Poland, the current rubella outbreak is almost exclusively affecting males, with a male-to-female ratio of 10:1.[212] The higher susceptibility among males is related to historic immunization practices that did not include boys in the vaccination schedule until 2003.[289,328] Figure 3.20 illustrates the number of rubella vaccination dosages likely to have been received by male and female birth cohorts according to the current and historic vaccination schedules. As of 2013, males born between 1995 and 2003 and females born between 1992 and 2003 are optimally protected against the disease, provided that all scheduled vaccines have been received. Children of both sexes born between 2004 and 2012 should have been vaccinated with one MMR dosage and are schedule to receive the second at the age of 10 years. Females born between 1976 and 1992 also received a single RCV dosage according to historic vaccination recommendations.[31] However, until as late as 2011, males born before 1995 had not been vaccinated against rubella at all. As such, a disproportionately high numbers of cases among male adolescents and men of the 1990 to 1995 birth

cohorts were described in recent years.[328] Catch-up vaccinations introduced in 2011 for those below the age of 20 years are helping to close the immunization gaps among adolescents. Nonetheless, as the current epidemiological situation in Poland shows, young adult men continue to be susceptible and the overall incidence among males remains significantly higher than among females.[154,212]

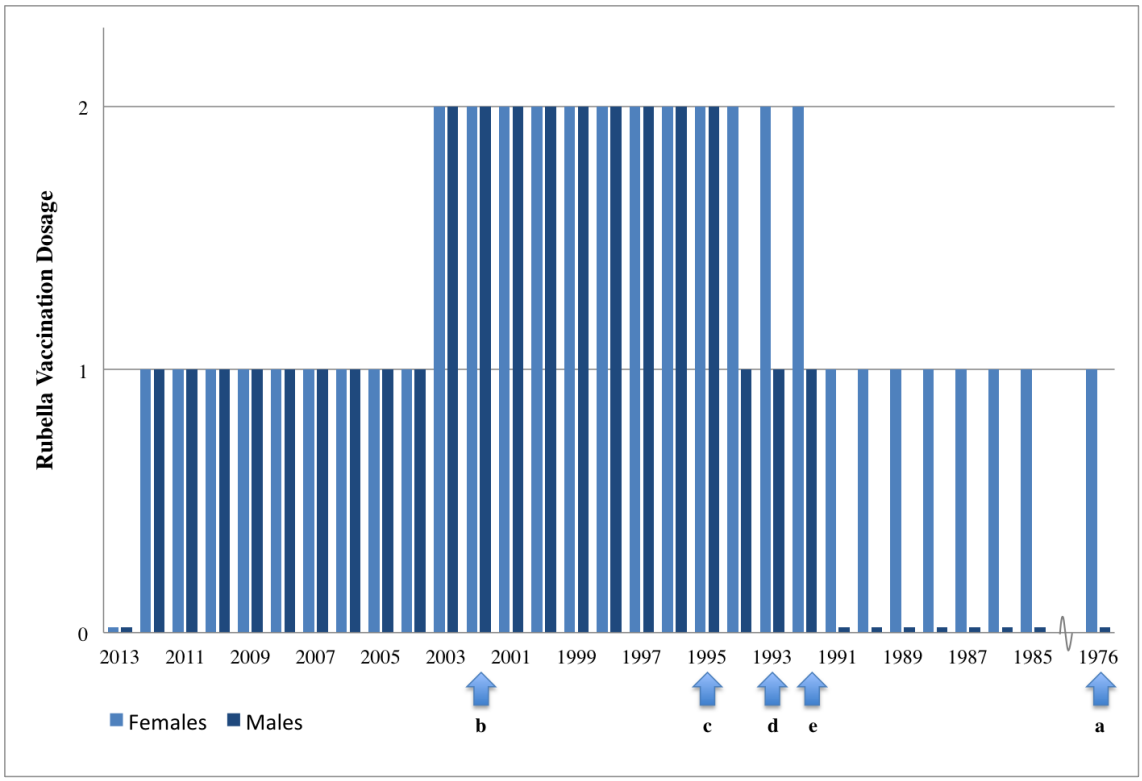

Figure 3.20. Rubella Vaccination Dosages Received in Poland based on the Current and Historic National Immunization Plans, by Birth Cohort and Gender, 2013. Shown are the number of rubella vaccination dosages likely received by males or females born between 1983 and 2013 in Poland. Those birth cohorts affected by changes to the national vaccination schedule have been marked, as follow: **a** (born 1976-1992): monovalent rubella vaccine for 13-year-old girls, effective 1989-2005; **b** (born 2002 or later): first-dosage MMR vaccine at 13-15 months of age, effective since 2003; **c** (born 1995 and later) second-dosage MMR vaccine at 10 years of age, effective since 2005; **d** (born 1993-1996): single MMR vaccination dosage for previously unimmunized girls at 12 years of age, effective 2005-2008; **e** (born 1992 or later): single catch-up MMR vaccination dosage for those under the age of 20 years, effective since 2011. ***Sources***: *ECDC, Vaccine Schedule: Poland, 2013*;[115] *Polish National Insitute of Public Health, 2013*;[31] *Zimmerman et al., 2011*.[328]

Similarly, a considerable difference in rubella susceptibility can be observed among boys and girls in Germany. According to national data obtained through the KiGGS study,[227] the proportion of boys without anti-rubella antibodies was with 12.2% significantly higher than the 9.6% among girls ($p<0.001$). Noteworthy gender differences in vaccination coverage were found for those between the ages of 11 and 17 years.[226] Particularly among adolescents aged 14 to 17 years, significantly less boys were fully vaccinated with two RCV dosages than girls were (53.7% vs. 65.0%).[226]

Such a divergence in vaccination rates was no longer observed among younger age groups, however.

In the Italian study by Bechini et al.[53] (see above), significant gender differences showing higher susceptibility among boys were found only among children aged 2 to 4 years and 10 to 14 years. In both of these age groups, the girls participating in the study had 100% anti-rubella IgG seropositivity rates, while the boys were seropositive in 82.1% and 77.4% of cases (17.9% and 22.6% susceptibility), respectively.[53]

In Turkey, on the other hand, gender differences in rubella susceptibility were not observed. The vaccination against rubella was not commonly available until 2006 and was then recommended for girls as well as boys. Studies analyzing gender as a factor of rubella seroprevalence, such as those by Akkoyunlu et al.,[40] Aytac et al.[47] and Kurugöl et al.,[161] did not find significant differences between males and females.

Though only few studies assessed the influence of gender on rubella susceptibility, the results show that differences among the sexes are closely related to the historic immunization practices of each country.

Pregnancy Due to the serious complications arising from congenital rubella infections, the disease susceptibility among pregnant women is of particular interest. Anti-rubella antibody seroprevalences among pregnant women and women of childbearing age were assessed by 12 studies. The results of these studies are summarized in Table 3.24.

Three studies[64,95,165] from different parts of Italy describe rubella seroprevalence rates of 75.3% to 94.6% among women between the ages of 15 and 45 years. The highest susceptibility of nearly 25% was described among young pregnant women aged 15 to 25 years in southern Italy,[64] the lowest among women aged 25 to 39 years in north-eastern Italy.[95] As described above, a generally decreasing risk of infection can be observed with increasing age.

Ramos et al.[236] determined the seroprevalence of anti-rubella IgG antibodies among pregnant native and immigrant women in Spain to be 94.8%. Among just the native Spanish women, nearly 98% were protected against a rubella infection.[236]

High seroprevalence rates were also measures in Sweden by Kakoulidou et al.[151] Among a total sample of over 41,500 pregnant women, 95.8% had positive anti-rubella IgG titers. As in the study by Ramos et al.,[236] the study results were also analyzed according to native and immigrant women. A positive antibody seroprevalence was found among 97.2% of the native Swedish citizens. Further details about the susceptibility among immigrants are addressed in the *Migration* subsection below.

In the UK, Byrne et al.[63] report the rubella seroprevalence among over 435,000 blood samples of antenatal women between 2004 and 2009. An overall high seroprevalence of 97.5% was determined, whereby a significant increase with age was observed.[63] The highest risk of infection with nearly 14% was reported for the youngest study participants, aged <19 years at the time of the study.[63] Moreover, a slight but noteworthy increase in susceptibility was described over time. The proportions of pregnant women with negative anti-rubella IgG titers were significantly higher in 2007 (2.7%), 2008 (2.9%) and 2009 (3.5%) compared to those in 2004 (2.1%, $p<0.001$).[63] Hardelid et al.[130] report similar findings for the North Thames region of England. Anti-rubella IgG antibody levels were measured from newborn screening blood spots to determine the regional seroprevalence among women recently having given birth. Low rubella susceptibility rates of about 2-5% were found, whereby young mothers <20 years of age had the highest susceptibility with 5.2%.[130] Among women who were born in the UK, the proportion of negative antibody titers was even lower, reaching 1.1% across all age groups.[130]

Vilibic-Cavlek et al.[294] measured a 94.6% rubella seroprevalence rate among 502 women in Croatia. A comparison between pregnant and non-pregnant women showed no significant differences in susceptibility.[294]

In Turkey, five rubella seroprevalence studies[97,153,160,283,290] were conducted in different regions. Generally high anti-rubella IgG antibody titers >92% were measured among women of child-bearing age in southern,[160] western,[283,290] and south-western Turkey,[153] as shown in Table 3.24. Of note are the different definitions used to determine which antibody titer levels are considered to be positive, however. Whereas most used 10 IU/ml as the "cut-off" value, Koksaldi-Motor et al.[160] used 5 IU/ml and Uysal et al.[290] did not indicate a positive titer definition. Caution should therefore be used when comparing these results. Much lower seroprevalence rates were described in a 2005-2006 study by Demirdal et al.[97] A positive anti-rubella IgG titer was determined for 76.5% of adult women 18 to 50 years of age.[97] As a rubella vaccine was not part of the national immunization plan at the time of the study, none of the women had been vaccinated. The seroprevalence therefore indicates which percentage of the population had already been exposed to rubella.

Overall, a considerably high number of pregnant women and women of child-bearing age are protected against rubella. In many countries, including Spain, Sweden, Turkey and the UK, anti-rubella antibody seroprevalences above the 95%-threshold for herd immunity have been described. However, regional and age-based differences do occur.

Education The extend to which education plays a role in rubella susceptibility was analyzed by six studies. The educational status of either study participants or their parents were examined.

Only one publication assessed the rubella seroprevalence among adult women as a factor of their own educational status. In the middle Anatolia region of Turkey, more than 1,200 women participated in the rubella seroprevalence study of Demirdal et al.[97] Though a higher percentage of women with a high educational status (high school, 88.9%) was seropositive compared to those with a low educational level (primary or no school, 77.1%), these findings were not significant.

Several studies involving the parental educational status of children, on the other hand, found significant differences in rubella susceptibility among those with low and high educational levels. As described in Section 3.3.7, Borrás et al.[55] observed a significant, positive association between the vaccination coverage among children in Spain and the educational level of their mothers. Opposite, but also significant, results were found by the KiGGS study[227] in Germany. Children of mothers with a high education level were found to be more susceptible to rubella than children of mothers with a medium or low educational status were (13.8% seronegative vs. 9.8% and 9.4%, respectively). These findings suggest that less parents with a high educational status vaccinate their children than parents of lower educational statuses do.

Aytac et al.[47] assessed that Turkish pre-school-aged children (<5 years old) with parents who had received at least a primary education were significantly more susceptible to rubella than those with parents who were not educated were; this difference was found for both maternal and paternal educational status. The study was performed in 2005, before the introduction of nation-wide MMR vaccination campaigns, however, and none of the study participants had been vaccinated against rubella; the seroprevalence is thus a reflection of positive rubella infection history. In addition, the authors report that the school attendance by siblings of the study participants positively influenced the rubella seroprevalence,[47] which also reflects a higher proportion of infections among these children.

Parental educational status was not determined to be a factor influencing the vaccination status of children and adolescents in Greece. Only non-significant differences in full vaccination coverage among children of mothers with a primary or secondary school completion (up to 12 years of education) or tertiary school enrollment (more than 13 years of education) were found in Athens, Greece, as reported by Pavlopoulou, et al.[215] Similarly, Sakou et al.[259] show that the parental education status does not significantly impact the completion of vaccination schemes among adolescents in Greece.

The various studies presented here do not allow for a clear conclusion as to whether educational status influences rubella susceptibility. The results vary among the different countries, ranging from a positive impact of higher education on vaccination rates in Spain to a negative impact in Germany and no significant impact in Turkey and Greece.

Socioeconomic Status Whether socioeconomic status affects the risk of rubella infection was analyzed by five studies. In various regions of Turkey, no significant differences in rubella seroprevalence were found between study participants of a low, moderate or high socioeconomic status.[58,97,161] However, the study by Bozkurt et al.[58] did show a large difference of 12.2% in anti-rubella IgG seroprevalence among female students residing in a low or high socioeconomic area, whereby the rubella susceptibility was higher among the low SES students. In Catalonia, Spain, the parental social class and occupational status also did not have a significant influence on the primary vaccination status of children.[55]

On the contrary, Poethko-Müller, Kuhnert and Schlaud[226] report that children and adolescents in Germany were slightly but significantly less often vaccinated against rubella if they belonged to families with a high SES compared to those with a medium or low SES (87.1% vs. 90.9% and 92.1%, respectively). Differences in vaccination coverage among these children were more pronounced for the second rubella vaccination dosage (61.8% vs. 68.3% and 65.7%).[226] Overall, no clear conclusions regarding the impact of SES on rubella susceptibility can be drawn from these results, however.

Residence Three studies compared the rubella seroprevalence of people residing in urban or rural areas. Although differences were found, with typically higher susceptibility among people living in rural areas, they were not statistically significant. Kurugöl et al.[161] described a 22.2% rubella IgG seronegativity among participants living in the rural Izmir area of Turkey, compared to 19.6% among those living in the urban area. Likewise, Demirdal et al.[97] report a 25.2% and 20.7% susceptibility

among rural and urban residents of the Central Anatolia region of Turkey, respectively. In Croatia, Vilibic-Cavlek, et al.[294] showed that among women of childbearing age, 5.2% of those living in urban areas and 7.0% of those living in rural areas were susceptible to rubella. None of these study results were significant, however.

Sakou et al.[259] analyzed the vaccination status among adolescents living in rural or urban areas of Greece and found a significant association between higher overall completed vaccination rates and urban residency. Specific differences in rubella or MMR vaccination were not reported, however.

In the German KiGGS study, differences in rubella susceptibility were analyzed among study participants residing in former East German and former West German regions. Although the rubella vaccination was not introduced in the former East German federal states until 1990, a significantly lower susceptibility of 7.8% was found among children and adolescents living in this region compared to the 11.6% susceptibility among children and adolescents residing in former West German federal states ($p<0.001$).[227] The annually conducted vaccination surveys among German children entering the school system further support these findings. From 2007 to 2011, the differences in rubella vaccination between first graders living in the former East German and West German federal states ranged from 1.5% to 2.9% for the primary dosage and from 1.4% to 6.1% for the secondary dosage.[240–243,246] Although assimilation between both groups has occurred over time, those children living in the eastern parts of Germany still have slightly improved vaccination rates compared to those living in the western parts (data as of 2011).[246]

The literature results indicate that residency can impact rubella vaccination rates and susceptibility even if national vaccinations recommendations are in effect. These differences tend to be small, however, and do not significantly impact the overall risk of infection within a country.

Migration Immigrants and refugees residing in the European countries studied have been shown to have a higher susceptibility to rubella infections.[180] Anti-rubella-

virus seronegativity has been reported by six studies among children as well as pregnant women, who are at risk of transmitting the infection to their unborn children. The map in Fig. 3.21 provides an overview.

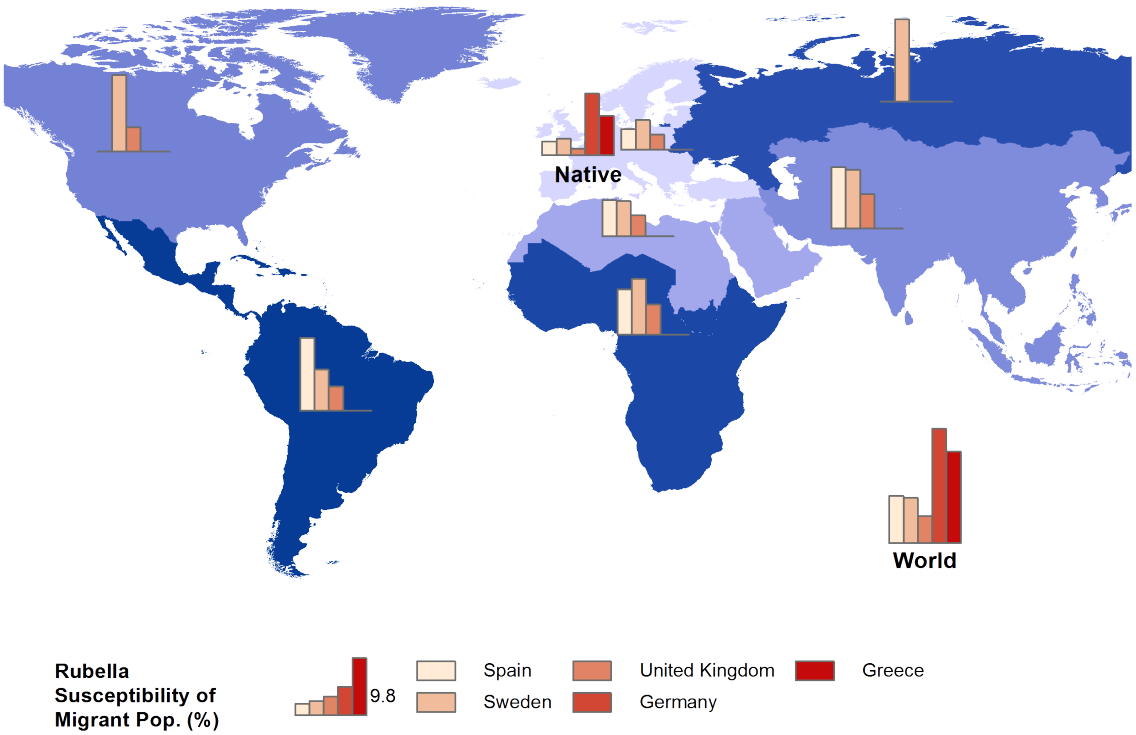

Figure 3.21. Rubella Susceptibility among Immigrant Populations Residing in Europe. Shown are the results of five seroepidemiological studies regarding immigrant and native rubella susceptibilities conducted in the indicated nations. Rubella susceptibilities are based on the percentages of the study populations with negative anti-rubella IgG titers. The bar graphs illustrate the relative risks among migrants originating from the following global regions: North America, Central and South America, North Africa and Middle East, Sub-Saharan Africa, Asia, Eastern Europe, and Central and Western Europe (excluding the respective study locations). The relative rubella risks among native citizens have been marked. Average seronegative rates among immigrant study populations, regardless of origin, are shown in the "World" insert. Throughout all five studies, a much higher risk of rubella infection was observed among non-European immigrants. Due to variances in study size, populations and methods, these data should be evaluated with caution, however. See Section 3.5.6, *Migration*, and Appendix E for detailed study descriptions. ***Sources***: *Hardelid et al., 2009*,[130] *Kakoulidou et al., 2010*,[151] *Poethko-Müller and Mankertz, 2012*,[227] *Ramos et al., 2012*,[236] *Sakou et al., 2011*.[259] Geographic data obtained from www.naturalearthdata.com.

In the 2012 article by Poethko-Müller and Mankertz[227] (see KiGGS study above), the rubella susceptibilities among German children with and without a migratory background are described. The authors report that the susceptibility for a rubella infection (negative anti-rubella titer of <8 IU/ml) is with 19.5% among foreign-born children significantly higher than among native German children (10.5%).[227] Small proportions of the immigrant and native populations (0.9% and 1.5%, respectively) have borderline anti-rubella IgG titers (8-11 IU/ml), whereas the remaining are sufficiently protected (titers of ≥11 IU/ml).[227] Children and adolescents of families

with a migratory background, who are German-born themselves, on the other hand, have rubella antibody seroprevalence rates comparable to those of native children (10.0% seronegative and 88.6% seropositive).[227]

As described previously, Pavlopoulou et al.[215] determined the vaccination rates of young children between the ages of 10 months and 5 years as a factor of paternal nationality in Greece. A significantly higher percentage of children with fathers of a Greek nationality had a complete immunization status at 2 years of age than those with fathers of other nationalities had (p=<0.001).[215] However, the same comparison was not true for children at the age of 1 year, where paternal nationality had no influence on the vaccination status.[215] Among adolescents in Greece, a significant difference in vaccination rate of 8.9% between natives and non-natives was observed by Sakou et al.[259] However, the validity of these findings is limited due to a very small immigrant sample size (see Section 3.3.7 for further details).

Ramos et al.[236] analyzed the rubella susceptibility among pregnant women who were either immigrants or native citizens of Spain. Data were collected for nearly 3,000 women between 2006 and 2010, and a significant difference in anti-rubella IgG seropositivity of nearly 6% was found between the two groups (92.0% among immigrants, 97.7% among native Spaniards, $p<0.001$).[236] The seroprevalence also varied depending on the geographic area the immigrants originated from: The women from Latin America and the Caribbean as well as those from Asia (mainly China) had a positive rubella IgG level in less than 90% of cases, those from Africa and the Middle East in 92-94% of cases, and those from other European nations in 96-98% of cases (comparable to the seroprevalence among native Spanish women).[236]

A study by Kakoulidou et al.[151] showed that among a sample of 34,074 pregnant women in Sweden, those who were either native or came from other Nordic countries had a significantly higher rubella IgG antibody seroprevalence than women originating from other countries had. While 2.8% (709/25,342) of Swedish women and 3.5% (25/707) of immigrants from other Nordic countries had negative IgG titers, 7.7% (616/8,025) of immigrants from other nations were susceptible, in particular

those from Baltic and North American countries.[151] A sample of recent immigrants and refugees of unknown origin had the highest rubella susceptibility with 10.2% (118/1,155).[151]

Likewise, the rubella seroprevalence study by Hardelid et al.[130] showed that immigrant women living in the UK were more susceptible to the disease. The authors analyzed the newborn screening blood spots of 18,882 infants born in 2004 and found that the mothers originating from countries other than the UK had significantly larger rubella seronegativity rates.[130] Particularly those from South Asia and Sub-Saharan Africa were susceptible in 6.2% and 5.1% of all cases, respectively.[130] Among the mothers from other European countries, the rubella seronegativity was with 2.5% significantly higher than among those native to the UK (1.1%), but nonetheless fairly low and comparable with those of other studies (see above).[130]

As illustrated in Fig. 3.21, large differences in rubella susceptibility between native and foreign residents were found. The highest susceptibilities were observed among immigrants from baltic countries, North America, South America and Asia. These data should be evaluated with caution, however, as only few studies reported rubella susceptibility by international regions and the numbers of immigrants participating in these studies were generally low. The extend to which immigrants were more susceptible than natives also varies. Regardless of origin, however, immigrants were found to have higher rubella susceptibilities in all of the included studies.

As described in Section 3.3.7, several traveling ethnic minority populations in Europe are susceptible to vaccine-preventable diseases, mostly due to gaps in immunization coverage. Between September of 2011 and January of 2012, a large rubella outbreak involving over 1,800 cases occurred in Romania and was later spread to Spain.[180] Particularly adolescents belonging to the Roma ethnic minority group were affected.[180] The primary dosage RCV immunization rate was with 2.1% extremely low.[180] The ECDC recommends the targeted provision of immunizations and monitoring of vaccination coverage among these difficult-to-reach populations.[180]

The sociodemographic factors that clearly influence rubella susceptibility are age, gender and migration. Particularly young children, males and recent immigrants or refugees are at risk for infection. The susceptibility varies among the countries, however, and is dependent upon each nation's vaccination practices in regard to vaccination age, historic immunization recommendations, and migrant health policies. Education, socioeconomic status, and place of residency do not seem to have a major impact on rubella susceptibility. Women of child-bearing age are generally well-protected against the disease in the studied countries. However, gaps in vaccination coverage are seen among younger women and women with a migratory background. Long-term rubella and CRS elimination is therefore not yet achievable in many of the included nations.

3.5.7. Effects of Migration within Europe

The studies described in the previous subsection show that many international migrants are significantly more susceptible to rubella than native residents living in the respective European countries are. The study results further indicate that non-European immigrants typically have a higher risk of infection than European migrants do (see Fig. 3.21). However, the substantial differences in rubella susceptibility among the studied European nations also contribute to an increased infection risk among travelers and migrants within the continent.

In Fig. 3.22, the 2012 migratory flows and potential rubella susceptibilities among children and adolescents in Europe are illustrated. For each indicated nation, the number of individuals below the age of 18 years who migrated to Germany, along with the respective national rubella primary-dosage coverage rates and incidences, are shown. The level of protection against the disease is considerably high among the majority of the included countries, predominately due to adequate vaccination coverages and high seroconversion rates of a single vaccine dosage. As such, the estimated migrant populations susceptible to rubella are much smaller than for measles and mumps (see Figs. 3.14 and 3.16 for comparison). An estimated 1,394

(vs. 3,385) unimmunized children and adolescents arrived in Germany from the included European nations in 2012: 414 from Italy, 233 from Poland, 209 from Austria, 150 from France, 115 from Greece, 88 from Croatia, 75 from the UK, 65 from Spain, 37 from Turkey and 9 from Sweden. Although these numbers are approximated based on the 2012 migration and vaccination rates of each nation, the differences in rubella susceptibility among migrants from various European nations are nonetheless evident.

Variances in rubella transmission risks also become apparent when comparing the different disease incidences among the European nations, as shown in Fig. 3.22. Rubella incidences were generally low in 2012, suggesting that the intracontinental risk of transmission was considerably low as well. A notable exception is Poland, however, for which high annual case numbers have been reported consistently in recent years (see Section 3.5.4). With a 2012 incidence of 16.24 cases per 100,000 population, the risk of rubella transmission from Poland to other European nations was substantially higher than from all other countries included in this report. Potential reasons for these large discrepancies in rubella susceptibility will be further addressed in Chapter 4 below.

The risk of rubella infection and transmission varies greatly within the European continent. Migrants and travelers originating from or traveling to nations with high disease incidences and/or low vaccination rates are at an increased risk of contracting and spreading the disease. Efforts must therefore be made to reduce the susceptibility among all European residents.

3.5.8. Rating of Vaccination Programs

Taking into account the nationally reported rubella and CRS cases as well as vaccination coverage data and susceptibility analyses, some conclusions can be drawn about the best-practice immunization strategies in preventing rubella infections and eliminate the disease. Table 3.25 provides a summary of the key performance in-

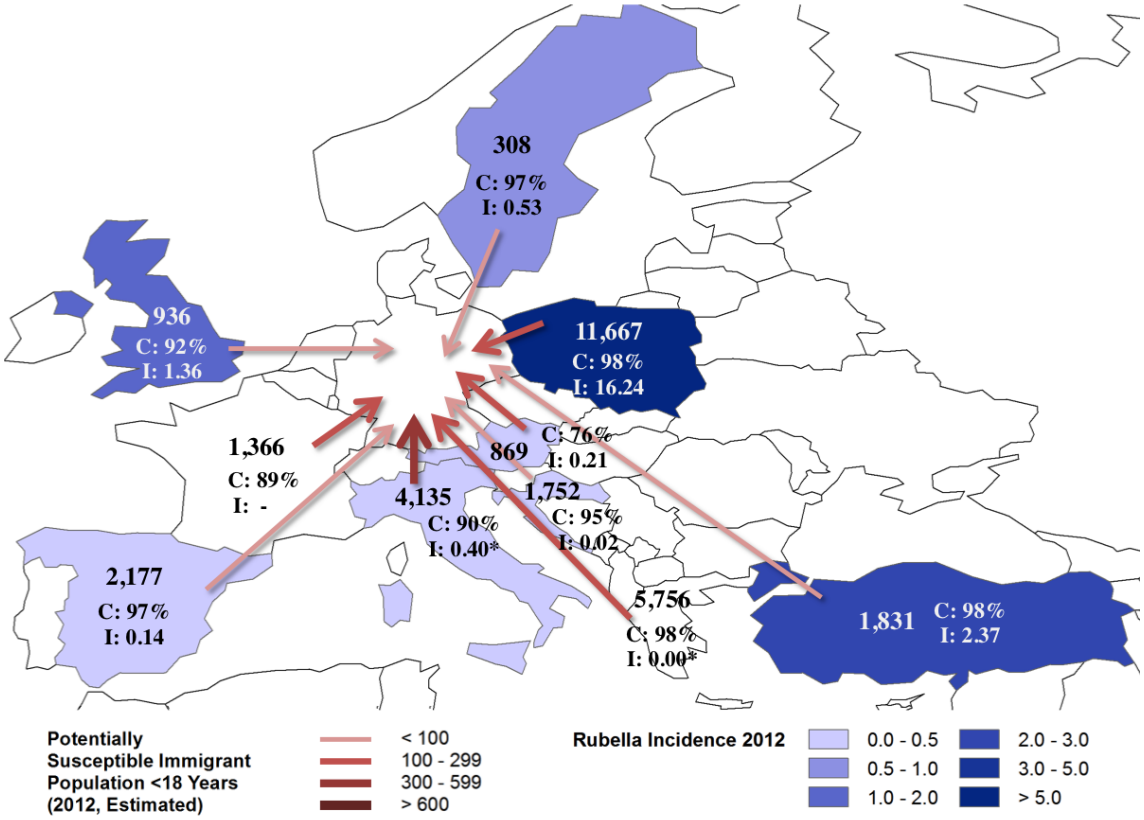

Figure 3.22. Migratory Flows and Potential Rubella Susceptibilities Among Immigrant Children and Adolescents in Germany, 2012. The 2012 migratory flows to Germany among children and adolescents below the age of 18 years are indicated for the respective migrant source nations. National primary-dosage rubella coverage rates (C) and incidences per 100,000 population (I) are listed for each country, as shown. All data are for 2012 or the most recent year available (2011 incidence for Turkey; 2011 coverages for Greece, Spain and Turkey; 2009 coverage for Austria). Nations with uncertain rubella incidences due to known or likely errors in reporting have been marked with an asterisk (∗). The estimated numbers of potentially susceptible children and adolescents are represented by arrows of varying strengths, whereby the national coverage rates have been applied to determine the likely numbers of insufficiently immunized individuals. The with <100 lowest populations of potentially susceptible children arrived from Croatia, Spain, Sweden, Turkey and the United Kingdom, the with >400 largest population arrived from Italy. ***Source***: *Statistisches Bundesamt Deutschland, 2014*.[33] For rubella incidence and coverage sources see Tables 3.20 and 3.21. Geographic data obtained from www.naturalearthdata.com.

dicators of each country's immunization plan. Average, minimum and maximum rubella incidences for the years 2006-2012 are shown, as are the numbers of CRS cases reported between 2009 and 2012. Most countries had mean incidences below 1.00 per 100,000 people in the past years. Italy, the UK and Poland are exceptions, whereby Poland had by far the largest average incidence, reaching nearly 30 per 100,000. The numbers of CRS cases were generally low.

The most recent vaccination coverage data among children aged 1 to 5 years and 6 to 14 years (upon availability) are also provided in Table 3.25. With the exception of Austria, for which exact immunization rates could not be determined due to

major reporting discrepancies, primary-dosage vaccination coverages are provided for all studied nations. The vaccination rates among pre-school-aged children reach or surpass the WHO-recommended threshold of 95% in nearly all included nations, with the exception of France and Italy. National coverage rates among school-aged children (6 to 14 years old) are only available for Sweden, Croatia, Poland and Turkey.

The primary-dosage rubella vaccination coverage among children 1 to 5 years old and the maximum incidence rates were used to grade each nation's immunization program, as described in the Methods Section 2.4. If the national surveillance systems did not require the reporting of cases (such as in France) or if under-reporting of cases is known to occur (such as in Germany and Greece), only the vaccination coverage data was used to determine the grade. Likewise, if the immunization coverage was unknown (such as in Austria), the grade was based solely on the maximum incidence, as described in Section 2.4.

The countries with the most successful rubella vaccination programs (grade level 2) are Germany, Greece, Spain, Sweden, Poland and Turkey. When factoring in the numbers of recent rubella and CRS cases, the highest overall success can be attributed to programs in Greece and Sweden. Greece is the only here included country that meets all of the WHO-criteria for rubella elimination, provided that the actual number of cases does not vary significantly from the reported cases due to under-reporting.[307] The other countries listed above, as well as Croatia, are also near the elimination goal. Austria, France, Italy, and the UK still require further strategies in order to successfully eliminate rubella.

Comparison of National Rubella Vaccination and Surveillance Programs

Nation	Incidence 2006-2012 (per 100,000)			CRS Cases 2009-2012	1-Dose Vaccination Coverage 2012 (%)		Mandatory National Surveillance		Mand. Pregnancy Screening/ Surveillance	Reporting Errors	Grading Level
	Mean	Min	Max		Age 1-5	Age 6-14	Post-natal	CRS			
Austria	0.63	0.02	3.20	-	-[a]	-	Yes	Yes[b]	Yes	Unknown	4
France	0.01	0.00	0.01	5	89.4[c]	-	No[d]	No[d]	Yes	Yes	4*
Germany	0.27[e]	0.07[e]	0.89[e]	3	96.3[c]	-	Yes[f]	Yes	Yes	Yes	2*
Greece	0.01	0.00	0.04	0	98.0[c,g]	-	Yes	Yes	Yes	Yes	2*
Italy	1.65	0.10	9.44	6	89.2	-	Yes	Yes	Yes	Yes	4*
Spain	0.10	0.02	0.20	3	97.1	-	Yes	Yes	Yes	No	2
Sweden	0.10	0.00	0.53	1	97.4	97.2	Yes	Yes	Yes	No	2
UK	1.48	0.78	2.09	1	94.3	-	Yes[h]	No[h]	Yes	No	3
Croatia	0.13	0.00	0.77	0	94.8	97.9[c]	Yes	Yes	-	Unknown	3
Poland	29.58	10.99	60.05	3	95.8	99.4	Yes	Yes	No	Unknown	2
Turkey	0.88	0.09	2.37	2	98.0[c]	88.0[b]	Yes	No	No	Unknown	2

[a] The exact immunization coverage is unknown due to reporting discrepancies.
[b] CRS surveillance since 2007.
[c] 2011 vaccination coverage data.
[d] Voluntary surveillance of rubella cases among pregnant women and newborns.
[e] Incidence based on 2012 regional population of those German federal states reporting rubella cases 2006-2012. *Source: Federal Statistical Office, Wiesbaden, Germany (Statistisches Bundesamt)*.[278]
[f] Sub-national surveillance until April of 2013.
[g] WHO/UNICEF estimate.
[h] Mandatory surveillance of laboratory-confirmed rubella cases only.
* Grade level refers only to vaccination coverage data due to inadequate disease surveillance or under-reporting of cases.

Table 3.25. Comparison of National Rubella Vaccination and Surveillance Programs. Each country's national immunization program is summarized in terms of key performance indicators. Recent average annual incidences and ranges (2006-2012), total number of recent CRS cases (2009-2012), and average vaccination coverage data among 1-5 year and 6-14 year age groups (2012 or most recent available) are shown. The surveillance system performance indicators are presence of mandatory surveillance (yes/no), mandatory pregnancy screening for rubella or pregnancy surveillance (yes/no), and errors in reporting (yes/know/unknown). ***Source***: *Survey on rubella, rubella in pregnancy and congenital rubella surveillance systems in EU/EEA countries, ECDC, 2013*.[30] (For data sources see Tables 3.20 and 3.22.)

4. Analysis and Discussion

Measles, mumps and rubella control may be attainable in the European region. However, the large numbers of annually affected individuals in the studied nations alone may make reaching the elimination goals by the end of 2015 difficult. In the following sections, the progress the nations have made thus far in eliminating the three diseases are described. Those populations that contribute to the perpetuation of measles, mumps and rubella in Europe as well as potential methods for improving the vaccination coverages among them are also addressed. The most successful immunization programs and their strategies are discussed, and the "best-practice" methods incorporated into a proposed uniform, European-wide vaccination schedule. The advantages and challenges of introducing such international recommendations are furthermore examined. Finally, the research limitations are addressed and the necessity for future studies and analyses presented.

4.1. Disease Elimination Progress

To date, the elimination of measles, mumps and rubella from the WHO European region has not yet been achieved. According to the WHO, the endemic transmission of measles and rubella must be disrupted for a period of at least one year to meet the elimination definition and at least three years for verification (see Section 1.3.1).[307] So far, only the North and South American continents have been able to successfully prevent the endemic spread of measles and rubella since 2002 and 2009, respectively.[304] In Europe, large outbreaks involving thousands of peo-

ple continue to be reported annually, however, and the current data suggest an increasing rather than a decreasing trend (see Tables 3.10 and 3.20). Whether the European-wide elimination goals can be reached by the end of 2015 thus remains disputable.

Nonetheless, the wide-spread transmission of measles, mumps and rubella has been prevented temporarily by several European nations, suggesting that sustained elimination may be attainable. A low annual disease incidence of $<0.1/100{,}000$ has been reported at least once by nearly all of the selected nations. The overall vaccination rates also surpass the WHO-recommended 95% threshold in several countries. However, a clear correlation between high immunization coverage and low disease incidence can not always be observed, as will be further discussed below. The following subsections detail the developments in measles, mumps and rubella elimination among the selected European nations.

4.1.1. Cessation of Endemic Transmission

Disease transmission is classified as endemic if it occurs continually within a country over the course of twelve or more months.[307] Imported cases and any resulting short-term outbreaks are not considered in the elimination definition.[303] However, as the source of an outbreak can not always be identified, its classification as endemic or import-related can be challenging. In this report, the WHO target incidence for elimination verification of less than one case per one million population[303] has been used to determine which nations have achieved a disruption of endemic measles, mumps or rubella transmission for at least one year. In addition, non-endemic transmission has been determined in countries reporting large proportions of imported cases or confined outbreaks lasting less than twelve months. In nations not meeting these criteria, the endemic viral circulation may also have ceased, but insufficient data exist to verify such a claim.

Measles

The endemic transmission of measles has been disrupted in eight of the included nations: Austria, Croatia, France, Greece, Poland, Spain, Sweden and Turkey. Of these nations, Croatia and Sweden have had the most success in continually suppressing the spread of the disease. Croatia has reported very low overall incidences in the past years, as shown in Table 3.10. In 2008, a moderate outbreak caused by a measles D4 strain was reported, but it was contained within a period of three months and endemic transmission was not reestablished.[149] Similarly, Sweden has observed only sporadic cases and minor outbreaks in the past years, none of which persisted for twelve or more months.[113] Furthermore, about half of all cases reported in Sweden since 2006 have been imported from other nations and were not the result of an endemic spread. The low population density in Sweden (see Table 3.1) and high immunization coverages are likely contributing to the successful measles control in the country. Both Sweden and Croatia qualify for measles elimination verification.

The remaining nations listed above have been able to eliminate the disease only temporarily and have not yet met the criteria for elimination verification. In Greece, sporadic measles cases were reported between 2007 and 2009; in January of 2010, however, a sizable outbreak caused by the D4-Hamburg genotype began and lasted until Mid-2011.[173,179,218] Unlike the 2008 outbreak in Croatia, endemic transmission was reestablished as a result of this outbreak. Low case numbers reported in 2012 and 2013 do suggest that Greece may achieve sustained measles elimination again in the near future, though.

Austria has also reported only small to moderate outbreaks in the past years. Of the reported cases since 2006, about 8% were imported (see Table 3.10). Although disruptions in transmission are documented,[113] they have not lasted for prolonged periods of time. Nonetheless, Austria may also be close to achieving sustained measles elimination.

Less optimistic is the current trend in Turkey. While the annual incidences had been <0.1/100,000 between 2006 and 2010, they have increased sharply since. In 2013, more than 7,000 people were affected by the disease, resulting in a nearly 100-fold increase in incidence. Whether the reported cases were endemic or import-related is unclear, however.

Only a brief cessation of endemic measles transmission was achieved in France, Spain and Poland, as well. France reported low measles incidences in 2006 and 2007, but has since experienced a tremendous increase in case numbers, reaching nearly 15,000 in 2011. Similar trends can be observed in Spain and Poland, where the annual measles incidences dropped below the WHO target in 2009 and 2010/11, respectively, but increased again thereafter. Although the total number of cases in Poland was considerably low in 2012, they were reported continuously throughout the year,[113] suggesting that endemic transmission is taking place.

In Germany, Italy and the United Kingdom, evidence for a recent interruption of measles transmission has not yet been observed. All three nations have reported generally high annual case numbers and incidences. Although about 5% of the cases in Germany and 3% of those in the UK were classified as imported (see Table 3.10), the endemic spread of measles has nonetheless been maintained. Further progress is necessary for these nations to reach the WHO elimination goals.

Mumps

The progress in mumps elimination among the selected European countries is difficult to assess objectively. The disease is not currently targeted as part of the European-wide elimination goals, and as such, the surveillance of cases is less stringent. Data on imported cases has not been reported by any of the included nations, for instance, thus limiting the extend to which the persistence of endemic mumps transmission can be identified. In addition, insufficient reliable case data exist for three of the nations—Austria, Germany and France—due to voluntary, regional and

sentinel surveillance systems (see Section 4.1.2 below). Therefore, a comparison between these and the other included nations is not practical.

Among the remaining eight countries, mumps case numbers and incidences vary greatly. While Greece and Sweden have reported only few annual cases around 50 or less in the past years, Italy, Spain, Poland, Turkey and the UK, have reported several thousand affected individuals annually. The WHO target incidence for disease elimination has only been reached by Greece, where incidences of $<0.1/100{,}000$ were observed in 2008 and 2010 to 2012. Low case numbers reported in Greece in other years further suggest that the endemic spread of mumps has been successfully disrupted. Similarly, the low numbers of annual mumps cases observed in Sweden in the past eight years are unlikely to be associated with a continuous intra-national transmission. In those nations frequently reporting mumps incidences of 10.0/100,000 or more (see Table 3.16), on the other hand, endemic transmission is presumably continuing. The elimination of mumps may be attainable along with measles and rubella elimination, but more specific disease control measures seem to be necessary in order to reduce the tremendous case numbers in many of the selected nations.

Rubella

The transmission of rubella and subsequent occurrence of congenital rubella infections has been successfully prevented in the past years in four of the included European countries: Austria, Croatia, Spain, and Sweden. Low viral activity has been observed in Austria for several years. However, in 2008 and 2009, an outbreak affecting over 300 people threatened to reinstate the endemic rubella transmission within the country.[155] Successful outbreak control measures could hinder a long-term spread of the disease, though. In Croatia and Sweden, a continual interruption of endemic transmission has been achieved as well. Only sporadic post-natal rubella cases and one CRS case in Sweden were observed in the past eight years. Both countries did report minor outbreaks in 2007 and 2012, respectively, but neither lasted

long enough to meet the definition of an endemic transmission. In Spain, incidences below the WHO-recommended elimination target and a total of three CRS cases were reported between 2009 and 2011. Generally low case numbers in other years suggest that the prevention of rubella has been adequate. All four nations qualify for rubella elimination verification.

A temporary cessation of rubella transmission was achieved in both Turkey and Italy. Both countries reported incidences <1.0/100,000 in 2010. However, much larger case numbers were notified during the following years, as shown in Table 3.20. Particularly in Turkey, where more than 1,700 cases were reported in 2011, endemic transmission was likely reestablished. Unfortunately, no outbreak descriptions regarding the cases after 2010 were found during the literature search, so that the temporal distribution and importation status of these cases can not be ascertained.

Other countries reporting low post-natal and congenital rubella case numbers in recent years were France, Germany and Greece. However, the data from all three countries may not be reliable due to weak surveillance systems (see below). A clear statement regarding the extend of endemic rubella transmission can not be made.

In the UK, the disease burden of rubella is also difficult to determine. In England and Wales alone, several hundred cases are notified annually to the Health Protection Agency Centre for Infections. However, physicians are required to report all suspected cases, regardless of laboratory confirmation.[172] Data from oral fluid anti-rubella immunoglobulin M (IgM) and viral polymerase chain reaction (PCR) testing, performed among 70-88% of the annually notified cases, show that only a small percentage of these cases is confirmed as positive (see Table 3.20).[172,234] The number of notified rubella infections may therefore be grossly overestimated,[172] as further addressed below. Whether the endemic transmission of rubella has been disrupted in the UK can not be accurately determined based on the available data.

Laboratory rubella confirmation is also lacking in Poland. Among the thousands of cases notified each year,[116] less than one percent are confirmed. However, epidemi-

ological linking, insufficient rubella vaccination statuses among affected individuals, and the age and gender distribution of cases suggest that rubella is the most likely cause of the outbreaks.[212] Although the exact numbers of annual rubella cases are unknown, the tremendous amount of clinically suspected cases indicate that the viral activity is extremely high. As shown in Fig. 3.18, Poland is significantly contributing to the persistence of rubella in the European region.[116] Further strategies are required in order to control rubella transmission and meet the European-wide elimination goals.

4.1.2. Surveillance System Performance

As noted in the subsection above, the verification of disease elimination depends not only on the reported clinical cases and incidences but also on the types of surveillance system used and the disease confirmation rates. Various measles, mumps and rubella surveillance methods are employed in Europe, ranging from voluntary case notifications to mandatory, enhanced surveillance (see Sections 3.3.3, 3.4.3 and 3.5.3 for details). The quality of each nation's notification system has been assessed for all three diseases, as delineated in Tables 3.15, 3.18 and 3.25. Well-performing systems were identified based on case notification requirements, nation-wide regulations, laboratory confirmation and reporting, and the minimization of reporting errors.

The following nations have satisfactory measles, mumps and rubella surveillance systems:

- Measles: Croatia, Poland, Spain, Sweden, Turkey and the UK;
- Mumps: Germany (as of 2013), Greece, Italy, Sweden and the UK;
- Rubella: Spain and Sweden.

Among the countries not listed above, diverse surveillance shortcomings exist: Measles reporting errors are known to occur in France and Germany due to under-reporting and are possible in Austria, Greece and Italy due to inadequate laboratory confirma-

tions (see Table 3.15). Likewise, the validity and reliability of mumps notifications are limited in Austria and France, as well as Germany prior to 2013, due to voluntary, sentinel or non-national surveillance methods. Inaccurate case reporting may also occur in Spain, Croatia, Poland and Turkey as a result of insufficient disease verification through laboratory testing or epidemiological linking. Errors in rubella notifications are likely in France, Turkey and the UK due to non-mandatory surveillance of post-natal or congenital rubella cases (see Table 3.25). Furthermore, the notified case numbers in the UK, Poland and Turkey are likely inaccurate due to over-reporting, as many clinical cases can not be verified. In France, Germany, Greece and Italy, on the other hand, the likelihood of rubella under-reporting is high, as revealed by a cross-sectional survey conducted by the ECDC in 2012.[30] Whether rubella notification errors occur in Austria and Croatia is not known, but possible.[30] In all of these countries, improvements in national surveillance systems are necessary in order to fulfill the WHO requirements for disease elimination.

Reporting Errors

Errors in the annual case notifications due to under- and over-reporting are the most common cause of inadequate surveillance. Such inaccuracies limit the extend to which the selected nations can be compared and the elimination progress assessed. Potential reasons for both of these types of reporting errors are manifold, as addressed below.

Under-Reporting Although the notification of clinical or laboratory measles, mumps and rubella diagnoses is mandatory in most European nations, this requirement is not always followed. Physicians may forget to report cases, delay reporting due to time constrains, or not know the necessary reporting procedures.[182] Notification of closely-linked, familial or household cases may also occur only once instead of separately for each individual case.[270] Misdiagnoses or uncertainty about the diagnosis due to similar clinical patterns are other possibilities for under-reporting.

Laboratory testing can help to identify the causative viral agent, but such procedures are not commonly performed in all of the included nations. Monetary and time constraints as well as reservations about obtaining serum samples from patients with only mild symptoms or who are very young may be further reasons for not confirming clinical diagnoses. In addition, affected individuals may not visit a physician or hospital at all, particularly if the infection is mild or clinically silent. Certain population groups, including recent immigrants, traveling ethnic groups and others identified by the ECDC as "hard-to-reach" (see Section 1.2.2), may not have access to health care or be reluctant to see a physician.[180] Measles, mumps or rubella cases may thus be missed. Under-reporting likely occurs to some extend in every country, which should be kept in mind when assessing the case data.

Over-reporting Similarly, the over-reporting of cases is another phenomenon that may be occurring in several European nations. Especially in countries where measles, mumps or rubella have been nearly eliminated and only few, sporadic cases occur, misdiagnoses may be common. A study in Poland that assessed serum samples from patients with "measles-like illness" regarding the presence of various viral antibodies, showed that only about 30% of the patients were actually infected with a measles virus.[268] The remaining samples were positive for rubella virus, parvovirus B19, Epstein-Barr virus or human herpesvirus type 6, or they were negative for all of the tested agents.[268] Lack of laboratory confirmation may therefore lead to erroneous case notifications. Similar observations were made in the United Kingdom, where regular oral fluid antibody testing has led to the identification of misdiagnoses among the majority of notified rubella cases.[234] Between 1999 and 2008, 84% of nearly 14,000 clinically suspected cases were tested and of these, only 1% was confirmed as rubella positive.[172] Such phenomena may be taking place in other nations as well, as the clinical symptoms of many viral infections are similar and may be easily misinterpreted. All nations with low disease confirmation rates, as shown in Tables 3.10, 3.16 and 3.20, may therefore be subject to reporting errors.

4.1.3. Vaccination Coverage

Another aspect of disease elimination is the existence of a sufficient population-wide, or herd, immunity. In highly immune populations, an imported disease agent can not be effectively transmitted, thus protecting those individuals who are not able to receive immunizations. Among pockets of susceptible individuals, on the other hand, a disease agent can spread easily and disrupt the protective herd immunity effects. Progress towards measles, mumps and rubella elimination thus includes the establishment and maintenance of a high population immunity. According to the WHO, at least 95% of the national population should be protected through vaccinations in order to reach the disease elimination goals.[304]

As described in the Introduction Sections 1.3.1 to 1.3.3, measles and mumps seroconversion is reached by the majority of people after two dosages of a respective vaccine have been received, and rubella seroconversion after at least one dosage has been received. The national immunization coverage of each country has consequently been assessed in regard to the proportions of the population immunized with one (rubella) or two (measles, mumps) vaccine dosages. The following countries have reached or surpassed the WHO-recommended 95%-threshold, either among preschool-aged children or among school-aged children (noted with an asterisk ($*$)):

- Measles: Croatia*, Poland*, and Sweden*;
- Mumps: Croatia* and Sweden*;
- Rubella: Croatia*, Germany, Greece, Poland, Spain, Sweden and Turkey

Other nations with considerably high vaccination coverage rates between 90% and 95% are Croatia (rubella), Germany (measles, mumps), Italy (rubella), Spain (measles, mumps) and the UK (rubella). These nations may be able to reach the recommended vaccination coverage of the indicated diseases in the near future. Among those countries with lower immunization rates, improvements in national vaccination strategies may be necessary in order to establish a sufficient herd immunity.

Correlation Between Vaccination Coverage and Disease Incidence

Immunization coverage is typically negatively associated with disease incidence. However, there is not always a clear correlation between these factors, as nations with high coverage rates have reported high case numbers and vice versa. In Table 4.1 and Fig. 4.1, the mean 2006-2012 measles, mumps and rubella incidences are shown in respect to the national 2012 coverage rates among preschool-aged children or school-aged children, depending on the nations' individual vaccination schedules. Pearson correlation coefficients (r) were calculated for measles and mumps primary and secondary dosage rates as well as for rubella primary dosage rates, as shown. Strong negative correlations, as expected, were observed only for the measles and second dosage mumps coverages and incidences. The primary mumps dosages were only weakly associated with mumps incidences, and the primary rubella dosage rates correlated positively. Several factors could explain these discrepancies:

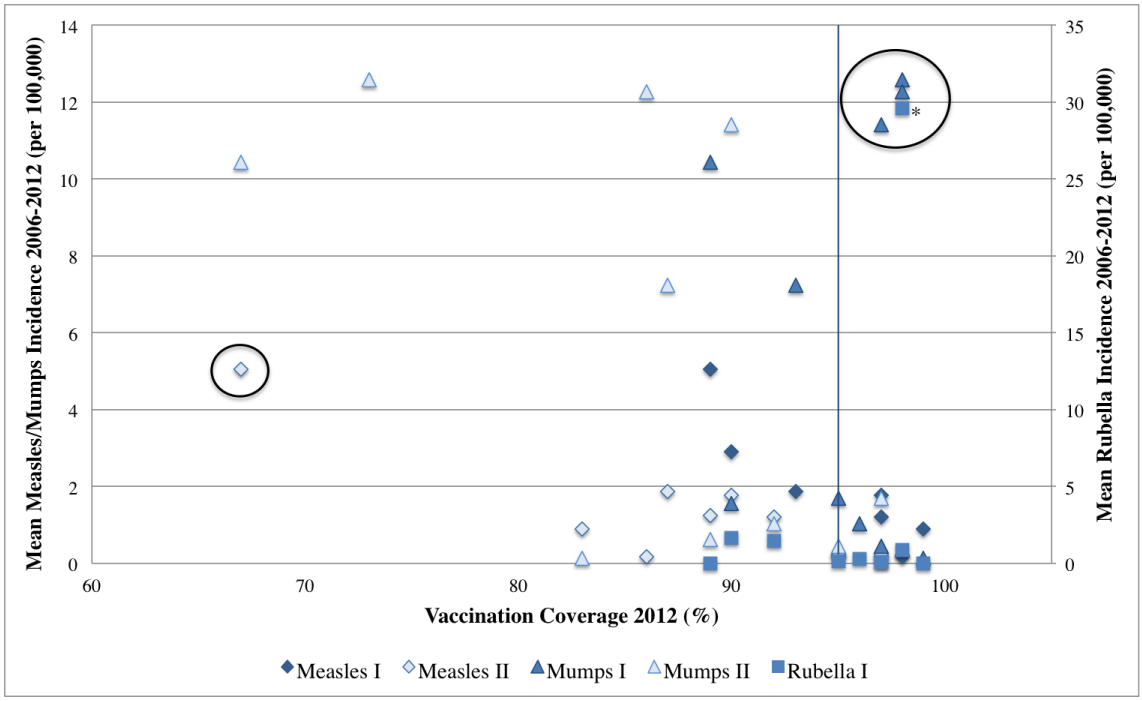

Figure 4.1. Plot Diagram: Correlation between Vaccination Coverage and Disease Incidence. The mean 2006-2012 measles, mumps and rubella incidences (per 100,000 pop.) of each included country have been plotted in relation to the respective 2012 (or earliest available) vaccination coverages among the child populations of that nation. Each point represents a country. Reference data for each plot is shown in Table 4.1. The WHO-recommended 95%-threshold for optimal immunization coverage has been marked. Pearson correlation coefficients (r) were calculated, as shown in Table 4.1. Expected strongly negative correlations are observed only for the Measles I, Measles II and Mumps II plots, not, however, for the Mumps I and Rubella I plots. Data pairs that vary noticeably from the expected have been marked. Potential reasons for these discrepancies are discussed in the text.

Correlation between Measles, Mumps and Rubella Incidences and Immunization Coverages

Nation	**Mean Incidence 2006-2012** (per 100,000)			**National Immunization Coverage Rate 2012** (%)				
	Measles	Mumps	Rubella	Measles I	Measles II	Mumps I	Mumps II	Rubella I
Austria	1.24	0.62	0.63	-[a]	89[b]	-[a]	89[b]	-[a]
France	5.05	10.44[c]	0.01	89	67	89	67	89
Germany	1.21	1.03[d]	0.27[d]	97	92	96	92	96
Greece	0.90	0.13	0.01	99	83	99	83	98[e,f]
Italy	2.90	1.56	1.65	90	-[g]	90	-[g]	90
Spain	1.78	11.41	0.10	97	90	97	90	97
Sweden	0.17	0.44	0.10	97	95	97	95	97
UK	1.86	7.24	1.48	93	87	93	87	92
Croatia	0.26	1.69	0.13	95[e]	97	95[e]	97	95
Poland	0.22	12.57	29.58	98	95	98	73	98
Turkey	0.17	12.26	0.88	98[e]	86[e,f]	98[e]	86[e,f]	98[f]
Pearson Correlation Coefficient (r)				-0.85	-0.87	0.02	-0.59	0.23

[a] The exact immunization coverage is unknown due to reporting discrepancies.
[b] 2009 vaccination coverage data.
[c] Incidence based on sentinel surveillance estimates.
[d] Incidence based on 2012 regional population of those German federal states reporting mumps/rubella cases 2006-2012. Source: Federal Statistical Office, Wiesbaden, Germany (Statistisches Bundesamt).[278]
[e] WHO/UNICEF estimate.
[f] 2011 vaccination coverage data.
[g] MMR-2 immunization coverages are not reported.

Table 4.1. Correlation between National Measles, Mumps and Rubella Incidences (2006-2012) and Immunization Coverages (2012). Shown are the national mean 2006-2012 measles, mumps and rubella incidences (per 100,000 pop.) as well as 2012 (or most recent available) vaccination coverage data among children residing in the respective countries. Primary (I) and secondary (II) dosage immunization rates are indicated as shown. Pearson correlation coefficients (r) were calculated to determine the correlation between respective vaccination rates and disease incidences. Expected strongly negative correlations are observed only for the primary measles and secondary measles and mumps coverages, not, however, for the primary mumps and rubella coverages. Possible reasons for these variances are discussed in the text.

One difficulty in comparing vaccination coverages and disease incidences is that the immunization rates are provided predominantly for young children, whereas the incidences are measured for the nations' entire populations, regardless of age. The vaccination rates therefore do not accurately reflect the population-wide immunities. An example is the high mean incidence of rubella in Poland in spite of the very high immunization coverage (marked with an asterisk ($*$) in Fig. 4.1). The reported vaccination rate describes the protection among children, not among the predominantly affected adolescent and adult male population, however (see Section 3.5.4 for details). When Poland is not included in the analysis, the correlation among the remaining countries is with an r of -0.45 closer to the expected.

Aside from age, other variances in population immunity should also be considered when assessing coverage rates. Communicable diseases frequently spread among susceptible population subgroups who may refuse vaccinations or face various challenges in accessing the appropriate health care services. The vaccination statuses of these individuals or groups may not necessarily be denoted in the nation-wide reported coverages, however. Regional and outbreak analyses have shown that insufficiently immunized individuals tend to provide vaccination history data less often than sufficiently vaccinated individuals do.[238] The coverage rates may therefore be overestimated and the correlation results skewed. Further details about susceptible subgroups that may influence the overall population-wide immunity will be addressed in Section 4.2 below.

Large disease incidences in spite of vaccination rates surpassing the WHO-recommended 95%-threshold could also be explained by insufficient immune responses. As highlighted in Fig. 4.1, several nations with primary dosage mumps coverages of 97-98% have unexpectedly high average disease incidences between 11 and 13 per 100,000 population. Studies have shown that the effectiveness of a single mumps dosage ranges between 60% and 90%,[300] suggesting that primary vaccine failure is common. In addition, waning immunity, or secondary immune failure, may also play a role. These factors could explain the large numbers of cases reported in several countries despite the adequate vaccination rates and will be further addressed in Section 4.2.2 below.

Another reason for the lack of correlation between immunization rates and incidences may be case estimates and reporting errors, as addressed in Section 4.1.2. Particularly in France and Germany, as well as to some extend in Austria, Greece, Italy and Spain, the notified incidences may not be accurate due to regional, sentinel or voluntary reporting systems or the known occurrence of under-reporting. The considerably low measles incidence in France in spite of a low MCV-2 coverage (marked by the small circle in Fig. 4.1.), for instance, could be explained by the under-reporting of cases.[270] Particularly mumps and rubella incidences may

be affected, as the surveillance of these diseases is weak in several nations with non-mandatory notification systems (see above).

The unclear correlation between vaccination coverage and disease incidence observed among the selected European nations may be explained by undocumented variances in population immunity, reduced immune responses to single-dosage vaccines or potential case reporting errors. Increases in population-wide MMR-2 coverages as well as improvements in vaccination and disease surveillances are necessary in order to prevent measles, mumps and rubella cases and better monitor their elimination success.

Taking all of the above factors into consideration, progress towards measles, mumps and rubella elimination has been made in many of the selected European countries. However, only few of the nations have been able to successfully and persistently eliminate the diseases. Among them, Sweden has had the most success in reaching high population immunities, establishing well-performing surveillance systems and preventing the endemic transmission of all three disease. Croatia has had similar success with measles and rubella elimination. Furthermore, mumps has been effectively controlled in Greece and rubella in Spain. Among the remaining nations, measles, mumps and rubella elimination is possible, but different approaches may be necessary to reach the elimination goals in the near future. European-wide immunization recommendations, based on the strategies of successful vaccination programs (see Sections 4.4 and 4.5 below) may promote the establishment of a measles-, mumps- and rubella-free Europe.

4.2. Susceptible and "Hard-to-Reach" Populations

In spite of considerably high vaccination rates among many of the selected nations, outbreaks of measles, mumps and rubella continue to occur in nearly all European countries. Non-immune populations subgroups likely contribute to the persistence

of these three diseases. As part of the literature search, several population groups with increased susceptibilities were identified, including young children, adolescents, males, recent immigrants, refugees and traveling ethnic minority groups. Reasons for the low immunity among these populations as well as potential strategies for improving their vaccination rates will be discussed in the following subsections.

4.2.1. Infants and Young Children

Infants and pre-school-aged children have an increased susceptibility towards measles, mumps and rubella. They are at an age where vaccinations can not yet be effectively administered or the complete two-dosage immunizations are not yet recommended. Particularly the Southern European and Eastern European nations, as well as Sweden, recommend MMR-2 vaccinations at comparatively late ages (see Table 3.8 for details). In these countries, children are not fully immune until the age of 5 years (Italy), 6 years (Croatia, Sweden, Turkey) or even 10 years (Poland). In Poland, more than half of all rubella cases reported between 2003 and 2008 occurred among children younger than 10 years old,[328] raising the question of whether this vaccination age is suitable for providing an adequate population-wide protection. Several recent studies and reports regarding measles cases among young children have also shown that thousands of cases occurred among those too young to be vaccinated according to the current immunization schedules in their respective countries of residency (see Table 3.9). Many of these cases could have potentially been prevent had the vaccination recommendations been at an earlier age.

Recommendations for the primary dosage MMR vaccination age are made by the WHO.[301] Infants with a high risk of measles infection and mortality due to high national transmission rates should receive their first immunization at the age of 9 months, and infants with a low risk of infection due to low regional transmission rates should receive the vaccine at the age of 12 months.[301] Reasons for this rationale are an increased protection at an earlier age among highly susceptible children, in spite of lower seroconversion rates (82-95% for measles at age 8-9 months), and a

higher chance of seroconversion (93-100% for measles at age 11-12 months) among less susceptible children.[301] Among the included European nations, most follow the recommendations for a low measles exposure risk and vaccinate children at the age of 11 to 12 months. Italy, Poland and Sweden, on the other hand, advice later vaccination ages, potentially leaving larger susceptibility gaps among the youngest population members. An earlier vaccination age could better protect these children. For subnational regions, frequent travelers, or populations in which the measles, mumps or rubella transmission is high, an additional vaccination at the age of 9 months could be considered. France, Germany and Spain already have such a recommendation in place, providing early vaccinations or post-exposure prophylaxis to infants as young as 6 months old. However, no such protective procedures are advised in the remaining countries. Particularly with the goal of measles and rubella elimination in mind, such measures could further limit the transmission of these diseases and prevent infections and complications among infants.

Unfortunately, clear recommendations for an ideal second dosage MMR vaccination age do not exist. The WHO states: "In countries with low measles transmission (that is, those that are near elimination) and where MCV-1 is administered at age 12 months, the optimal age for delivering routine MCV2 is based on programmatic considerations that achieve the highest coverage of MCV2 and, hence, the highest population immunity".[301] Difficulties arise when attempting to determine the time at which the highest vaccination coverage can be achieved.

Some countries, including Austria, France, Germany and Spain, have chosen to vaccinate children early on, before or at the age of 2 years. Advantages of these vaccination strategies are an early protection among young children, even if the primary dosage failed to induce seroconversion, the possibility of reaching previously unvaccinated children in their first years of life, and an opportunity to promote other preventative measures and immunizations at an early age, such as against diphtheria, tetanus and pertussis.[301] Disadvantages are that less children may be reached in comparison to in-school vaccination campaigns, parents may be more reluctant to vaccinate younger children due to perceived vaccine risks,[54,60] and existing immu-

nity may decline at an earlier age, potentially increasing the susceptibility among adolescent and adult populations (see below).[227]

In Sweden, Croatia, and Turkey, MMR-2 dosages are administered in schools, where large percentages of the respective birth cohorts can be reached, including children who may not regularly visit a physician. Other advantages of this vaccination method include the school-based educational materials regarding immunization benefits,[252] a potentially wider acceptance among parents due to the child's older age and the ability to share experiences and concerns with other parents,[60,122] the prevention of local transmission within educational facilities,[57] and the decreased chance of waning immunity among adolescents and adults due to a later vaccine uptake.[227] Disadvantages are the increased susceptibility among pre-school-aged children, particularly in cases with primary vaccine failure,[301] the limited immunization consultation through health professionals and potential reductions in preventative medical checkups,[60] as well as the delayed notice of missed immunizations and administration of catch-up vaccinations. Both early (at age 1 or 2 years) and late (at age 5 to 7 years) second dosage MMR vaccinations have their benefits and drawbacks. However, in order to better protect pre-school-aged children, earlier vaccination schemes should be considered. The potential for pre-school-based, instead of school-based, immunizations should be explored, as will be further addressed below in Sections 4.5 and 4.6.

Although the vaccination practices and immunization age recommendations vary widely among the studied countries, efforts are made by all nations to optimally immunize large percentages of the population. Supplementary vaccination campaigns, as are conducted in several of the countries, can serve as an additional tool in regions with low vaccination coverage. Reminder systems and bonus systems for parents may be further methods for increasing the immunization rates.[46,78,253,264] In addition, infants and young children may be protected through the immunization of their immediate contacts. Mothers who are sufficiently vaccinated can also provide protection to their newborns and young infants through passive immunity. All of

these measures could lead to an elevated protection among the youngest population members.

4.2.2. Adolescents and Adults

An increased susceptibility to measles and mumps has been observed among adolescents and young adults. Reasons may include historic vaccination practices that did not sufficiently immunize the respective birth cohorts as well as waning immunity over time in vaccinated populations. Rubella vaccination rates among adolescents and adults have also been found to be lower than among younger children, but the overall population immunity against rubella is, with few exceptions, generally high, likely due to the high level of protection from a single rubella vaccination dosage and naturally acquired immunity through past infections, particularly among older individuals.

Historically, measles, mumps or rubella vaccines were either not included in the vaccination schedules or administered at varying ages in several of the studied countries, thus leading to insufficient immunizations among various birth cohorts. In Croatia, for example, the MMR-2 dosage was scheduled for children at the age of 7 years in 1994, then changed to 12 years in 1997, and back to 7 years in 1999.[115] These schedule changes affected the 1990 and 1991 birth cohorts, aged 6 to 7 years in 1997 (younger than the recommended vaccination age) and aged 8 to 9 years in 1999 (older than the recommended vaccination age). In Poland, past rubella immunization recommendations have affected predominantly the birth cohorts born prior to 1992, as they received only one (females) or no (males) vaccination dosages (see Fig. 3.20 on Page 184). Mumps immunizations were not introduced until 2003 for the primary dosage and 2005 for the secondary dosage, also leaving many adolescent birth cohorts susceptible to the disease. Recent MMR catch-up recommendations for those under the age of 20 years have contributed to an improved protection among the 1992 to 1996 birth cohorts; however, the majority of adults, particularly males, remain susceptible.[212] Similar immunization patterns can be observed

in Turkey. The country did not introduce mumps and rubella vaccinations until 2006,[39] and existing measles recommendations were not truly enforced until 2003, when the *Health Transformation Program* came into effect (see Section 3.2.11).[39] Measles vaccination campaigns, conducted between 2003 and 2005, did help to close immunization gaps among children and adolescents up to the age of 14 years.[39] Nonetheless, many young adults remain susceptible, particularly those born prior to 1991.

Catch-up vaccinations for adolescent and young adult birth cohorts, as well as supplementary immunization activities (SIA) in the form of targeted vaccination campaigns, could reduce the susceptibility among these previously neglected populations. In other European countries, as well as on the American continents, supplementary vaccination campaigns have successfully contributed to measles, mumps and rubella elimination efforts.[67,157] Strategies in North and South America included routine "catch-up" campaigns for unvaccinated children between the ages of 1 and 14 years, "follow-up" campaigns for pre-school-aged children and "speed-up" campaigns for adolescents and adults.[67] Based on these SIA initiatives across 32 countries and territories, about 450 million people were immunized in addition to routine vaccinations by the end of 2010.[67] Past adolescent and adult measles campaigns in Albania, Azerbaijan, Kazakhstan, Turkmenistan, the Republic of Moldova, and the Russian Federation have also been extremely successful, with coverage rates surpassing 90% of the targeted populations.[157] A recent MMR vaccination campaign conducted in the United Kingdom during 2013 for the 1997 to 2003 birth cohorts (aged 10-16 years), has not been as successful, but the results are nonetheless promising.[269] At the campaign midpoint in August of 2013, about 11% (95%-CI: 6.97-14.57) of previously unvaccinated children and adolescents, corresponding to an estimated 20,000 people, were immunized;[269] a final report is not yet available. Regional immunization strategies targeting adolescents in Germany have also been beneficial in reaching insufficiently vaccinated individuals. In the city of Essen, Germany, the second-dosage MMR coverage among students could be increased from 43% to 59% within the scope of the campaign.[253] Furthermore, Austria, France, Germany, Italy,

Poland, Spain, and the UK provide catch-up MMR vaccinations for teenagers, and France, Germany and Austria additionally for adults up to the age of 35 years (1980 birth cohort) or 45 years (1970 birth cohort), respectively.[24,115,132,245] Such strategies may help to improve vaccination rates among the adolescent and young adult populations.

A further reason for the higher susceptibility among these age groups, particularly in vaccinated individuals, may be primary or secondary immunization failures. Particularly measles and mumps vaccines may not lead to an adequate immune response after a single dosage, which is a common vaccination status among adults due to historic vaccination recommendations (see above). Primary measles vaccine failure may be as high as 7% or even 18%, depending on the vaccination age, and may explain the lower level of immunity.[301] Failure to induce mumps antibody seroconversion may also occur in about 10%, and the long-term effectiveness is with 60-90% even lower.[300] Primary rubella vaccination failure is less of a concern due to high seroconversion rates, reaching 95-100% after a single dosage.[302]

The occurrence of secondary measles, mumps, and rubella vaccination failure was observed in the German KiGGS study by Poethko-Müller et al.[227] IgG antibody seroprevalences among nearly 14,000 participants were analyzed, and adolescent age groups (11-13 years and 14-17 years of age) were found to be consistently less immune to all three diseases than their younger counterparts (3-6 years and 7-10 years of age) were (see appropriate *Sociodemographic Factors, Age* subsections in Sections 3.3.7, 3.4.6 and 3.5.6).[227] This finding could be explained, at least partially, by waning immunity over time.[227] In study participants who had received full MMR (or single-antigen) immunizations, the time that has passed since the last vaccination significantly affected the disease susceptibility, as described by the authors:[227] "In two-dose vaccinees who had received the last dose 3-4 years ago, the odds of being seronegative was 34% higher than in those who had received the last vaccination no more than two years ago and was 76% higher if the vaccination had been given more than 8 years ago." These findings suggest that the immunity to measles, mumps and rubella decreases over time, even in fully vaccinated individuals.

Waning immunity is a concern particularly in populations with a low level of viral circulation, as natural boosting through recurrent exposure is lacking. This is often the case in countries near disease elimination, including most European nations. Whereas older adults may be better protected through past infections and repeated exposures to the diseases, younger generations who received immunizations as children may become susceptible again as adolescents and adults. This findings is particularly disconcerting when the rubella immunity decreases among women of childbearing age. Furthermore, with the changing demographics towards aging populations, the susceptibility among older generations is also likely to increase. Immune system functions decline with age,[211,298] and other factors, such as malignancies, metabolic disorders, malnutrition or medications, can further induce secondary immunodeficiencies. The results of immunosenescence are an increased risk of infections and a decreased efficacy of vaccinations.[211,298] An effective herd immunity is therefore necessary in order to protect these population members. Booster vaccinations and targeted vaccination campaigns among adolescents and young to middle-aged adults may be approaches for improving the overall population immunity. Later second-dosage vaccination ages could also help to reduce the susceptibility among adolescents and adults.

4.2.3. Males

A gender difference in mumps and rubella susceptibility has been observed. Males have a higher risk of rubella infection due to lower vaccination rates in consequence of historic immunization practices. The incidence of mumps is also higher among males, though clear differences in immunization rates could not be determined in recent studies. Possible gender-associated genetic variations in immune response to vaccination may be a cause for this observation.[129,209,260] Efforts should be made to strengthen the overall population immunity by continually providing routine immunizations to both genders and catch-up or booster vaccinations to susceptible males, as further discussed below.

A significantly higher susceptibility to *rubella* among males than among females was determined by several of the included studies, as described in Section 3.5.6, *Gender*. In many European nations, including Austria, Croatia, France, Germany, Greece, Poland, and the UK, only pre-adolescent and adolescent girls were vaccinated when rubella vaccines were first introduced. These immunization practices, though effective in reducing congenital infections, could not entirely eliminate CRS because women of childbearing age were exposed to rubella through contact with infected males.[42] The changes in vaccination plans to include both genders have helped to further reduce both the risk of infection among young women and the incidence of CRS. However, adolescent and adult males remain susceptible in many of the aforementioned countries, as exemplified by the tremendous rubella outbreak currently prevailing in Poland (see Section 3.5.4).[116,212] Consequent immunization strategies targeting both sexes should alleviate the problem with time, but further supplementary vaccination campaigns targeting susceptible males are necessary in order to establish an adequate population immunity in the near future.

The increased susceptibility to *mumps*, on the other hand, is not a result of different gender-based vaccination practices. All of the selected European countries introduced mumps vaccines as part of MMR preparations concomitantly for both males and females.[115] Nonetheless, males seem to be disproportionately more often affected in outbreaks than females are, as described in Section 3.4.4. During a recent mumps epidemic in the Netherlands, for instance, predominantly young adult males were affected, even though the majority of cases had been vaccinated (about 80% with at least one dosage and about 70% with two dosages).[260] Higher mumps incidences among males were also observed during outbreaks in Ireland and the USA, in spite of high vaccination coverages among the affected individuals.[66,131,162] Furthermore, in several antibody seroprevalence studies among vaccinated individuals in Germany, the Netherlands and the USA, lower antibody levels were found among males than among females.[209,227,271] Although the study conducted in Germany did not find a significant difference, a trend could nonetheless be observed (see Section 3.5.6, *Gender*).[227]

Reasons for the different immune reactions between males and females remain unclear. Varying humoral and cellular immune responses to mumps vaccines based on genetic polymorphisms in human leukocyte antigen and interleukin cytokine receptor genes could potentially explain the gender difference.[209] A different rate in antibody reduction after an initial response to the vaccination is also conceivable.

Booster vaccination campaigns targeting specifically susceptible adolescent and adult males could help to prevent future outbreaks. Some success of third dosage MMR vaccinations during mumps outbreaks has been reported recently.[117,203,206] As suggested in Section 4.2.2 above, booster dosages and targeted immunization campaigns could help to alleviate the gender-specific susceptibilities.

4.2.4. Recent Immigrants and Refugees

The ECDC has identified immigrants and refugees as "hard-to-reach" populations in terms of MMR vaccinations.[180] An increased susceptibility has been described in particular for measles and rubella, as delineated in the appropriate *Sociodemographic Factors, Migration* subsections of Sections 3.3.7 and 3.5.6. Several studies have shown that recent and first-generation migrants are particularly likely to suffer from either of the diseases, as they are typically less well vaccinated than native citizens or long-term migrants are.[151,223,225,227,282] Second-generation immigrants, on the other hand, tend to be better protected than recent immigrants and sometimes even native citizens are.[227] Such finding suggest that successful integration and targeted vaccination campaigns could decrease the susceptibility of recent immigrants and refugees.

Reasons for the low vaccination coverage among many foreign residents are manifold and a result of the conditions in both the country of origin and the host nation. The immigrants and refugees may stem from regions in which routine MMR immunization practices are not yet well established, as is the case in many African, Eastern Mediterranean and South-East Asian nations. According to the WHO, 35 nations

had MCV-1 coverages below 80% in 2012; three of them, Nigeria, Somalia, and the Central African Republic, even had coverages below 50%.[312] Furthermore, financial, political, or humanitarian challenges may prevent the access to health services and foster disease susceptibility. Refugees, asylum seekers and other displaced persons due to natural disasters or armed conflicts are especially at risk of contracting communicable diseases due to crowding, reduced living conditions and limited access to health care.[304] Even in highly-developed industrialized nations, however, different immunization schemes may be a reason for the insufficient vaccination status among immigrants. Within Europe alone, variances in current and historic immunization practices, implementation strategies and enforcement policies have led to different vaccination coverages among the member states (see Tables 3.14 and 3.22).

Within their new countries of residency, recent immigrants and refugees face further challenges that may sustain the high susceptibility to communicable diseases. Language and financial barriers as well as limited health insurance coverage may hinder the use of routine immunization services. Migrants may be unaware of the existence of such services or where to access them, they may have difficulties with the administrative procedures and fully understanding the information provided through consultations, and they may face discrimination.[80,180] In addition, some individuals may be reluctant to receive immunizations due to cultural and religious reasons or misperceptions about the risk of adverse events outweighing the benefits.[180,304] These barriers often impede the vaccination efforts.

Strategies for reaching immigrant and refugee population members include targeted immunization campaigns as well as migrant-sensitive health care services. Immigrant catch-up vaccinations are already recommended by some nations, including Greece, Italy, Spain and the UK.[293] In countries with routine school-based vaccinations, such as Sweden, Croatia, and Turkey, migrant and refugee children may also be reached as part of the general immunization schemes. The success of such measures has not been well-documented, however, as many of these nations do not monitor the separate vaccination coverage of specific subgroups.[180] Studies and sur-

veys do suggest that gaps in susceptibility remain.[180] In order to close these gaps, the ECDC suggests the following strategies:[104]

- "*Exploring and developing good practice approaches to maximise access to healthcare, particularly for undocumented and uninsured migrants.*
- *Investigating the factors that limit access to and utilisation of health services and develop 'migrant-friendly' services and strategies to increase coverage and uptake, for example, outreach, information about services and involvement of migrant communities in service design and delivery.*
- *Developing training curricula and materials for public health and clinical care professionals to increase awareness of the specific needs of migrants and skills and competencies required to provide culturally sensitive services.*"[104]

Such "migrant-friendly" procedures were successfully employed during a local MMR vaccination campaign in Stade, Germany in 2002 and 2003. Key persons from within the immigrant communities were asked to support the campaign by providing information and encouraging fellow community members to immunize their children.[210] As a result, the local rate of unvaccinated children could be reduced from 44% to 16% within a 3-year time period.[210] Immunization campaigns that not only target immigrant and refugee populations but also accommodate their particular needs, cultural characteristics and language differences could lead to higher vaccination coverages among these population subgroups.

4.2.5. Traveling Ethnic Minority Groups

Other migrating subpopulations that have been identified by the ECDC as highly susceptible to measles, mumps and rubella include the Roma and Irish Traveller ethnic minority groups.[180] In recent years, several studies[79,125,137,169,207,279] have described low vaccination coverage and outbreaks among these populations, emphasizing the need for a better protection.

Reasons for the reduced immunization rates among these minority populations were analyzed in an international MMR survey conducted as part of the VENICE II project in 2010.[205] The following difficulties and obstacles in utilizing vaccination services were identified:[180,205]

- Frequent changes in place of residency
- Lack of identity documents or registration through government agencies
- Unknown population sizes within the communities
- Lack of registration in schools and lower educational status
- Language barriers
- Financial barriers, low socio-economic status and poverty
- Substandard living conditions in settlements
- Limited access to health care
- Vaccination refusal among some population members
- Cultural and religious differences
- Discrimination

Particularly the latter was described as a fundamental problem precluding the equal access to public health care services.[180] Despite anti-discrimination laws, Roma, Irish Traveller and other migrating minority groups continue to face racism and intolerance throughout Europe.[180]

Potential approaches for reaching traveling minority populations are similar to those described for immigrants (see Section 4.2.4 above). Targeted as well as culturally sensitive vaccination campaigns that are easily accessible and include the involvement of key community members are likely to be more successful than standard public immunizations campaigns are. In Pulawy, Poland, such a strategy was successfully employed in a Roma settlement in 2009 (see Section 3.3.7, *Migration*, for details).[279] In addition, general improvements in health care accessibility and social services that are sensitive to the needs and specific barriers of these minority popu-

lations may lead to an overall higher acceptance of immunization efforts. European-wide, uniform recommendations could also improve the vaccination coverage among Roma and Irish Traveller populations frequently changing their country of residency, as will be further addressed below in Section 4.5.

4.2.6. Other Susceptible Groups

Other populations that have been identified as "hard-to-reach" by the ECDC, but have not been focused on in this report, include various religious groups, anthroposophic communities, and, to some extend, supporters of complementary or alternative medicine.[180] In the 2010 VENICE MMR survey described above (see Section 4.2.5), six European nations (Greece, Ireland, Italy, the Netherlands, Slovenia and the United Kingdom) provided the following reasons for low vaccination coverages among religious and anthroposophic population subgroups:[205]

- Anti-vaccination websites and groups
- Fear of adverse effects
- Perceived low risk of disease
- Perceived mildness of disease
- Natural immunity preferenced over vaccine-induced immunity
- Preference of an older vaccination age for children
- Belief that the number of routine vaccines is too high
- Distrust of health services
- Distrust of government policies
- Fear of thiomersal-containing vaccines
- Religious objections
- Limited access to primary health care

- Minimal contact with health care services

These concerns should be taken into considerations when attempting to reach populations that are reluctant to receive immunizations. Potential strategies may be the provision of educational material, consultations through medical or public health professionals, and, if possible, involvement of key persons from within the groups.[180] Positive media representations that portray the preventative benefits of vaccines may also serve to educate the general public and counteract the negative, often inaccurate, media reports that have been disseminated in recent years.

In groups and individuals that continue to refuse vaccinations, however, the only available strategy to prevent disease transmission during outbreaks may be the exclusion of all non-immune persons from schools and other public institutions until the outbreak has subsided.[180] Such control measures have been successful in Austria, where the measles transmission in two separate outbreaks (2008 in Salzburg and 2009 in Styria) could be reduced by closing the affected anthroposophic schools for one to two weeks and allowing only students with a sufficient immunization status to return during the following three weeks.[156,262] Such measures may not protect all susceptible people in an educational facility, as transmission typically occurs before the onset of symptoms in the primary case, but they could greatly reduce the extend of an outbreak.

In order to reach the European-wide measles, mumps and rubella elimination goals, efforts must be made to provide better immunization strategies to all of the susceptible population subgroups described above. The number of children and adults who can not be immunized with live, attenuated vaccines due to health reasons or because they are too young to be vaccinated is constantly increasing. Only a sufficient herd immunity can protect these individuals, and attempts should thus be made to immunize all susceptible population members able to receive vaccinations.

4.3. Migration and Travel

Infectious diseases, such as measles, mumps and rubella, are not bound by state lines. They must therefore be analyzed on an international level, taking the factors of travel and migration into account. The numbers of tourists, migrants and refugees to and within Europe are constantly increasing,[285] as is the role of travel in disease transmission and population immunity (see Section 3.1.6 and Fig. 3.2).

The risk of international measles, mumps and rubella transmission is contingent upon several factors, including the numbers of infected and potentially infected travelers and the susceptibilities of the individual populations they enter into, as well as the numbers of susceptible travelers and the disease prevalences of the regions they travel to. Several studies and various data regarding these factors have been assessed, as shown in Chapter 3 above.

Particularly for measles viruses, the transmission across state borders has been well documented. Epidemiological linking of viral nucleotide sequences isolated during outbreaks with those accessible through the WHO *Measles Nucleotide Surveillance* database provides essential information regarding the likely routes of importation. As such, many instances of transmission through travel and migration have been identified and the international endurance of particular strains determined.

In Table 3.11 on Page 88, probable transmission routes are provided for various measles genotypes discovered in the selected European nations. While several viruses were imported by travelers from African, Asian and Eastern Mediterranean regions, most originated from within the European continent. This may be explained by the geographic proximity as well as effortless travel between most European nations. A 2006-2007 outbreak in Italy, for example, could be traced back to families who had migrated to the region from Romania; the same viral genotype was later transported to Spain by traveling ethnic minority groups.[83] Aside from migration and tourism, travel for educational or religious purposes has also contributed to the spread of measles across European state lines in the past years. A 2008 outbreak in Germany,

for instance, had been initiated by German students who attended a school in Austria, where, in turn, an outbreak likely linked to a visiting student from Switzerland was occurring.[262,295] In 2010, several measles cases among German residents were also linked to a religious gathering in France, from where the non-immune attendees imported the virus to Germany.[221] The spread of measles, as well as mumps and rubella, through infected travelers thus continues to be a challenge to the disease elimination effort.

However, the size and severity of disease outbreaks are not only dependent upon those individuals transmitting the disease, but also upon the level of immunity among the populations they enter into. In populations with a high level of protection through adequate vaccinations, measles, mumps and rubella viruses can not spread effectively and outbreaks are limited. As shown in Section 4.1.3 above, regions with high MMR-2 vaccination coverages tend to have low disease incidences. While the travel among infected or potentially infected individuals can not be prevented, disease transmission can nonetheless be stopped through high population immunity levels.

These immunity levels are affected by changes in the regional populations, however, presenting a further challenge in disease elimination efforts. When a significant number of susceptible individuals enters a previously sufficiently immune population, the herd immunity effect is disrupted and the risk of disease transmission increases. Travel and migration among non-immune individuals may therefore alter the regional susceptibilities to measles, mumps and rubella, contributing to the persistence of all three diseases in Europe.

As described in Section 3.1.6, not only the numbers of travelers, but also the numbers of immigrants and refugees within and to Europe have sharply increased in recent years. Several of the studies analyzed in this report describe that individuals with a migratory background are often more susceptible to measles, mumps, and rubella than their native counterparts are (see subsections *Migration* in Sections 3.3.7, 3.4.6 and 3.5.6 for details). The data suggest that particularly recent immigrants and

refugees often lack a complete MMR vaccination status. As such, the risk of infection tends to be higher among these populations.

In addition, varying immunization rates among the general populations of different European nations further contribute to the increased susceptibilities among migrants in Europe. As Figs. 3.14, 3.16 and 3.22 illustrate, the estimated 2012 population sizes of insufficiently vaccinated migrant children and adolescents differ greatly between the selected European countries. While children originating from nations with high vaccination coverages, such as Croatia or Sweden, are likely to be sufficiently immunized themselves, those from nations with lower vaccination coverages, such as Austria, France or Greece, are likely to be at a higher risk of infection, particularly when migrating to or traveling though higher-prevalence areas. The susceptibility among migrants in Europe is therefore not only dependent upon the individual vaccination statuses but also on the epidemiological situation in all countries visited. The need for consequent vaccination practices among all population members thus becomes apparent.

The spread of measles, mumps and rubella is facilitated through all types of travel and migratory movements of infected and susceptible individuals. Although travelers from countries with large outbreak numbers are more likely to contribute to the spread of these diseases than travelers from regions with no or low case occurrences are, all insufficiently immunized individuals traveling within Europe may increase the risk of international transmission. Particularly within the European Union, the tremendous growth in tourism and migration, as well as the uncomplicated travel between the member states, has increased the likelihood of communicable disease transportation across state lines. Combined regional elimination and control efforts are therefore necessary to reduce the risk of infection of such diseases.

Until measles, mumps and rubella viruses are eliminated globally, their transmission through international travel and migration can not be prevented. Even in nations that have successfully controlled all three diseases, such as the USA, small outbreaks continue to occur as a result of importation from other countries.[68,69,71,76] The

overall population immunity must consequently remain high in order to prevent the reestablishment of an endemic transmission. Vaccination practices in Europe should therefore focus on establishing not only a short-term disease elimination but also a long-term protection of the entire population. In Section 4.5, a possible model for European-wide immunization recommendations is described, based on the most successful measles, mumps and rubella elimination strategies among the representative nations chosen.

4.4. Successful Vaccination Strategies

The results of the literature review have shown that the vaccination programs of some nations are more effective in reducing the prevalences of measles, mumps and rubella than those of other nations are. Well-working, or "best practice", programs are characterized by both high immunization coverages and consequently low case numbers and incidences. Of the selected European nations, Sweden and Croatia have had the most success in fulfilling the WHO elimination criteria. In this section, the immunization programs are assessed in terms of factors involved in effective measles, mumps and rubella control. The following strategies are compared and discussed: national vs. regional immunization schedules, public vs. private vaccine financing, compulsory vs. voluntary vaccines, younger vs. older vaccination ages, public vs. private vaccine administrations, and strictly routine vs. supplementary immunization activities.

4.4.1. National vs. Regional Schedule

A national schedule with clear vaccination recommendations, as established by a central public health ministry or institution, appears to be a substantial factor of well-performing immunization programs. Flexible revisions to the schedule should also be possible with changing temporal and spatial epidemiological situations. Among

the included nations, all have such centralized and adaptable recommendations in place. However, in Germany, Italy and Spain, regional health authorities can decide whether to follow the national recommendations or to provide individual, local recommendations.

Whether a single nation-wide schedule or regional adaptations are more beneficial remains unclear. National schedules have been successful in Croatia and Sweden, but not in France or the UK. Likewise, regional schedule variations have contributed to successful disease control in Spain, but not in Italy or Germany. While the flexible adaptation to epidemiological changes and outbreak situations may be easier in locally regulated areas, confusion and variances in susceptibility, particularly among individuals residing in different regions, may ensue. Uniform national recommendations, on the other hand, provide unambiguous vaccination schemes and promote equal immunization statuses among all population members, including those who have changed residency within the country. An important disadvantage, however, is the decreased ability to adequately respond to the individual needs of smaller regions based on the local population structure and epidemiology. Vaccination schedules that provide wide-spread recommendations for the entire population but can also be regionally complemented through alternative strategies may advisable.

4.4.2. Public vs. Private Vaccine Financing

The financing of routine vaccinations plays an important role in successful immunization programs. Among the studied nations, most routine childhood immunizations are financed by the government or through statutory health insurances and social security schemes. In Austria, France and the United Kingdom, some of the recommended childhood vaccines must be paid by the vacinees or their families, however.[24,232,293] Figure 3.5 provides an overview.

Currently, MMR immunizations for children are offered free-of-charge in all of the included nations. In Austria, Germany, Greece, Sweden and the UK, vaccines for

susceptible adults are provided at no cost as well. In France, however, public financing is only available for children up to the age of 13 years; catch-up immunizations at a later age must be paid out-of-pocket.[293] This strategy may not be as effective as offering free vaccinations to all children, adolescents and even adults.

The cost-effectiveness of routine two-dosage MMR vaccination schemes has been described among countries all over the world, both regarding direct savings through disease aversion (in terms of hospital and health care costs, for instance) and indirect saving through societal benefits (in terms of mortality reduction and less work days missed due to sickness or caring for ill children).[299,301,327] The willingness to receive vaccinations may also be higher if they are available at no additional cost. A recent review regarding barriers to human papillomavirus (HPV) vaccine uptake described that out-of-pocket costs for inoculants are a predominant reason for not obtaining the vaccine.[235] Prior to the *Health Transformation Program* in Turkey, the uptake of rubella vaccinations was also low, partially due to their availability solely through the private health sector.[97] Successful disease control strategies should therefore include public vaccine financing.

4.4.3. Compulsory vs. Voluntary Vaccines

Whether vaccinations should be required by law continues to be a topic of discussion among many European countries.[99,133,266] As the vaccinees are typically too young to make adequate decisions about the risks and benefits of immunizations, their parents decide for them in most European nations. In other countries, the vaccination decision in interest of the child's welfare and overall population protection is instead made by the government. Both strategies have advantages and disadvantages.

Nations in which MMR vaccinations are mandatory, such as Croatia and Poland, have expectedly high vaccination rates. However, the high coverages do not always correlate with low disease incidences, as exemplified by the large rubella outbreak

in Poland (see Section 4.1.3). In addition, the parental rights and freedom to choose in the anticipated best interest of the child are limited.

Countries with voluntary immunization schemes, on the other hand, often have lower vaccination coverages and missing herd immunity effects. Susceptible persons unable to receive vaccines are therefore at a higher risk of infection and subsequent complications. However, high MMR coverages have been reached in several nations, such as Sweden, Greece, Spain, Germany and Turkey, as well. In these countries, public education, immunization campaigns and catch-up vaccinations likely contributed to the successful coverage. Mandatory vaccinations are certainly an effective strategy in reaching high immunization rates, but they may not be necessary, as alternative methods can induce similar results.

4.4.4. Younger vs. Older Vaccination Age

A notable difference among the various immunization programs studied is the age at which children receive MMR vaccines. In most nations, the primary dosage vaccination age is set at 11 to 14 months. In Sweden, however, the first dosage is not recommended until the age of 18 months, thus leaving a larger percentage of the young child population susceptible. Such an approach may be warranted in nations with overall high vaccination coverages that can uphold the herd immunity effect, but may not be the best course of action in regions with lower immunization rates.

On the other hand, parents who are reluctant to immunize their children may be more willing to do so if the vaccine is administered at a later age, as the VENICE MMR survey regarding common reasons for vaccine refusal suggests (see Section 4.2.6).[205] A similar reason may also explain the higher second-dosage MMR immunization rates among nations recommending the dosage for older children. In both Croatia and Sweden, the MMR-2 immunization is administered at the age of 6 to 7 years and 6 to 8 years, respectively. Other nations that have reached and sustained measles, mumps and rubella elimination recommend comparable vaccina-

tion ages, including the USA at 4 to 6 years and Finland at 6 years.[73,237] Countries currently vaccinating children at the age of 1 to 2 years could consider adapting this strategy as well, particularly if the primary dosage coverages and overall population immunities are adequately high.

The MMR-2 immunization age of 10 years in Poland may be set too high, however. Particularly rubella cases are frequently reported among Polish children below the age of 10 years. Many of these cases could be prevented if the protection among the child population were higher. A reduction in the vaccination age to match those of successful immunization programs may be advisable.

4.4.5. Public vs. Private Vaccine Administration

Vaccines are provided through both private and public health sectors, with international variances regarding the respective sector's relevance. In Fig. 3.6, an overview of the estimated distribution between private and public vaccine administrations is shown. While children living in the Western European countries are predominantly vaccinated in private practices, those residing in the Eastern European nations, as well as Italy and Sweden, are generally immunized in public clinics, health-care centers and schools.

Particularly those countries routinely providing MMR vaccines in schools, including Croatia, Turkey, and Sweden (see Fig. 3.6), have attained high coverages. Regional immunization campaigns in educational facilities have been found to be successful in other nations as well.[100,213] The benefits of school-based vaccinations strategies include the provision of student and parent educational materials regarding immunizations, the peer-to-peer exchange about vaccination concerns and experiences, the broad reach of entire birth cohorts, and the local prevention of outbreaks. In addition, children belonging to susceptible population groups, such as immigrants or traveling ethnic minorities, may be better reached through school-based immunization programs.

A higher susceptibility among pre-school-aged children is a considerable drawback, however, particularly due to the high measles and rubella incidences and complication rates among this young population.[106,200,217] In nations with a sufficient herd immunity through high vaccination rates, this disadvantage may be negligible. In countries with low MMR coverages, on the other hand, the strategy may not be sufficient to provide an adequate population-wide protection.

4.4.6. Strictly Routine vs. Supplementary Immunization Activities

As described in Section 4.4.1 above, the strict adherence to a national vaccination schedule may have several benefits. However, flexible adaptations to changing population characteristics and disease epidemiology are also necessary. Supplementary Immunization Activities (SIA) may be an effective strategy. Past vaccination campaigns for particular age groups and subpopulations have been beneficial in establishing high MMR coverages.[157] In several European nations, including Croatia, Germany, Poland, Sweden, Turkey and the UK, as well as many North and South American countries, SIA have been successful in reaching inadequately immunized population members (see Sections 4.2.2, 4.2.4 and 4.2.5 for details). Targeted vaccination campaigns are likely to be an effective strategy for increasing the MMR coverages in all nations that have not yet eliminated measles, mumps and rubella.

Based on the experiences of the selected nations, the immunization strategies that appear to be the most effective in controlling measles, mumps and rubella in Europe include uniform nation-wide schedules that are regionally adaptable through supplementary campaigns, public vaccine administrations, particularly in educational institutions, and public vaccine financing for children, adolescents and susceptible adults. Evidence also supports that changing the MMR-2 vaccination age to about 6 years may lead to a higher immunization acceptance in the population and may further reduce the risk of infection among school-aged children. However, the strat-

egy is not likely to be effective in countries with national coverages below the herd immunity threshold, as the immunization and health statuses of younger children could be jeopardized. Lastly, mandatory immunization laws are an effective strategy for reaching high national MMR coverages; they are not essential for disease elimination, though, as exemplified by the vaccination successes in nations with voluntary immunization schemes. All of these factors should be considered in the attempt to eliminate measles, mumps and rubella from the European region. A European-wide immunization plan that utilizes the "best-practice" strategies could be an effective tool in reaching the elimination goals. Recommendations for such a schedule as well as its feasibility in Europe will be further addressed in the sections below.

4.5. European-Wide Vaccination Recommendations

As described in Section 4.4, a uniform, European-wide MMR immunization schedule that takes the successful methods of various nations into consideration may be a potential strategy for eliminating measles, mumps and rubella from the entire European region. A model for such a vaccination plan is provided in Table 4.2.

In the exemplary schedule, the common usage of two routine MMR dosages has been maintained, whereby additional dosages for susceptible individuals were added. Supplementary vaccination campaigns are also advisable. The recommendations should include voluntary vaccinations that are encouraged and financed publicly. The main purpose is to provide an adequate coverage of the entire population, regardless of age, gender or subpopulation.

Vaccine	Age in Months (M) or Years (Y)														
	0-5M	6-10M	11M	12M	13M	14M	15-23M	2Y	3Y	4Y	5Y	6Y	7-10Y	11-14Y	15-18Y	>18Y
MMR		P[a]	1				Catch-up[b]			2[c]			Catch-up[b]		(Booster)[d]	

[a] Post-exposure prophylaxis for infants who have come in contact with measles or pre-primary dosage for those traveling to countries with an endemic measles circulation.
[b] Catch-up dosage for unvaccinated children aged 15 to 47 months and unvaccinated or single-dosage vaccinated individuals above the age of 7 years.
[c] The second routine dosage should be administered in schools or other educational facilities, such as pre-schools or kindergartens.
[d] A third booster dosage for adolescents and adults could be considered in nations with a very low measles, mumps or rubella circulation.

Table 4.2. Model of European-Wide MMR Vaccination Schedule. A possible measles, mumps and rubella immunization plan that takes the "best-practice" strategies of various European nations into consideration was created. Included are two routine dosages at the age of 11 to 14 months and 4 to 6 years (dark gray) as well as additional dosages for those at an increased risk of infection (light gray). For infants aged 6 to 10 months who have had contact with a measles-infected person or are traveling to a country where measles is endemic, post-exposure prophylaxis (P) or a pre-primary MMR dosage are advisable. The regularly scheduled dosage at 11 to 14 months should nonetheless be administered. Catch-up immunizations are suggested for pre-school-aged children who have missed the primary dosage and school-aged children, adolescents and adults who have missed the secondary or both dosages. Supplementary immunization activities for hard-to-reach populations are also advisable. In addition, a third or booster dosage could be considered for susceptible adolescents and adults in areas with low measles, mumps or rubella transmission due to the reduced immunoprotection over time. Further studies on efficacy and safety may be necessary, however.

4.5.1. Primary MMR Dosage

The MMR-1 dosage is recommended for children aged 11 to 14 months, as is the common practice in most European nations. The vaccination at this age has been deemed safe and effective and is recommended by the WHO for countries with a low measles, mumps and rubella circulation.[301] For younger infants at risk of exposure to the three diseases, the pre-primary and post-exposure vaccination practices of France, Germany and Spain have been adopted. Particularly in the case of measles, severe complications may occur when unimmunized children come in contact with the virus. Once the passive immunity through maternal antibodies has subsided around the age of 6 to 9 months, infants are highly susceptible and should receive an appropriate immunization after measles exposure or prior to travel to an endemic measles region. Due to the inadequate immune response at such an early age,[301] the regularly scheduled primary dosage at 11 to 14 months should not be omitted, however. Young children who missed the routine primary dosage should receive a catch-up vaccine as soon as possible.

4.5.2. Secondary MMR Dosage

The MMR-2 dosage is suggested for children aged 4 to 6 years, based on the vaccination ages of countries with effective measles, mumps and rubella control. Vaccine administrations at schools or pre-schools are advisable. In educational facilities, large percentages of birth cohorts can be vaccinated, including children from "hard-to-reach" populations (see Sections 4.2.4 and 4.4.5). As the enrollment in pre-primary and primary schools is high in most of the studied nations, a wide-spread reach may be possible (see Section 3.1.5 and Table 3.6). Countries with low pre-primary enrollment rates, including Greece, Croatia, Poland and Turkey, should focus on continuing or introducing school-based vaccinations, preferably for students in the first grade. Additional campaigns for those children not attending either pre-primary or primary schools are recommendable in nations with $<100\%$ enrollment.

Countries with primary MMR coverages <95% should increase the national vaccination rates prior to adapting school-based vaccinations, however. The risks of infections and subsequent complications among pre-school-aged children are too high if vaccinations are pushed back to a later age in spite of low herd immunity effects. Targeted SIA may be advisable.

4.5.3. Catch-up Dosages

For children, adolescents and adults who have missed either one or both of the routine dosages, catch-up vaccines should be provided. Currently, MMR immunizations for adults are either not recommended or the recommendations are capped at a certain age, the highest being 45 years. The cost-effectiveness of MMR vaccinations[299,301,327] justifies the provision of free, voluntary vaccines to all population members, however. Although the measles, mumps and rubella infection rates among adults are generally lower than among children and adolescents, cases are nonetheless reported across all age groups.[106,109,110] The susceptibility among older adults is also likely to increase with the aging population dynamics (see Section 4.2.2). Catch-up immunization campaigns should continue to focus primarily on younger generations, but the risk of infection among older individuals should also be kept in mind, so as to prevent a shift in disease epidemiology towards older generations.

4.5.4. Booster Dosages

Several studies have shown that the protection provided through MMR vaccinations wanes over time and that the effects of immunosenescence may lead to an increased susceptibility among adults. Particularly affected are populations in which the transmission of measles, mumps or rubella viruses are low and the natural antibody boosting effects correspondingly reduced. A booster MMR dosage for adolescents and adults should therefore be considered in countries that have controlled the diseases but struggle to uphold the population-wide immunoprotection. The recent

positive experiences with third MMR dosages in highly vaccinated populations in the USA[117, 203, 206] appear promising. Adverse events as a result of the third-dosage immunizations were described as mild and did not differ from those of primary or secondary dosages.[36] However, further and particularly long-term studies are necessary before such vaccination practices can be generally recommended in all countries.

4.5.5. Supplementary Immunization Activities

In spite of the considerably high vaccination rates that are already reported by most European nations, pockets of susceptible individuals contribute to the persistence of measle, mumps and rubella viruses. Therefore, in addition to the vaccination strategies outlined in the schedule, immunization campaigns targeting susceptible population subgroups are advisable. Groups that have been identified as particularly at risk, as well as specific strategies for attaining higher vaccination rates among them, are described in Section 4.2. Through such supplementary campaigns, a population-wide immunity may be achievable.

4.5.6. Surveillance

Next to effective vaccination strategies, well-performing surveillance systems are also essential for monitoring disease elimination. Improvements in both vaccination and disease surveillance are necessary.

Vaccination monitoring may be achieved through documentation during school-based or pre-school-based immunizations as well as during public campaigns. Data on vaccines purchased and distributed in various regions could also be used to monitor the vaccination uptake; however, as vaccines may be thrown out due to inaccurate storage, expiration or administration errors, the data may not be as accurate as well-documented immunization records are.

Disease surveillance requires improvements in monitoring systems, laboratory confirmation rates and the minimization of reporting errors. As described in Section 4.1.2, several of the studied nations already have adequate surveillance systems for at least one of the diseases in place; however, there is room for improvement in monitoring all three diseases among the majority of the countries. Particularly as the incidences decrease, the notification and investigation of every suspected case is relevant for monitoring and verifying the elimination progress. Policy changes that require measles, mumps and rubella case reporting are necessary in nations with voluntary or sentinel monitoring systems. Campaigns and the use of media to educate health care workers and stress the importance of accurately reporting cases may also be advisable. In nations with known or suspected under-reporting, active surveillance should be considered, particularly during outbreaks. The establishment of clear laboratory confirmation policies as well as the appropriate funding to support the laboratories should be further public health initiatives.

The schedule introduced above could serve as a model for European-wide vaccination policies. In the effort to eliminate measles, mumps and rubella from the region, those practices that have been successful should be used as guidance in nations that have not yet been able to control the diseases. Even in countries with adequate vaccination coverages, continued participation in international immunization efforts may also be necessary in order to uphold a long-term measles, mumps, and rubella control. However, the diversity among the European countries may make the introduction of such uniform recommendations challenging. In Section 4.6, the feasibility of such a schedule in Europe is discussed.

4.6. Feasibility of European-Wide Vaccination Schedule

Whether a single, uniform immunization schedule, such as the one proposed in Section 4.5, is practical in the WHO European Region is not certain. On one hand, equal vaccination policies may be beneficial in reaching and supporting the joined disease elimination efforts. On the other, the European countries vary widely in culture, economics and politics, and may be reluctant to adapt their existing policies to an international guideline. In this section, both the advantages and challenges of implementing a synchronized vaccination schedule are outlined.

4.6.1. Advantages

Some of the benefits of common immunization recommendations in Europe have been previously published by the ECDC.[166] The following points have been addressed:[166]

Simplified immunization procedures for foreign residents Those individuals migrating between the EU member states can follow the same vaccination schedule, regardless of where the immunization program was started. The difficulties and confusion many migrants experience due to different vaccination schemes and schedules could be reduced and the compliance to the vaccination recommendations raised. In addition, physicians, nurses and other health care staff could be relieved of the often complex and time constraining catch-up algorithms and recommendations for immigrants.

Common European vaccine market A uniform schedule could make Europe more interesting for vaccine manufacturers. Inoculants could be produced specif-

ically for the European market, taking the regionally circulating pathogens and strains into consideration.

Improved vaccination safety Common surveillance of adverse reactions and the exchange about the correct number of dosages, timing and administration of routine and booster immunizations could further increase the overall safety of vaccination procedures.

Reduced number of immunogenicity and safety studies for new vaccines In the presence of many different vaccination schedules, new inoculants must be tested in each of the countries they are marketed. A single, uniform schedule could reduce the number of necessary studies and subjects, thus avoiding many blood tests among small children.

Enhanced public information and communication To counteract vaccine opponents in Europe, correct, scientific and transparent information for the general public must be available. Highly varying immunization procedures among neighboring countries make the rationale for national vaccination recommendations challenging, however. A common program with safe and well-working immunization schemes could promote the public trust in preventative health care recommendations and services.

Improved program surveillance Both vaccination program performance and safety could be better monitored in a European-wide setting. Currently, comparing the vaccination rates and delays in different nations is difficult due to varying surveillance types and time points. Standardized monitoring procedures would allow for clearer analyses of performance and recognition of specific improvement needs. Similarly, the common monitoring of adverse events in a wider population could ex-

plicitly address the needs for procedural changes as well as allow for a fast response to reported adverse reactions.

In addition to the reasons provided by the ECDC, further advantages to uniform vaccination recommendations exist:

Centralized policy making A central organ could take over the responsibilities for creating, organizing, and modifying the European-wide schedule. Joined international research committees, in conjunction with already existing organizations, such as the ECDC and WHO, could regularly assess and evaluate the current epidemiological situation in Europe and work together to recommend appropriate disease prevention measures. The workload of each nation's individual vaccination committees and advisory boards could be reduced and instead an international collaboration supported. The public health ministries and departments of each nation could focus on implementing and monitoring the vaccination recommendations instead of creating and regularly modifying them themselves.

Shared vaccine financing Next to establishing a common vaccine market (see above), which can reduce the cost of inoculants due to "bulk purchasing", the public financing of vaccines and immunization campaigns could also be centrally organized and distributed. This would alleviate the financial burdens of low income nations and allow an adequate protection among all European population members.

Improved immunization plans for foreign residents from non-European nations The vaccination policies for non-European immigrants and asylum seekers could be determined on an international level. General and uniform recommendations for providing missing vaccinations would facilitate the immunization procedures and campaigns conducted by public health services. Vaccination schemes started upon arrival to Europe could therefore be easily continued in other host nations.

Enhanced vaccination campaign strategies for susceptible population subgroups Next to a better protection among immigrants and refugees, common immunization policies and campaigns for reaching religious, anthroposophic or traveling ethnic minority groups could also be established. Many highly susceptible population groups exist in Europe, and combined international efforts could lead to a wider coverage among these "hard-to-reach" individuals.

Clear vaccination recommendations for travelers International tourists and business travelers to Europe would benefit from simple, uniform vaccination recommendations, particularly when visiting several different countries within the region. In order to protect travelers, particularly those visiting areas with larger outbreaks, the appropriate immunizations could be provided prior to leaving the country of residency. A single set of recommendations would greatly facilitate the process.

All of the points listed above are justifiable reasons for considering the implementation of a common European-wide vaccination scheme.

The schedule proposed in Section 4.5 above could serve as a model for such uniform recommendations. Through its implementation, the vaccination coverages in the entire European region could be increased. Susceptible infants and toddlers would be protected through primary and pre-primary vaccination policies, young children through pre-school-based immunizations and SIA, school-aged children through school-based vaccinations, and adolescents and adults through booster immunizations. Particularly the vaccinations in educational facilities could reach large percentages of the child population due to the mandatory education policies in most European countries. The possible booster dosages for adolescents could also be provided in schools, and a combination with other vaccines, such as against tetanus, diphtheria, polio or HPV, could be considered. Both the later second-dosage vaccination age and an additional booster dosage could prevent the waning immunity to measles, mumps and rubella observed in many nations with low viral transmission. Women of childbearing age could thus be optimally protected and the occurrence

of congenital rubella syndrome and post-natal measles, mumps or rubella infections among young infants prevented. The suggested targeted immunization campaigns for susceptible subpopulations would furthermore close the gaps in MMR coverage. The model schedule could therefore greatly support the measles, mumps and rubella elimination efforts.

4.6.2. Challenges

In spite of the many advantages to a common immunization schedule, several challenges must also be recognized. The vaccination programs in Europe are a result of historic immunization practices and adaptations, and they are tied to national traditions, health care schemes and sometimes school systems.[166] A fusion of the different vaccination practices may therefore be difficult. The nations may also be reluctant to change their existing and often well-working vaccination programs, as such procedures are time-consuming and costly. In addition, differences in cultural and political orientation may be barriers to collaboration, and financial burdens may limit the willingness to implement new programs. Further challenges specific to the in Section 4.5 proposed MMR immunization schedule are detailed below.

Implementation The European nations could face several challenges implementing the suggested vaccination schedules. In some countries, existing programs would need to be expanded, and in others changed entirely.

The questions of where and by whom inoculants are administered and vaccination counseling is provided arise. In some nations, physicians predominantly provide vaccines, in others, nurses, and in yet others, public or school health personnel are responsible for vaccinations. Counseling is also provided by various health care workers, depending on the individual nation (see Section 3.2 for details). A clear recommendation regarding the type of health care personnel that should provide immunizations and vaccination counseling can not be made. In countries such as

Sweden, where the physician-to-nurse ratio is very low (0.3, see Fig. 3.1), the proposition that only physicians should administer vaccines is not sensible. Likewise, in nations such as Greece, where the physician-to-nurse ratio is extremely high (31.0, see Fig. 3.1), the recommendation that only nurses should provide vaccinations is not feasible. Regardless of who administers the vaccines and provides the appropriate immunization information, however, the individuals must be adequately trained, informed about specific contraindications, and able to quickly respond to adverse reactions should they arise. Staff shortages and extensive training procedures may be burdens to implementation.

The introduction of routine vaccinations in schools or pre-schools could also be difficult, particularly in nations without a corresponding program in place. Organizational and financial aspects must be considered, as well as the chances of reaching the entire population of a certain age group within the educational system. The attendance in pre-primary and primary education facilities must be monitored and plans for reaching those children not attending school established. The size of schools and enrollment in public or private institutions should also be examined. Small educational facilities may have difficulties fulfilling staff and financial requirements, whereas larger institutions may face organizational challenges. Some private educational institutions may furthermore be reluctant to participate in immunization procedures at all. Public health institutions or services could assume the organizational and financial responsibilities on a communal or regional level, but certain burdens would nonetheless remain on the schools. Policies for when and where the children should be immunized as well as catch-up procedures for those unable to attend the in-school vaccinations would need to be established. Furthermore, vaccination-relevant information for students and parents must be provided, parental consent obtained, and adequate responses to immunization refusal trained. Vaccination and safety surveillance, emergency response systems and quality control assurance must also be in place. All of these considerations may pose difficulties in implementing school-based vaccination strategies.

The financial aspects of implementing a new vaccination plan must also be considered. In the proposed schedule, additional booster immunizations, vaccines for susceptible adults of all ages and supplementary vaccination campaigns are recommended. All of these changes are costly. In addition, the expenses of altering policies, training health care staff and providing public education must be kept in mind. Proposed improvements in surveillance systems and laboratory confirmations of cases are further financial strains. Some of the low income nations, such as Croatia (see Table 3.4), may have difficulties providing the public funding for these altered immunization policies. The economic recession that affected most European nations during the past years may make the implementation challenging in other countries as well. Although the public proportion of health financing is considerably high in most of the studied nations, as shown in Table 3.5, financial burdens may also fall onto private providers or the vaccinees themselves (either directly or indirectly through increased taxation or health insurance payments). These financial challenges may hinder the implementation of a uniform European vaccination strategy.

Acceptance The nations may face challenges in the public acceptance of new immunization policies, potentially impeding their actualization. Some people may be reluctant to comply with regulations imposed by a more distant, central organ than their national or regional government. Others may be against changing the existing vaccination policies. In countries with mandatory immunizations, reduced vaccination coverage due to the introduction of voluntary schemes may also be a valid concern.

Nations without current school-based vaccination regulations (see Fig. 3.6) may encounter low acceptance of the new recommendations and associated organizational and financial needs. Schools may be reluctant to introduce immunization programs into their regular schedules. Concerns could include organizational challenges, staff shortages, cost coverages and time constraints. Whether the families of children with special needs, chronic diseases or conditions can be adequately counseled regarding necessary vaccinations and relevant contraindications is also questionable in the

scope of mass vaccinations. Parents may be concerned about the well-being of their children, of not being present during vaccinations and potentially not knowing who is providing the inoculants. Further apprehensions of some parents may regard the later vaccination age and susceptibility among younger children.

In countries where the current vaccine administration occurs predominately in the private health sector (see Fig. 3.6), physicians and private practices or clinics may be affected by the economic aspects of loosing patients due to public and school-base immunizations. The motivation to provide vaccination counseling and promote the benefits of vaccines may be reduced. Regular health check-ups scheduled at the time of vaccinations may also occur less frequently. On the other hand, the physicians and public health personnel of some nations may be responsible for administering vaccines at schools and other public institutions, thereby being required to work more and longer hours. The acceptance among health care workers may therefore be reduced as well.

The recommendation for booster immunizations may raise further concerns among health care providers and the general public alike. Both the short-term or long-term effects are not yet well known. Studies are needed to assess the safety, immunogenicity and compatibility with other vaccines. Adolescents, who would be predominantly targeted by booster vaccination campaigns, may be concerned about obtaining additional immunizations, or they may be reluctant to do so due to self-evaluations of disease invulnerability. They may also struggle with having opposing views to their parents' and not being able to decide for themselves whether or not to partake in immunization campaigns. Currently, only minors in the UK are allowed to provide vaccination consent, regardless of the parental opinion.[98] The inability to provide their own consent may be an important barrier to vaccinations among teenagers in other countries, however.[120] All of the listed concerns and challenges must be recognized and addressed before a uniform vaccination schedule can be introduced.

Valid arguments for and against a uniform European vaccination plan exist. The implementation and acceptance of new policies are never without challenges. Nonetheless, the benefits may be worth at least discussing a uniform immunization schedule within a European-wide setting. Many of the challenges could be reduced through public education and political support of the endeavor. The experiences of nations that have effectively eliminated measles, mumps and rubella can serve as examples for other nations in which the elimination efforts have not yet been as successful. A vaccination schedule like the one proposed here may be an effective tool for reaching the agreed upon disease elimination goals, certainly not by the end of 2015, but potentially in the next couple of years to come.

4.7. Research Limitations

4.7.1. General Limitations of the Literature Search

A systematic review of relevant literature regarding the measles, mumps and rubella elimination progress of eleven European nations was performed in regard to vaccination practices, immunization coverages, and disease surveillance and epidemics. A major limitation to the research was the low number of countries able to be considered. Of the 53 WHO European Region member states, only eleven were assessed due to logistic reasons and time constrains. They were chosen as representative nations for Western, Eastern, Northern and Southern Europe, as outline in the Introduction Section 1.2.1. A more concise evaluation of the European-wide measles, mumps and rubella control could be achieved through the inclusion of all member states.

Language barriers were another impediment. Due to the evaluation of nations with several different languages, the availability of English or German research literature, reports, and websites was limited. Efforts were made to assess reports in other languages with the help of computerized translation softwares, but the texts may have

been subject to translation misinterpretations. Furthermore, literature in foreign languages was eliminated during the scientific database searches, and some published data may have been missed. The epidemiological and vaccination coverage reports of organizations such as the WHO, ECDC, and the former EUVAC.NET did allow for national data accession in English. Nonetheless, language and publication bias can not be ruled out.

An unbalanced amount of literature regarding the three assessed diseases was observed. Most articles and reports regarded measles (333 total, 138 included), followed by rubella (230 total, 87 included) and mumps (160 total, 59 included). A reason for this discrepancy may be the higher public interest in measles and rubella due to their often more severe symptoms and complications. The significantly fewer available references for mumps may restrict the comparability to the other diseases, however.

Further imbalances were noted among the types of literature found. The measles search resulted predominantly in case reports (59% of the included literature) and fewer vaccination coverage (34%) and seroepidemiological studies (6%). A similar distribution was observed for mumps. The rubella search, however, resulted in an equal amount of case and vaccination coverage reports (40% each), and a comparatively large amount of seroepidemiological studies (22%). These findings may be a result of a larger number of recent measles outbreaks, on the one hand, and an increased interest in the level of rubella protection among women of childbearing age, on the other. As few vaccination coverage surveys have been conducted among adults, the rubella antibody seroepidemiological studies serve to provide an overview of the susceptibility among a population at risk of transmitting the disease to unborn children during pregnancy. Interestingly, most of these studies stem from Turkey, where rubella vaccinations were not commonly available until recent years. Many of the seroepidemiological surveys are therefore indicative of past infections and less of vaccination coverage. This should be taken into account when evaluating the country-specific data results.

4.7.2. Data and Analysis Limitations

An attempt was made to compare the eleven included nations in regard to immunization rates and case reports. However, these comparisons must be assessed with caution, as each nation has different methods for obtaining and reporting data. Vaccination coverages, for instance, are surveyed at different ages, using diverse techniques. Many are based on sentinel methods, and the reported values are projected estimates. In some countries, disease-specific coverages are not available at all or only for regional populations. In others, different surveillance methods are used to determine the coverages in various parts of the same nation. A sizable margin of error should therefore be considered.

Case reports and incidences are also error-prone. Disease occurrences are notified by diverse organs of the health care systems, with varying urgency and level of obligation. The case reports may be delayed or missed entirely. They may also be wrongly notified due to inadequate confirmations. Voluntary, sentinel and subnational reports further lack accuracy.

The validity of national epidemiological data may be additionally limited due to the considerable variances in reporting between sources. Reasons for these differences may be manifold: In some countries, such as Italy, major changes in the national surveillance systems may contribute to reporting discrepancies (see Section 3.3.4 for details). In this particular example, the different case definitions stipulated by the old and new measles monitoring systems are likely responsible for the incongruous results. Other nations, such as the United Kingdom, use regionally varying surveillance methods that may lead to notification inconsistencies. The separate public health agencies of England and Wales, Scotland and Northern Ireland report either clinically suspected cases, laboratory confirmed cases or clinical confirmed (through oral-fluid antibody testing) cases, thus affecting their comparability.[16,135,233] Similarly, sources providing exclusively confirmed case numbers can vary significantly from those reporting all suspected cases. Delayed notifications are also handled differently by various sources; some may report the cases at the time of notification,

others retrospectively at the time of actual occurrence. Corrections of erroneously reported case numbers may furthermore be updated in some, but not all reports. Finally, human error in recording and transcribing data must also be considered. For the purposes of this report, the average case numbers from a variety of sources were used. The calculated standard deviations shown in Tables 3.10, 3.16 and 3.20 reflect the extend of variance between the sources.

As described above, only a restricted comparability is possible between the studied nations. In order to evaluate the nations' immunization program successes, some comparisons needed to be made, however. A grading system that purposefully precludes data with known inaccuracies was thus developed. The grade, composed of the maximum disease incidence between 2006 and 2012 and the most recently available immunization coverage among pre-school-aged children, takes only those data values into consideration that are likely to be accurate. The missing or omitted data may lead to misinterpretations, however, and errors in included data can not be ruled out entirely. The vaccination program grading should therefore be viewed as a tendency rather than an exact appraisal. In the final measles, mumps and rubella elimination progress evaluation, delineated in Section 4.1, not only case reports and vaccination coverage data, but also the overall performances of national surveillance systems were taken into consideration.

As secondary outcomes of the literature research, highly susceptible population subgroups were identified. Limitations were encountered regarding the amount of available literature on the various risk factors associated with measles, mumps or rubella susceptibility. Although some factors, such as age, are clearly related to an increased disease risk, others, such as educational status, are less apparent and require further research. Even among those factors likely to correlate with an elevated risk of infection, the outcomes are not definite. For example, immigrants and refugees were identified by several studies to be significantly more susceptible to measles, mumps or rubella than native citizens were. In other reports, migrants were found to be less or equally susceptible, however. The overall vaccination coverages and immunization attitudes in both the country of origin and the host country likely affect these

findings. A generalization about all migrants can therefore not be made. Similarly, the traveling ethnic minority populations vary greatly in their extent of susceptibility. Even within the same minority group, differences can be observed between the regional populations. A lack in adequate studies that incorporate entire populations make concise analyses difficult, however. In order to accurately determine the degree of susceptibility among various subpopulations in Europe, further and more extensive research is necessary. Other pockets of at-risk individuals, including members of various religious and anthroposophic groups, must also be identified and considered in future research, so that strategies may be developed to respond to the individual needs and concerns of these groups and to ultimately achieve a sufficient disease protection among all population members.

5. Conclusion

The infectious diseases measles, mumps and rubella, including their potentially severe complications, could be prevented entirely through adequate vaccination strategies. The WHO European Region member states are thus aiming to control or eliminate the three diseases by the end of 2015. In spite of ongoing efforts, recent outbreak data show that the diseases continue to spread within the European continent, however. Particularly the sharp increases in measles and rubella case numbers during 2013 are worrisome and may hinder the disease elimination progresses.

Reasons for the persistent transmission of all three diseases are manifold and may be a result of both inadequate vaccination practices and gaps in protective population immunity. The systematic literature review and analyses revealed insufficient immunization coverages among several European countries as well as pockets of susceptible population subgroups in nearly all of the studied nations. Populations particularly at risk for contracting and transmitting measles, mumps or rubella include adolescents and young adults, recent migrants and refugees, and traveling ethnic minority groups. Furthermore, infants and children who are too young to be vaccinated as well as persons with illnesses or conditions that prevent adequate immunizations have a high risk of infection. International travel among susceptible members of these populations or other unvaccinated individuals may contribute to the persistence of all three diseases within Europe. As the number of travelers and migrants to and within European nations increases, so does the risk of transmission. The WHO goals of eliminating measles and rubella are therefore unlikely to be met by the end of 2015.

Nonetheless, some progress in controlling measles, mumps and rubella has been made by the majority of the included countries. The WHO elimination criteria for at least one of the three diseases could be met in Croatia, Greece, Spain and Sweden. Temporary disruptions of endemic disease transmission were also achieved in Austria, France, Italy, Poland, and Turkey, suggesting that a long-term elimination may be possible in the future. The immunization coverages have generally improved as well, and high MMR-1 vaccination rates surpassing the WHO-recommended 95%-threshold have been reported in seven of the eleven studied nations. Equally high MMR-2 coverages have been reported in Croatia, Poland and Sweden. The remaining nations have not yet reached sufficient levels of population-wide protection, but their vaccination rates reveal and overall increasing trend over the course of the past years. In order to fulfill the WHO elimination criteria, however, continued immunization efforts are necessary.

For those European nations struggling to control measles, mumps and rubella, alternative immunization practices based on the experiences of countries that have successfully eliminated the three diseases may be a worthwhile approach. Particularly among hard-to-reach groups with low immunization coverages, improved strategies for addressing the individual needs and concerns of their members as well as targeted vaccination efforts are necessary. In this report, the immunization policies of several nations were assessed and a model vaccination schedule based on the "best practice" strategies created. The proposed schedule could be applied internationally and includes methods for reaching large percentages of the European population able to receive MMR vaccinations. Suggested catch-up and supplementary vaccinations would further enhance the overall immunization coverages. In addition, a third or booster MMR dosage for adolescents and young adults is recommended to prevent waning immunity over time, particularly as viral circulation is reduced. Future research is required to test the safety and immunogenicity of such an additional dosage before implementation, however. The possible co-administrations with other adolescent and adult vaccines, such as against HPV, influenza or pneumococcal disease, should also be considered and researched accordingly. The implementation of

a uniform vaccination plan in Europe would not be without its challenges, but the benefits of international cooperative immunization efforts certainly make the implementation of such a European-wide MMR vaccination schedule worth considering.

The immunization recommendations and practices among European nations also differ widely regarding other vaccine-preventable diseases. In the future, similar data analyses in regard to tetanus, polio, diphtheria, influenza, hepatitis B or tuberculosis may provide further insight into the immunization and epidemiological differences prevailing in Europe. The uniform schedule proposed in this report could certainly be expanded to include many other vaccines. MMR combination preparations with varicella vaccines (MMRV) could also be considered, as the control of varicella may be attainable concomitantly with measles, mumps and rubella elimination. Studies on such tetravalent vaccine preparations have shown that they are both safe and effective.[84,126,128,229,258] The future control and elimination of measles, mumps and rubella, as well as a myriad of other vaccine-preventable diseases, may be possible in the European region through adequate immunizations and international collaboration.

6. Summary

Measles, mumps and rubella are viral infectious diseases that may cause severe and devastating complications among affected individuals. The disease burden of all three diseases is high, but could be reduced entirely through successful vaccination strategies. As such, the WHO has established the goal of globally eliminating measles and rubella and concomitantly controlling the frequently co-vaccinated mumps.

In 2010, the WHO European Region member states agreed to strengthen efforts to eliminate measles and rubella from Europe by the end of 2015. As this date draws closer, progress analyses become increasingly relevant. In this systematic literature review, the immunization strategies, vaccination coverages and disease incidences of eleven European nations were assessed and their progress towards disease elimination evaluated.

Successful prevention of the endemic transmission of measles, mumps, or rubella could be achieved in several nations, including Sweden, Croatia, Greece and Spain. Austria, France, Germany, Italy, Poland, Turkey and the United Kingdom of Great Britain and Northern Ireland, though having improved their overall immunization rates, have not yet been able to reach the elimination goals. In Turkey, Italy and Poland, sharp increases in case numbers during recent years are potentially threatening the successful measles, mumps and rubella control in Europe.

Pockets of susceptible population groups that may contribute to the perpetuation of the diseases have been identified. They include infants and young children, adoles-

cents and young adults, adolescent and adult males, recent immigrants and refugees, and traveling ethnic minority groups. Reasons for the increased risk of infection among these groups are manifold and a result of various historic and current vaccination practices, cultural, political and religious differences, as well as individual believes and concerns. Travel and migration of infected individuals to and between the various European nations also play an essential role in the continual transmission of measles, mumps and rubella in Europe. Only an adequate population-wide immunity can prevent the occurrence of major outbreaks due to viral importation. Efforts should therefore be made to immunize all population members able to receive vaccinations and to offer additional immunization opportunities to those susceptible population subgroups that are difficult to reach through routine vaccination programs.

In countries struggling to meet the WHO elimination goals, alternative immunization practices may be necessary. A uniform, European-wide MMR vaccination schedule based on the successful immunization methods of countries that have eliminated measles, mumps and rubella may be an effective tool for improving the overall population-wide immunity and controlling the three diseases. A model for such a schedule was created and includes strategies for reaching population members regardless of age, gender or migratory background. The implementation of uniform immunization recommendations is challenging, but the advantages in terms of improved vaccination, surveillance and disease control methods may be worth at least considering such a strategy in Europe.

Measles, mumps and rubella elimination may be attainable in the WHO European Region. The current epidemiological situation suggests that the goal is unlikely to be reached by the end of 2015, but through continued international efforts and collaboration, effective disease control could be achieved in the near future. In the meantime, improvements in immunization strategies, vaccination coverages, supplementary campaigns as well as disease notification systems and confirmations should be made on a national and international level, so that an adequate population-

wide immunity can be established and the disease elimination progresses effectively monitored within the entire European region.

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A. Inclusion and Exclusion Criteria of the Literature Search

The following limitations were applied to the literature search. Those criteria marked with an asterisk (∗) were amended during the search process, as the need for stricter inclusion and exclusion criteria became apparent.

A.1. Eligibility Criteria

Languages:

- English
- German

Publication Time Period:

- 2009 - 2013

Publication Types*:

- Article
- Book
- Booklet
- Conference Script
- Database
- Data table

- Periodical
- Technical Report
- Web page

Subjects:

- humans of any age and gender

Countries:

- Austria
- Croatia
- France
- Germany
- Greece
- Italy
- Poland
- Spain
- Sweden
- Turkey
- United Kingdom

Vaccine-preventable Diseases:

- Measles
- Mumps
- Rubella

Vaccines:

- Measles-containing vaccines (MCV)
- Mumps-containing vaccines
- Rubella-containing vaccines (RCV)
- Combination Vaccines (MR, MM, MMR, MMRV)

Validity of Data:

- Scientific Publications
- Reports by official and accredited organizations or institutions (see below)
- High pertinence to the searched item(s)

List of Official and Accredited Organizations and Institutions:

- World Health Organization (WHO)
- United Nations Children's Fund (UNICEF)
- European Center for Disease Prevention and Control (ECDC)
- Centers for Disease Control and Prevention (CDC)
- National or regional governmental health institutions
- The World Bank Database
- Universities

A.2. Exclusion Criteria

Publication Types*:

- Addresses
- Autobiography
- Biography
- Classical article
- Dictionary entry
- Directory entry
- Duplicate publication
- Historical article
- Interview
- Legal cases
- Letter
- News or newspaper article
- Patient education handout
- Personal narratives
- Pictorial works
- Portraits
- Video /audio media
- Webcasts

Content:

- Missing epidemiological or demographic data
- Country differing from the searched item in the category countries
- Pathogen differing from the searched item in the category vaccine-preventable diseases
- Vaccine differing from the searched item in the category vaccines
- Analysis of survey, screening or intervention method(s)*
- Potential side-effects of vaccine(s)
- Unofficial source or opinion

Subjects

- Non-human
- Single case reports
- Subjects with a specific disease, condition or co-morbidity
- Subject group limited to a specific employment, educational status, etc.

B. Variables

B.1. Demographics

The following demographic and geographic variables were obtained for each country for 2010 or annually for 2006-2012:

Geography

- Surface area (sq. km)

Population

- Total Population (in millions)
- Female Population (% of total)
- Population growth (annual %)
- Crude birth rate (births per 1,000 people)
- Crude death rate (deaths per 1,000 people)
- Population density (people per sq. km of land area)
- Population ages 0-14 years (% of total)
- Population ages 15-64 years (% of total)
- Population ages 65+ years (% of total)
- Rural population (% of total population)
- Urban population (% of total population)

Economy and Labor

- GDP (in current US$, in billions)
- GDP per capita (in current US$)
- GNI, at purchasing power parity (PPP) (in current international $)
- GNI per capita, at PPP (in current international $)
- Employment rate, 15+ (% employed of total population aged 15+ years)
- Unemployment rate (% of total labor force)

Health

- Health expenditure, total (% of GDP)
- Health expenditure per capita (in current US$)
- Health expenditure, public (% of GDP)
- Health expenditure, private (% of GDP)
- Out-of-pocket health expenditure (% of total expenditure on health)
- Improved water source (% of population with access)
- Improved sanitation facilities (% of population with access)
- Hospital bed density (per 1,000 people)
- Physician density (per 1,000 people)
- Nurse density (per 1,000 people)
- Infant mortality rate (per 1,000 live births)

Education

- Literacy rate, adults (% of population aged 15+ years)
- Primary school starting age (years)
- Primary education, duration (years)
- Secondary education, duration (years)
- Primary completion rate, total (% of relevant age group finishing primary schooling)
- Primary education, pupils

- School enrollment, preprimary (% gross)
- School enrollment, primary (% gross)
- School enrollment, secondary (% gross)
- School enrollment, tertiary (% gross)
- Public spending on education, total (% of government expenditure)
- Public spending on education, total (% of GDP)

Travel and Migration

- Net migration rate (5-year estimates, 2012)
- International migrant stock (% of population)
- International migrant stock, total (number of immigrants and refugees)
- Immigrant population, total
- Immigrant population, by nationality
- Refugee population, by country of asylum
- Refugee population, by country of origin
- International tourism, number of arrivals
- International tourism, number of departures
- Total travelers (arrivals and departures)

B.2. Immunization Programs and Vaccine-preventable Diseases

The following variables regarding national vaccination programs and VPDs were obtained for each country and/or disease:

Immunization Programs

- Vaccines recommended
- Vaccines mandated
- Childhood vaccines free of charge (yes/no)

- Percentage of routine vaccines funded by government
- Percentage of routine vaccines funded by health insurance or social security systems
- Estimated out-of pocket expenditure for routine vaccines (% total expenditure)
- Vaccination schedule (national/regional differences)
- Vaccinations administered in private sector (%, estimated)
- Vaccinations administered by public institutions (%, estimated)
- Vaccinations administered in schools (%, estimated)

Disease Surveillance Systems

- Mandatory national surveillance (yes/no)
- Regional surveillance (yes/no)
- Aggregated or case-based data
- Under-reporting (yes/no/unknown)

Vaccine-preventable Diseases and Vaccinations

- Annual cases reported, total
- Annual cases reported, confirmed (laboratory or epidemically linked)
- Annual cases reported, hospitalized
- Annual cases reported, deaths
- Annual incidence
- Vaccination coverage, total (estimated)
- Vaccination coverage, preschool-aged population ($\leq$5 years)
- Vaccination coverage, school-aged population (6-14 years)
- Vaccination coverage, adolescent population (15-19 years)
- Seroprevalence, by age group
- Seroprevalence/Vaccination coverage by gender
- Seroprevalence/Vaccination coverage by educational status
- Seroprevalence/Vaccination coverage by socioeconomic status
- Seroprevalence/Vaccination coverage by residence
- Seroprevalence/Vaccination coverage by migratory background

C. Literature Search Strategies

The following search strategies were employed during the literature research between August 2013 and February 2014 using the indicated databases. Here, all searches are indicated for the topic of measles. The mumps and rubella searches followed the same patterns, whereby an additional term was used for rubella, as shown. Bold-faced searches and results are those that were included in the further study selection process.

C.1. Pubmed

1. Measles [all fields] → 23,699 results (rubella: 13,406, mumps: 9,154)
2. 1 with Language filter: English and German
3. 2 with Publication date filter: 2009/01/01 to 2013/12/31 → 2,744 results (rubella: 1,335, mumps: 1,081)
4. 3 with Species filter: humans → 2,129 results (rubella: 1,069, mumps: 921)
5. Measles OR MMR [all fields]
6. 5 with filters (2-4) → 2,963 results (rubella: 1,880, mumps: 1,770)
7. Measles OR MMR [title or abstract]

8. 7 with filters (2-4) → 2,955 results (rubella: 1,874, mumps: 1,762)

9. Europe OR European [all fields]

10. 8 and 9 → 505 results (rubella: 350, mumps: 349)

11. Austria OR France OR Germany OR Greece OR Italy OR Spain OR Sweden OR "Great Britain" OR "United Kingdom" OR England OR "Northern Ireland" OR Poland OR Turkey OR Croatia [all fields]

12. 8 and 11 → 793 results (rubella: 524)

13. Austria OR France OR Germany OR Greece OR Italy OR Spain OR Sweden OR "Great Britain" OR "United Kingdom" OR England OR "Northern Ireland" OR Poland OR Turkey OR Croatia [title or abstract]

14. NOT ("addresses" OR "autobiography" OR "biography" OR "classical article" OR "dictionary" OR "directory" OR "duplicate publication" OR "historical article" OR "interview" OR "legal cases" OR "letter" OR "news" OR "newspaper article" OR "patient education handout" OR "personal narratives" OR "pictorial works" OR "portraits" OR "video audio media" OR "webcasts") [Publication Type]

15. NOT "major molecular response" OR "maternal mortality ratio" OR "maternal mortality rate" OR "mismatch repair" [all fields]

16. 8 and 13 and 14 and 15

17. 16 with filter Text availability: abstract available → 515 results (rubella: 298, mumps: 262)

18. Outbreak* [all fields]

19. Incidence* [all fields]

20. Cases* [all fields]

21. Epidemic* [all fields]

22. 18 or 19 or 20 or 21

23. 17 and 22 → 203 results (rubella: 118, mumps: 112)

24. Travel* [all fields]

25. Migration* OR Immigration* [all fields]

26. Migrant* OR Immigrant* [all fields]

27. Refugee* [all fields]

28. Import* [all fields]

29. 24 or 25 or 26 or 27 or 28

30. **23 and 29 → 51 results (rubella: 26, mumps: 18)**

31. Vaccination* OR Immunization* [all fields]

32. **17 and 29 and 31 → 74 results (rubella: 46, mumps: 6)**

33. "Vaccination Coverage" OR "Immunization coverage" OR "Vaccination rate" or "Immunization rate" [all fields]

34. **17 and 33 → 65 results (rubella: 33, mumps: 34)**

35. Seroprevalence [all fields]

36. Seropositiv* [all fields]

37. Seronegativ* [all fields]

38. 35 or 36 or 37

39. **17 and 38 → 36 results (rubella: 36, mumps: 31)**

40. Congenital* [all fields] (*Rubella only*)

41. **17 and 40 → 34 results (*Rubella only*)**

C.2. Medline (via Ovid)

1. Measles [All Fields] → 21,571 results (rubella: 13,443, mumps: 8,652)

2. 1 with Additional Limit: Languages: English and German

3. 2 with Limit: Publication Year: 2009 to 2013 → 2,243 results (rubella: 1,360)

4. 3 with Limit: Humans → 2,091 results (rubella: 1,065, mumps: 741)

5. Measles OR MMR [All Fields]

6. 5 with Limits (2-4) → 2,922 results (rubella: 2,131, mumps: 1,800)

7. Measles OR MMR [Title]

8. Measles OR MMR [Abstract]

9. 7 and 8

10. 9 with Limits (2-4) → 2,731 results (rubella: 2,030, mumps: 1,602)

11. Europe OR European [All Fields]

12. 10 and 11 → 257 results (rubella: 81, mumps: 36)

13. Austria OR France OR Germany OR Greece OR Italy OR Spain OR Sweden OR "Great Britain" OR "United Kingdom" OR England OR "Northern Ireland" OR Poland OR Turkey OR Croatia [All Fields]

14. 10 and 13 → 2,807 results (rubella: 898)

15. Austria OR France OR Germany OR Greece OR Italy OR Spain OR Sweden OR "Great Britain" OR "United Kingdom" OR England OR "Northern Ireland" OR Poland OR Turkey OR Croatia [Title]

16. Austria OR France OR Germany OR Greece OR Italy OR Spain OR Sweden OR "Great Britain" OR "United Kingdom" OR England OR "Northern Ireland" OR Poland OR Turkey OR Croatia [Abstract]

17. NOT ("addresses" OR "autobiography" OR "biography" OR "classical article" OR "dictionary" OR "directory" OR "duplicate publication" OR "historical article" OR "interview" OR "legal cases" OR "letter" OR "news" OR "newspaper article" OR "patient education handout" OR "personal narratives" OR "pictorial works" OR "portraits" OR "video audio media" OR "webcasts") [Publication Type]

18. NOT "major molecular response" OR "maternal mortality ratio" OR "maternal mortality rate" OR "mismatch repair" [All Fields]

19. 10 and 15 and 16 and 17 and 18

20. 19 with Limit: Abstracts → 851 results (rubella: 131, mumps: 262)

21. Outbreak* [All Fields]

22. Incidence* [All Fields]

23. Cases* [All Fields]

24. Epidemic* [All Fields]

25. 21 or 22 or 23 or 24

26. 20 and 25

27. Travel* [All Fields]

28. Migration* OR Immigration* [All Fields]

29. Migrant* OR Immigrant* [All Fields]

30. Refugee* [All Fields]

31. Import* [All Fields]

32. 27 or 28 or 29 or 30 or 31

33. **26 and 32 → 35 results (rubella: 12, mumps: 7)**

34. Vaccination* OR Immunization* [All Fields]

35. **20 and 32 and 34 → 28 results (rubella: 17, mumps: 10)**

36. "Vaccination Coverage" OR "Immunization coverage" OR "Vaccination rate" or "Immunization rate" [All Fields]

37. **20 and 36 → 42 results (rubella: 25, mumps: 20)**

38. Seroprevalence [All Fields]

39. Seropositiv* [All Fields]

40. Seronegativ* [All Fields]

41. 38 or 39 or 40

42. **20 and 41 → 14 results (rubella: 22, mumps: 10)**

43. Congenital* [All Fields] (*Rubella only*)

44. **20 and 43 → 25 results (*Rubella only*)**

C.3. SSCI/SCI-Expanded (Web of Science)

1. Measles [Topic] → 16,756 results (rubella: 9,118, mumps: 5,567)

2. 1 with Restriction: Language: English and German

3. 2 with Timespan: 2009 to 2013 → 3,260 results (rubella: 1,290, mumps: 1,035)
   *Note: *Humans* is not a limit option

4. Measles OR MMR [Topic]

5. 4 with filter (2-3) → 4,751 results (rubella: 2,806, mumps: 2,552)

6. Measles OR MMR [Title]

7. Measles OR MMR [Topic]

8. 6 and 7

9. 8 with filters (2-3) → 4,751 results (rubella: 2,806, mumps: 1,552)

10. Austria OR France OR Germany OR Greece OR Italy OR Spain OR Sweden OR "Great Britain" OR "United Kingdom" OR England OR "Northern Ireland" OR Poland OR Turkey OR Croatia [Title]

11. Austria OR France OR Germany OR Greece OR Italy OR Spain OR Sweden OR "Great Britain" OR "United Kingdom" OR England OR "Northern Ireland" OR Poland OR Turkey OR Croatia [Topic]

12. 9 and 10 and 11

13. 12 refined by Countries/Territories (as above) → 1,550 results (rubella: 175, mumps: 826)

14. 13 refined by Document Type: Article, Review, Meeting Abstract, Correction, Book Chapter → 1,446 results (rubella: 170, mumps: 787)
    *Note: Not selected: Proceeding Papers, Editorial Material, Letter, News Item, Hardware Review

15. NOT "major molecular response" OR "maternal mortality ratio" OR "maternal mortality rate" OR "mismatch repair" [Topic]

16. 14 and 15

17. Outbreak* [Topic]

18. Incidence* [Topic]

19. Cases* [Topic]

20. Epidemic* [Topic]

21. 17 or 18 or 19 or 20

22. Travel* [Topic]

23. Migration* OR Immigration* [Topic]

24. Migrant* OR Immigrant* [Topic]

25. Refugee* [Topic]

26. Import* [Topic]

27. 21 or 22 or 23 or 24 or 25

28. **16 and 21 and 26 → 35 results (rubella: 18, mumps: 16)**

29. Vaccination* OR Immunization* [Topic]

30. **16 and 26 and 28 → 42 results (rubella: 32, mumps: 26)**

31. "Vaccination Coverage" OR "Immunization coverage" OR "Vaccination rate" or "Immunization rate" [Topic]

32. **16 and 30 → 63 results (rubella: 40, mumps: 34)**

33. Seroprevalence [Topic]

34. Seropositiv* [Topic]

35. Seronegativ* [Topic]

36. 32 or 33 or 34

37. **16 and 35 → 24 results (rubella: 36, mumps: 19)**

38. Congenital* [Topic] (*Rubella only*)

39. **16 and 37 → 27 results (*Rubella only*)**

D. Literature Quality Assessment Tools

D.1. Quality Assessment Tool for Quantitative Studies

A slightly modified version of the Effective Public Health Practice Project's (EPHPP) *Quality Assessment Tool for Quantitative Studies*[5]was used to evaluate the quality of included publications. The *Study Design* component was altered to include cross-sectional and epidemiological study designs in the "moderate" category (see below), as these were not listed. A conflict of interest component was also added. The second reviewer rating did not apply, as only one author was available for the quality assessment.

The following component rating scheme was used (wording adapted from EPHPP[5,6]):

1. **Selection Bias**

   Q1) "Are the individuals selected to participate in the study likely to be representative of the target population?

      1. Very likely

      2. Somewhat likely

3. Not likely

4. Can't tell

Q2) What percentage of selected individuals agreed to participate?

1. 80 - 100% agreement

2. 60 - 79% agreement

3. less than 60% agreement

4. Not applicable

5. Can't tell"[5]

"**Strong**: The selected individuals are very likely to be representative of the target population (Q1 is 1) and there is greater than 80% participation (Q2 is 1).

Moderate: The selected individuals are at least somewhat likely to be representative of the target population (Q1 is 1 or 2); and there is 60 - 79% participation (Q2 is 2). 'Moderate' may also be assigned if Q1 is 1 or 2 and Q2 is 5 (can't tell).

Weak: The selected individuals are not likely to be representative of the target population (Q1 is 3); or there is less than 60% participation (Q2 is 3) or selection is not described (Q1 is 4); and the level of participation is not described (Q2 is 5)."[6]

2. **Study Design**

Q1) "Indicate the study design

1. Randomized controlled trial (RCT)

2. Controlled clinical trial (CCT)

3. Cohort analytic (two group pre + post)

4. Case-control

5. Cohort (one group pre + post (before and after))

6. Interrupted time series"[5]

7. Cross-sectional study

8. Epidemiological study/report

9. "Other, specify

10. Can't tell

Q2) Was the study described as randomized? (yes/no) If NO, go to Component C.

Q3) If Yes, was the method of randomization described? (yes/no)

Q4) If Yes, was the method appropriate? (yes/no)"[5]

"**Strong**: will be assigned to those articles that described RCTs and CCTs.

Moderate: will be assigned to those that described a cohort analytic study, a case control study, a cohort design, an interrupted time series,"[6] a cross-sectional study or an epidemiological study.

"**Weak**: will be assigned to those that used any other method or did not state the method used."[6]

3. **Confounders**

Q1) "Were there important differences between groups prior to the intervention?

1. Yes

2. No

3. Can't tell

The following are examples of confounders:

1. Race
2. Sex
3. Marital status/family
4. Age
5. SES (income or class)
6. Education
7. Health status
8. Pre-intervention score on outcome measure

Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?

1. 80 - 100% (most)
2. 60 - 79% (some)
3. Less than 60% (few or none)
4. Can't tell"[5]

"**Strong**: will be assigned to those articles that controlled for at least 80% of relevant confounders (Q1 is 2); or (Q2 is 1).

Moderate: will be given to those studies that controlled for 60 - 79% of relevant confounders (Q1 is 1) and (Q2 is 2).

Weak: will be assigned when less than 60% of relevant confounders were controlled (Q1 is 1) and (Q2 is 3) or control of confounders was not described (Q1 is 3) and (Q2 is 4)."[6]

4. **Blinding**

Q1) "Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?

1. Yes
2. No
3. Can't tell

Q2) Were the study participants aware of the research question?

1. Yes
2. No
3. Can't tell"[5]

"**Strong**: The outcome assessor is not aware of the intervention status of participants (Q1 is 2); and the study participants are not aware of the research question (Q2 is 2).

Moderate: The outcome assessor is not aware of the intervention status of participants (Q1 is 2); or the study participants are not aware of the research question (Q2 is 2); or blinding is not described (Q1 is 3 and Q2 is 3).

Weak: The outcome assessor is aware of the intervention status of participants (Q1 is 1); and the study participants are aware of the research question (Q2 is 1)."[6]

5. **Data Collection Methods**

Q1) "Were data collection tools shown to be valid?

1. Yes

2. No

3. Can't tell

Q2) Were data collection tools shown to be reliable?

1. Yes

2. No

3. Can't tell"[5]

"**Strong**: The data collection tools have been shown to be valid (Q1 is 1); and the data collection tools have been shown to be reliable (Q2 is 1).

Moderate: The data collection tools have been shown to be valid (Q1 is 1); and the data collection tools have not been shown to be reliable (Q2 is 2) or reliability is not described (Q2 is 3).

Weak: The data collection tools have not been shown to be valid (Q1 is 2) or both reliability and validity are not described (Q1 is 3 and Q2 is 3)."[6]

6. **Withdrawals and Drop-outs**

Q1) "Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

1. Yes

2. No

3. Can't tell

4. Not Applicable (i.e. one time surveys or interviews)

Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).

1. 80 - 100%
2. 60 - 79%
3. less than 60%
4. Can't tell
5. Not Applicable (i.e. Retrospective case-control)"[5]

"**Strong**: will be assigned when the follow-up rate is 80% or greater (Q2 is 1).

Moderate: will be assigned when the follow-up rate is 60 - 79% (Q2 is 2) OR Q2 is 5 (N/A).

Weak: will be assigned when a follow-up rate is less than 60% (Q2 is 3) or if the withdrawals and drop-outs were not described (Q2 is 4)."[6]

7. **Conflict of Interest**

Q1) Was a conflict of interest statement made?

1. Yes
2. No
3. Can't tell

Q2) Does a relevant conflict of interest exist?

1. Yes
2. No
3. Can't tell

4. Not applicable

Strong: will be assigned when a conflict or interest statement is made, but no conflict exists (Q1 is 1 and Q2 is 2).

Moderate: will be assigned when a conflict of interest is not reported (Q2 is 2 or 3) OR the conflict is not relevant to the study (Q2 is 2, 3, or 4).

Weak: will be assigned when a clear conflict of interest is described (Q1 is 1 and Q2 is 1).

8. **Other:**

"**Intervention Integrity**

Q1) What percentage of participants received the allocated intervention or exposure of interest?

1. 80 - 100%
2. 60 - 79%
3. less than 60%
4. Can't tell

Q2) Was the consistency of the intervention measured? (yes/no/can't tell)

Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results? (yes/no/can't tell)

Analyses

Q1) Indicate the unit of allocation (community; organization/institution; practice/office)

Q2) Indicate the unit of analysis (community; organization/institution; practice/office)

Q3) Are the statistical methods appropriate for the study design? (yes/no/can't tell)

Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received? (yes/no/can't tell)"[5]

D.2. AMSTAR

The quality of literature reviews was assessed using the eleven-item AMSTAR tool.[265] Each item consists of a question to be answered with "Yes", "No", "Can't answer" or "Not applicable". A copy of the questionnaire and notes published by Shea et al.[265] is provided below:

1. "**Was an 'a priori' design provided?** The research question and inclusion criteria should be established before the conduct of the review.

2. **Was there duplicate study selection and data extraction?** There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

3. **Was a comprehensive literature search performed?** At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

4. **Was the status of publication (i.e. grey literature) used as an inclusion criterion?** The authors should state that they searched for reports

regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

5. **Was a list of studies (included and excluded) provided?** A list of included and excluded studies should be provided.

6. **Were the characteristics of the included studies provided?** In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

7. **Was the scientific quality of the included studies assessed and documented?** 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

8. **Was the scientific quality of the included studies used appropriately in formulating conclusions?** The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

9. **Were the methods used to combine the findings of studies appropriate?** For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).

10. **Was the likelihood of publication bias assessed?** An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).

11. **Was the conflict of interest stated?** Potential sources of support should be clearly acknowledged in both the systematic review and the included studies."[265]

E. Study Characteristics

Akkoyunlu et al., 2013[40]

Topic	Rubella
Study Design	Retrospective cross-sectional study
Participants	Serum samples of 206 children (68 male, 138 female) and 1,189 adults (8 male, 1,181 female) presenting with fever were obtained between Feb. and Dec. of 2010 in a local hospital in Iğdır, Northeastern Turkey. None of the participants showed symptoms of a rubella infection.
Intervention/Data Collection	Anti-rubella IgM and IgG antibody levels were determined by the hospital's microbiology laboratory using standardized Enzyme-Linked Immunosorbent Assay (ELISA) methods.
Outcomes	Seroprevalence of anti-rubella IgM and IgG by gender and age.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: Although the study group was fairly large, participants were only recruited from one regional hospital and if they had fever as a symptom. The sample is therefore not likely to be representative of the area.
Study Design	Moderate	
Confounders	Weak	Comment: Potential confounders were not controlled and the groups were very much skewed by sample size (i.e. 1,181 women vs. 8 men).
Blinding	N/A	
Data Collection Method	Moderate	Quote: "IgM and IgG antibodies were tested with ELISA (Vitros ECI Q (J&J) Company Ortho Clinical Diagnostic Macro) method." Comment: Standardized, valid and reliable methods were applied; however, the cut-off levels used to determine seropositivity were not reported.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	A conflict of interest statement is not included.
Overall Rating	**Weak**	

Antona et al., 2013[44]

Topic	Measles
Study Design	Epidemiological report
Participants	Outbreak description involving 22,178 cases in France between 2008 and 2011.
Intervention/Data Collection	Data were collected based on notified rubella cases reported to regional health agencies between Jan. 2008 and Dec. 2011.

Outcomes	Outbreak description, including demographic characteristics of cases (age, gender, residence, vaccination status); Complications and hospitalizations; Involved measles genotypes.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: A large number of cases was included in the analysis; however, only half (52%) of the cases were laboratory confirmed or epidemiologically linked, suggesting that the data may not be representative, as missdiagnoses are possible.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Comment: Case data were collected using a nationwide surveillance system with pre-defined case definitions; however, the validity could only be determined in little over half of the cases.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Arenz et al., 2009[45]

Topic	Measles
Study Design	Retrospective case series study
Participants	115 children hospitalized with measles infections in Germany during the year 2006.
Intervention/Data Collection	Data was obtained through the nation-wide surveillance of rare pediatric diseases in Germany (*Erhebung Seltener Pädiatrischer Erkrankungen in Deutschland* (ESPED)). Demographic, clinical and outcome data regarding each reported case were collected using questionnaires sent to the treating physicians.
Outcomes	Laboratory confirmation of diagnoses; Clinical presentation, outcome and vaccination status among the reported cases.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: The reported cases were collected using a nation-wide surveillance system in which 99.2% of all pediatric clinics and departments participate. Physician questionnaires were completed for 83.4% of the reported cases.
Study Design	N/A	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Comment: Case data was collected based on a well-performing surveillance system. The validity and reliability of the questionnaires were not reported, but are likely adequate.
Withdraws/Dropouts	N/A	
Other	N/A	
Conflict of Interest	Moderate	Comment: The study was funded by the Bavarian State Ministry of the Environment and Public Health. A conflict of interest statement has not been included.
Overall Rating	**Strong**	

Aytac et al., 2009[47]

Topic	Rubella
Study Design	Cross-sectional study
Participants	331 unvaccinated children, 0-59 month of age, living in a rural area of Doğankent, Turkey.
Intervention/Data Collection	A systematic, age- and sex-stratified sampling method including 26.8% of all children below the age of five years living in the area was employed. Data was obtained using a questionnaire with socio-demographic variables, MMR vaccination status and rubella history of the participating child and all family members. Anti-rubella IgG seropoprevalence was determined using standardized ELISA methods.
Outcomes	IgG seropositivity in relation to sociodemographic variables (age, gender, parental educational status, parental employment status, household size, school attendance of siblings, and health insurance coverage, among others).

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: The sample is representative for the local, rural population studied, but may not be applicable elsewhere.
Study Design	Moderate	
Confounders	Strong	Quote: "A systematic sampling method stratified by age and sex was applied."
Blinding	N/A	
Data Collection Method	Moderate	Comment: The seroprevalence testing was performed using standardized, valid and reliable methods; validity and reliability of the questionnaire and the parental statements were not reported.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Quote: "This study was financed by Çukurova University Scientific Research Fund...as a thesis for a specialised medical degree." Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Bätzing-Feigenbaum et al., 2010[52]

Topic	Measles
Study Design	Epidemiological report (preliminary)
Participants	62 measles cases reported in Berlin, Germany between Jan. and Mar. 2007. Most infections were among young children whose parents had critical attitudes towards vaccinations.
Intervention/Data Collection	Data was obtained through regional enhanced surveillance. Case confirmation and genotyping were performed by the RKI National Reference Laboratory.
Outcomes	Outbreak description including case demographics and vaccination histories; Outbreak control measures and challenges; Molecular and phylogenetic analyses of involved measles strains.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: All reported cases were included in the analysis; however, the data are preliminary.
Study Design	Moderate	
Confounders	N/	
Blinding	N/A	

Data Collection Method	Strong	Comment: Case data was obtained through enhanced surveillance; sequencing and genotyping were performed by the National Reference Laboratory for Measles, Mumps and Rubella. Although validity and reliability were not reported, they are likely high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Barrabeig et al., 2011[50]

Topic	Measles
Study Design	Retrospective cohort study
Participants	Children exposed to measles in educational centers in the Barcelona-South Health Region of Catalonia, Spain, between Oct. 2006 and Jan. 2007. 15 primary cases and 62 secondary and tertiary cases were included. Centers that provided post-exposure prophylaxis (MMR vaccination within 72h of exposure) were excluded.
Intervention/Data Collection	Active surveillance of children at the educational centers was performed by public health staff; immunization records were provided by public health care centers.
Outcomes	Study population characteristics (educational center, gender, age, vaccination status); Number of confirmed measles cases at each center, attack rate and vaccine effectiveness; Basic and effective reproductive numbers; Number of avoidable cases if the recommended MCV-1 age were reduced from 15 to 12 months.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All children in the 15 selected day care centers were included; only centers that provided 72h post-exposure prophylaxis were excluded. The vaccination status of 96% of included children was determined.
Study Design	Moderate	
Confounders	Strong	Comment: The most important confounders were age and vaccination status. Quote: "To study direct vaccination effectiveness (VE), we excluded (a) children aged <15 months, (b) children with measles infection prior to the outbreak, and (c) children with unknown vaccination status. Children vaccinated during the study period were classified according to the vaccination status before the outbreak."
Blinding	N/A	
Data Collection Method	Strong	Comment: Although validity and reliabilty were not reported, data were collected by public health staff and were likely both valid and reliable.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: The study was partially funded by outside sources, but no conflict of interest has been declared.
Overall Rating	**Strong**	

Bassetti et al., 2011[51]

Topic	Measles
Study Design	Epidemiological report

Participants	83 patients at a hospital in Genova, Italy with confirmed measles infections, recruited between Jan. 2008 and Apr. 2009.
Intervention/Data Collection	A standardized questionnaire regarding demographic, clinical and disease outcome data of each patient was employed.
Outcomes	Case demographic data and clinical characteristics and symptoms; Results of selected laboratory tests; Molecular analysis and phylogenetic identification of involved measles strain.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: All included patients were selected from only one regional hospital in Genova, Italy and may not be representative of the region.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Quote: "A standardized form including demographic data, underlying medical conditions, clinical signs and symptoms, selected laboratory tests, radiographic findings, treatment course, and outcome, was used for data collection." Comment: The validity and reliability of the questionnaire were not reported, but are likely adequate. Standardized methods were used for molecular and phylogenetic analysis.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Moderate**	

Bechini et al., 2012[53]

Topic	Measles
Study Design	Cohort analytic study
Participants	Anonymous sera samples of 945 persons aged 1-49 years (stratified by age-groups, each representing 0.5‰ of the general Tuscan population) were collected in two hospitals in Florence, Italy (a pediatric emergency department and an adult outpatient laboratory) between June 2005 and July 2006.
Intervention/Data Collection	Anti-measles IgG seroprevalence was determined using standardized ELISA methods. The results were compared to a 2003 seroprevalence survey of the same region and nation-wide 2004 seroepidemiological data (both prior to a catch-up MMR vaccination campaign for seven- to fourteen-year-old children (in 2004 and 2005)).
Outcomes	Seroprevalence of measles among various age groups; Estimation of susceptible populations by age group; Differences in seroprevalence compared to 2003 survey of the same region; Inter-group (age and gender) comparisons of seroprevalence.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Quote: "Each stratum maintained the same sample size (0.5‰) of the respective age group of the general Tuscan population" Comment: The sample is representative; however, only individuals coming to either of the two hospitals were included. Children with immunodeficiencies were excluded from the sample.
Study Design	Moderate	

Confounders	Moderate	Comment: In the study design and data collection, age and gender were controlled for. However, confounding due to healthy vs. non-health individuals was only addressed for immunocompromised children. Comparisons to previous seroprevalence studies were matched only by age and showed large variances in sample size.
Blinding	Strong	Quote: "Samples were collected in an anonymous way: only age, sex and day of collection were recorded."
Data Collection Method	Strong	Comment: Seroprevalence was determined using standardized methods, previously shown to have high validity and reliability.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

***Bechini et al., 2012*[53]**

Topic	Rubella
Study Design	Cohort analytic study
Participants	Anonymous sera samples of 1,110 persons between the ages of 1 and 49 years (stratified by age-groups, as described above) were collected in Florence, Italy between June of 2005 and July of 2006.
Intervention/Data Collection	Anti-rubella IgG seroprevalence was determined using standardized ELISA methods. The results were compared to 2006 national incidence data and the WHO recommended threshold for the elimination of congenital rubella.
Outcomes	Seroprevalence of rubella among various age groups; Estimation of the susceptible female population of childbearing age (15-49 years).

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	(See above.)
Study Design	Moderate	
Confounders	Moderate	(See above.)
Blinding	Strong	(See above.)
Data Collection Method	Strong	(See above.)
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

***Borras et al., 2009*[55]**

Topic	Measles, Mumps, Rubella
Study Design	Retrospective cross-sectional study
Participants	630 children <3 years of age, randomly sampled and representative of the regional Oct. 2001 birth cohort in Catalonia, Spain; the sample was stratified by region and urban or rural residence.
Intervention/Data Collection	Telephone interviews were conducted with parents of the participating children. The following data were collected: sociodemographic variables, health care provider, information obtained regarding vaccines and parental attitudes towards them and the vaccination history of the child. Copies of vaccination cards were requested to validate the parental statements.
Outcomes	Vaccination coverage according to health care provider (public or private), residence (urban or rural), and sociodemographic factors (maternal education, parental occupation status, social class, number of children living in the household, birth-order of child, attendance of day-care center, etc.).

Quality Assessment		
	Author's judgment	**Support for judgment**
Selection Bias	Strong	Quote: "stratified random probabilistic sampling of children born in October 2001 and registered as resident in Catalan municipalities." Quote: "Of the 630 children selected, 12 families (1.80%) refused to participate and 25 families [4.0%] were not found."
Study Design	Moderate	
Confounders	N/A	Comment: Differences among the sample populations were analyzed as part of the study.
Blinding	N/A	
Data Collection Method	Weak	Comment: Although the interviewer was trained and photocopies of vaccination records requested, less than half of these copies were received and no other methods were used to validate the statements made by the parents.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: Funding was provided by the *Instituto de Salud Carlos III*, Madrid, Spain. No conflict of interest has been declared.
Overall Rating	**Moderate**	

Borras et al., 2012[56]

Topic	Measles	
Study Design	Prospective cohort study	
Participants	69 children in Catalonia, Spain, aged 9-14 months, were tested for anti-measles antibodies between Feb. and June of 2007.	
Intervention/Data Collection	Anti-measles IgG titers were determined before and after measles vaccination in order to determine the presence of maternal antibodies and vaccination response.	
Outcomes	Seroprevalence of maternal anti-measles IgG antibodies and seroconversion rate after vaccination.	
Quality Assessment	N/A	*Full text not accessible.*

Bozkurt, Bostanci, et al., 2010[57]

Topic	Measles	
Study Design	Prospective cohort study	
Participants	520 students in grade levels one through eight (approx. 7-15 years old) in Denizli, Turkey in 2003. The students attended two schools, one is a high and one in a low socioeconomic area.	
Intervention/Data Collection	A random sampling cluster technique was employed. Each participant's health and vaccination history was inquired through a short parental questionnaire. Anti-measles IgG seroprevalence was determined using ELISA methods before and after a mass-vaccination campaign at the schools.	
Outcomes	Anti-measles IgG seroprevalence among the participating students in relation to school location (low or high socioeconomic area) and grade level; Comparison between pre- and post-campaign seroprevalence rates.	

Quality Assessment		
	Author's judgment	**Support for judgment**

Selection Bias	Strong	Quote: "A stratified cluster sampling strategy was employed...To reach the total [sample] number, one primary school from each area and one classroom from each grade were randomly included in the sample." Comment: The pre- and post-campaign participation rates were with 95% and 87% high; hemolysed blood samples were not included.
Study Design	Moderate	
Confounders	Strong	Comment: The groups were stratified according to school (high or low socioeconomic area) and grade level.
Blinding	Moderate	Comment: Blinding is not described.
Data Collection Method	Moderate	Quote: "Measles specific IgG (<0.5 IU, negative; ≥d0.50 - <0.70 IU indeterminate; ≥d0.70 IU positive) was studied with ELISA [at the Pamukkale University Medical Microbiology Lab]." Comment: The validity and reliability of the methods used to determine the IgG titers were not reported, but were likely adequate.
Withdraws/Dropouts	Strong	Comment: 67 of the 520 participants (13%) were not tested after the mass-vaccination campaign. The follow-up rate was with 92% high.
Conflict of Interest	Strong	Comment: The study was funded by the Pamukkal University Research Fund. No conflict of interest was declared.
Overall Rating	**Strong**	

Bozkurt, Cevahir, et al., 2010[58]

Topic	Rubella
Study Design	Cross-sectional study
Participants	277 female students, aged 7-15 years, attending primary schools in Denizli, Turkey in Nov. of 2003. Four schools were from high and three from low socioeconomic areas.
Intervention/Data Collection	A random sampling technique of the participants by school, grade level and class was employed. Information regarding vaccination history were surveyed in a parental questionnaire. Anti-rubella IgG seroprevalence was determined using standardized ELISA methods.
Outcomes	Rubella seropositivity among the female students in relation to school location (low or high socioeconomic area), grade level and rubella vaccination status.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Quote: "The sample was selected by using a stratified...clustered (3 schools in low, and 4 schools in high [socioeconomic] class section) random sampling technique. To reach the total number, one primary school (consisting of 7-15 aged students) from each area and one classroom from each grade were randomly included in the sample." Comment: The participation rate was 85%; not included were students without parental consent or hemolysed blood samples.
Study Design	Moderate	
Confounders	Strong	Comment: groups were stratified according to socioeconomic status and age/grade level.
Blinding	N/A	
Data Collection Method	Strong	Quote: "Rubella specific IgG (<10 IU, negative; 10 - <15 IU indeterminate; 15 IU positive) was studied with ELISA (using a Vidas brand machine and Biomerix brand kits)." Comment: Standardized, valid and reliable, methods were applied.

Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: The study was funded by the Pamukkal University Research Fund. A conflict of interest statement is not included.
Overall Rating	**Strong**	

Brown et al., 2011[59]

Topic	Measles
Study Design	Epidemiological report
Participants	25 confirmed measles cases, caused by the G3 genotype strain, in Europe during 2010.
Intervention/Data Collection	Data was obtained through the WHO Measles and Rubella Laboratory Network (*LabNet*).
Outcomes	Case reports regarding 16 of the 25 included patients and epidemiological links between the patients, where applicable; Measles strain sequence analysis and phylogenetic linking of the cases.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All confirmed measles cases in which the G3 genotype had been identified within the study period were included.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Samples were sequenced and genotyped in various national laboratories connected through *LabNet*, which use standardized methods to detect measles viruses. Quote: "As of July 2010, the LabNet consists of 690 laboratories in 183 countries, all of which follow a standardised set of testing protocols and reporting procedures with a strong focus on quality assurance."
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Buffolano et al., 2011[61]

Topic	Rubella, CRI
Study Design	Cross-sectional study
Participants	2,344 newborns with suspected congenital infections (rubella, toxoplasmosis, syphilis, HIV, HCV), as reported to a regional register of perinatal infections in Campania, Italy, between Jan. 1997 and Dec 2009; 157 cases were suspected of having a congenital rubella infection.
Intervention/Data Collection	Suspected congenital infections among the infants (based on serology and/or maternal disease) were followed up and diagnosed according to standardized diagnostic criteria for each included disease. Those infants without diagnosis of a congenital infection at 12 (rubella, toxoplasmosis) or 18 (HIV, HCV, syphilis) months of age were excluded; those with a confirmed infection were followed up regarding treatment and outcome.
Outcomes	Annual number of infants diagnosed with congenital infections and estimated prevalence for the region; Comparison between prevalences among mothers with an immigrant or native status.

Quality Assessment		
	Author's judgment	**Support for judgment**
Selection Bias	Strong	Quote: "Prenatal and maternal records were provided to ASSRC-PIRC [Clinical regional coordination center of the Campania Regional Health Bureau] from a network of Maternity centers covering 89% of regional live births." Comment: The large sample size and high percentage of regional births analyzed suggest that the data are representative for the region.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Defined and standardized diagnostic criteria were used to confirm suspected congenital infections.
Withdraws/Dropouts	Strong	Quote: "Overall 165 (7%) patient were lost to follow up, including...25 (15%) to Rubella." Comment: Of 157 included infants with a suspected congenital rubella infection, 84% continued to participate in the study through follow-up.
Conflict of Interest	Weak	Quote: "The present study has been financially supported by Campania Region Health Bureau as Perinatal Infection Register..."
Overall Rating	**Moderate**	

Byrne et al., 2012[63]

Topic	Rubella
Study Design	Cross-sectional study
Participants	436,054 blood samples of antenatal women were tested for anti-rubella IgG antibody seroprevalence between 2004 and 2006. The women were born between 1951 and 1996 and were of various ethnicities.
Intervention/Data Collection	Antenatal screening of anti-rubella IgG titers was performed by two NHS Blood and Transplant Testing Centers using an enzyme immunoassay, and those samples with low titers were sent to a reference laboratory for more sensitive confirmation testing. Participant demographic data, such as date of birth and ethnicity, were collected in an electronic database and associated with the test results via sample numbers.
Outcomes	Rubella seroprevalence by year, birth cohort and ethnic group.

Quality Assessment		
	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: A large number of samples was included from two different regional testing centers; however, about 95% of the samples came from the same region and may not be representative for the entire area; multiple samples from the same women may have been included if more than one pregnancy occurred during the study period, potentially skewing the results.
Study Design	Moderate	
Confounders	Weak	Quote: "[Birth] cohorts were chosen to stratify data into adequately sized groups for analyses." Comment: While samples were stratified by age (birth cohort), other possible confounders, such as ethnicity, were not controlled for. The same women were included multiple times if multiple pregnancies occurred (see above).
Blinding	N/A	

Data Collection Method	Strong	Quote: "NHS Blood and Transplant (NHSBT) routinely screen a large number of samples from antenatal women for antibodies to rubella, using consistent and well-characterised assays....Samples with antibody levels of <15 IU/mL were sent to the NHSBT National Transfusion Microbiology Reference Laboratory (NTMRL), London, for confirmatory testing using a second, more sensitive assay, the Biokit Bio-ELISA Rubella IgG colour." Comment: Standardized methods with high validity and reliability were used and seronegative test results confirmed.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Calimeri et al., 2012[64]

Topic	Rubella
Study Design	Cross-sectional study
Participants	500 pregnant women, aged 15 to 45 years, in their 4^{th} to 39^{th} week of pregnancy. All women were enrolled in one of two clinics of the University Hospital in Messina, Italy, between July 2006 and Dec. 2007.
Intervention/Data Collection	Seroprevalence of anti-rubella IgG and IgM was determined using standardized, commercial Microparticle Enzyme Immunoassay (MEIA) kits. A questionnaire was used to interview all participants regarding demographic data, educational status, knowledge about CRS, disease vaccination and infection history, and previous rubella screening participation.
Outcomes	Seroprevalence of IgG and IgM antibodies, by age group; Results of the questionnaire (see above).

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: Although the participation rate was 100% and the sample considerable large, only women attending one of two clinics from the same hospital were included and may not be representative of the regional population.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Comment: Standardized methods were used to determine seroprevalence. Validity and reliability of the questionnaire and interview process were not reported, but are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Calza et al., 2009[65]

Topic	Measles
Study Design	Observational, longitudinal study
Participants	Measles cases (confirmed and suspected) at the Institute of Infectious Diseases, Bologna, Italy, between Dec. 2007 and May 2008.

Intervention/Data Collection	Data were collected at the Institute of Infectious Diseases. Hospitalized patients were observed over the course of their clinical stay and at one-week follow-up. Confirmation of measles infection occurred through anti-measles IgM using standardized ELISA methods.
Outcomes	Demographics of patients with confirmed measles infections; Clinical characteristics, symptoms, and complications among the cases; Vaccination statuses of cases; Results of selected laboratory tests.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: Only hospitalized patients with confirmed measles infections were included (26 of 80 suspected cases). Non-hospitalized patients were not considered as part of the study.
Study Design	Weak	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Validity and reliability are not reported, but are likely adequate due to direct observation of the patients by the authors.
Withdraws/Dropouts	Strong	Comment: Follow-up one week after hospital discharge was performed for all included patients.
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Weak**	

Cilla et al., 2011[77]

Topic	Measles
Study Design	Epidemiological report
Participants	23 people with confirmed measles infections between March and June 2011, living in Gipuzkoa, Spain (Basque Country).
Intervention/Data Collection	Data was collected though the regional epidemiological surveillance system.
Outcomes	Demographic description of index and secondary cases and epidemiological links, where applicable; Molecular and genotypic analysis of involved measles strains; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All confirmed measles cases occurring during the local outbreak were included.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Case data were collected through a regional surveillance system and confirmed using standardized ELISA procedures with a high sensitivity.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Cohuet et al., 2009[79]

Topic	Measles
Study Design	Epidemiological report
Participants	173 people associated with a measles outbreak among the Irish traveller community in England between March and June 2007.
Intervention/Data Collection	Data was collected through routine enhanced surveillance (demographics, symptoms, hospitalization, postal code of general practitioner and patient, contact to known measles cases, foreign travel, vaccination status). Additional information was requested per telephone interviews with the general practitioners. Molecular and phylogenetic analysis of strains was performed for available RNA samples.
Outcomes	Outbreak description, including case demographics, clinical outcomes, and vaccination statuses; Molecular and phylogenetic analysis of involved measles strains.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All confirmed and suspected measles cases occurring among the Irish traveller population and among persons who had come in contact with the population during the time-frame of the outbreak were included.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Data was obtained through enhanced surveillance of the Health Protection Agency's Virus Reference Department of the Center for Infections as well as through telephone interviews of general practitioners treating the included patients. Though validity and reliability are not reported, they are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Corbin et al., 2013[81]

Topic	Measles	
Study Design	Case series study	
Participants	113 adults with confirmed measles infections who were in- or out-patients of a local hospital in Clermont-Ferrand, France, between 2009 and 2011.	
Intervention/Data Collection	Demographic and clinical case data were obtained through national surveillance (French Institute for Public Health Surveillance, InVS) and through the hospital's internal database.	
Outcomes	Demographic description of reported cases; Hospitalizations, complications, and clinical outcomes; Vaccination statuses of cases.	
Quality Assessment	N/A	*Full text not accessible.*

Cova et al., 2010[82]

Topic	Measles
Study Design	Epidemiological report
Participants	23 reported (19 confirmed) measles cases during an outbreak in Ferrara, Italy, between Jan. and June 2010.

Intervention/Data Collection	Regional enhanced surveillance was employed to identify and confirm all suspected cases. Demographic and clinical data was obtained through pediatricians, general practitioners and health care authorities.
Outcomes	Outbreak description including demographic distribution and vaccination statuses of cases; Hospitalizations and clinical outcomes; Confirmation and epidemiological links between cases.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All confirmed measles cases occurring during the local outbreak were included in the analysis; non-confirmed or epidemiologically linked cases were excluded.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Enhanced, active surveillance was employed in order to identify the cases.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Curtale et al., 2010[83]

Topic	Measles
Study Design	Epidemiological report
Participants	449 confirmed measles cases in two overlapping outbreaks in Italy (one among a Roma/Sinti population, one among an Italian adolescent/adult population) between June 2006 and Aug. 2007.
Intervention/Data Collection	Data was collected through routine surveillance by the local Public Health Agency (*Agenzia di Sanità Pubblica*) and active epidemiological field investigations of confirmed cases (including demographic characteristics, vaccination status and hospitalizations). Molecular analysis and genotyping of measles strains was performed by the Italian National Institute of Health (*Istituto Superiore di Sanità*).
Outcomes	Outbreak descriptions including demographic, geographic and epidemiological case data; Genotypes of involved measles strains; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All confirmed measles cases occurring during the two outbreaks were included in the report.
Study Design	N/A	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Data was obtained through routine surveillance of the local Public Health Agency and confirmed cases were further investigated. Molecular analysis of measles strains was performed by the Italian National Institute of Health. Though not reported directly, the validity and reliability of the methods were likely high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

D'Agaro et al., 2010[95]

Topic	Rubella
Study Design	Epidemiological report; cross-sectional study
Participants	During a rubella outbreak involving 133 cases (111 confirmed) in the Friuli Venezia Giulia (FVG) region of Italy between Jan. and June 2008, clinical samples of 16 confirmed cases were obtained for viral molecular analysis. Data from a 2006 regional seroepidemiological survey of anti-rubella IgG seroprevalence among 1,416 women of childbearing age are also reported.
Intervention/Data Collection	Suspected rubella cases were reported to a local health department, and all cases were contacted and interviewed via telephone to obtain demographic data. Serological IgM antibody confirmation of rubella cases performed during the outbreak as well as the anti-rubella IgG seroprevelance determined two years prior were performed using standardized, commercial Enzyme-linked Immunoassay (EIA) methods. Viral rubella-specific RNA from the 16 clinical samples was isolated, sequenced and genotypically analyzed using standard methods.
Outcomes	Outbreak description, including demographic case data (age, gender, etc.); Molecular analysis of the involved rubella virus; Anti-rubella IgG seroprevalence among women of childbearing age.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All suspected cases reported during the outbreak were analyzed for serological confirmation; only confirmed cases were included in further analyzes. Quote: "[For the seroepidemiological study,] a representative sample of all women of childbearing age living in a limited urban area was enrolled."
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Quote: "Diagnostic serology was carried out with a Rubella IgG and IgM EIA commercial kit (Dia-Sorin, Saluggia, Italy)." Comment: The rubella virus genetic analysis was also performed using standardized methods, likely to be high in both validity and reliability.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

D'Agaro et al., 2011[96]

Topic	Measles
Study Design	Epidemiological report
Participants	42 cases with confirmed measles infections during two outbreaks in the Friuli Venezia Giulia region of Italy from April to May 2008.
Intervention/Data Collection	Case data was collected through regional surveillance and followed up with questionnaires and telephone interviews regarding demographic characteristics, vaccination status and contact to known measles cases. Serological antibody testing and molecular analyses of measles strains were performed using standardized methods.
Outcomes	Outbreak descriptions, including demographic and epidemiological case data; Molecular analysis of involved measles strains.

Quality Assessment

	Author's judgment	**Support for judgment**

Selection Bias	Strong	Comment: All measles cases that were laboratory confirmed or probable based on epidemiological links were included. Those with clinical presentation and symptoms of measles but without confirmed infection or those not consenting to the testing were excluded. Four cases were excluded because they did not occur as part of the two outbreaks described.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Comment: Data was collected through surveillance by the prevention departments of local health districts. Questionnaires and telephone interviews were used to follow-up on the reported cases. Laboratory confirmation of measles infections and molecular analysis of strains were performed using standardized methods. Validity and reliability of the data collection processes are not reported, but are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Delgado de los Reyes et al., 2012[168]

Topic	Measles
Study Design	Epidemiological report
Participants	109 confirmed measles cases in Elche, Spain, during an outbreak between Jan. and Mar. 2012.
Intervention/Data Collection	Demographic and clinical data was reported by local hospitals and primary health care centers.
Outcomes	Outbreak description, including demographic variables (age, gender) and vaccination statuses of cases; Local outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All cases that were reported by hospitals and health centers in the region during the time of the outbreak were included.
Study Design	N/A	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Comment: Reported cases and data were obtained from the local hospitals and primary health care centers. Validity and reliability were not reported, but are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Demirdal et al., 2012[97]

Topic	Rubella
Study Design	Cross-sectional study

Participants	Serum samples of 1,194 adult women and 215 girls between the ages of 0 and 17 years were analyzed for rubella seroprevalence in the central Anatolia region of Turkey between Nov. 2005 and Feb. 2006.
Intervention/Data Collection	Participants were selected randomly and asked to participate via telephone calls; serum samples were tested for anti-rubella IgG seropositivity using standardized, commercial ELISA methods; sociodemographic variables (such as age, residency, educational level, economic status, marital status, and disease or vaccination history) were obtained through face-to-face interviews.
Outcomes	Rubella seroprevalence by age group (babies, preschool-age, school-age, childbearing age and post-childbearing age) and various sociodemographic variables (see above).

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Quote: "Rural and urban inhabitants selected for the study were detected from local health data recordings randomly. The candidates were informed by telephone and the volunteers who accepted to participate were included into the study." Comment: The number of contacted individuals who agreed to participate is not reported. Those who did participate may not be entirely representative for the region.
Study Design	Moderate	
Confounders	N/A	Comment: possible confounders are among the sociodemographic factors that were analyzed as part of the study.
Blinding	N/A	
Data Collection Method	Strong	Quote: "Rubella-specific IgG antibodies were screened qualitatively using a commercial immunoassay (Trinity Biotech, Ireland). The procedure and the interpretation of the results were performed according to the manufacturer's instructions."
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Filia et al., 2011[119]

Topic	Measles
Study Design	Epidemiological report
Participants	2,151 suspected and confirmed measles cases in Italy between July 2009 and Sep. 2010.
Intervention/Data Collection	Data was obtained through the Italian enhanced surveillance system. Genotyping of measles strains occurred at the Italian National Institute of Health and at regional reference laboratories throughout the country.
Outcomes	Measles cases and incidence; Demographic characteristics and vaccination status of cases; Hospitalization and complications; National immunization coverage; Molecular and phylogenetic analysis of involved measles strains.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All measles cases reported through the national enhanced surveillance system were included in the report.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	

Data Collection Method	Strong	Comment: Data collection occurred through enhanced surveillance. Molecular and phylogenetic analysis of strains was performed using standardized methods at the Italian National Institute of Health and at local reference laboratories. Although validity and reliability are not reported, they are likely high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Filia et al., 2013[118]

Topic	Measles
Study Design	Epidemiological report
Participants	5,568 suspected measles cases (2,085 (37%) confirmed) were reported in Italy between Oct. 2010 and Dec. 2011. Genotypic analysis was performed for 257 of the confirmed cases.
Intervention/Data Collection	Data was obtained through the Italian enhanced surveillance system. Genotyping of measles strains occurred at the Italian National Institute of Health Reference Laboratory.
Outcomes	Measles cases and incidence; Demographic characteristics and vaccination status of cases; Hospitalizations and complications; Suspected routes of measles transmission; National immunization coverage; Molecular and phylogenetic analysis of involved measles strains.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All measles cases reported through the national enhanced surveillance system were included in the report.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Data collection occurred through enhanced surveillance. Genotyping of strains was performed using standardized methods at the Italian National Institute of Health and at local reference laboratories. Although validity and reliability are not reported, they are likely high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Friedrichs et al., 2012[121]

Topic	Measles
Study Design	Cross-sectional study
Participants	Clinical samples from 5,015 people between the ages of 1 and 70 years were analyzed regarding anti-measles IgG seroprevalence in the greater Frankfurt am Main area of Germany in 1999 (1441 participants), 2005 (1070 participants) and 2009 (1945 participants).

Intervention/Data Collection	Standardized methods were used to determine the IgG titers. The immunization status of 230 participants who had visited the outpatient vaccination clinic of the Frankfurt/Main University's Institute for Medical Virology were collected between Sep. and Dec. of 2010 by reviewing vaccination cards. Data collection occurred anonymously.
Outcomes	Regional anti-measles seroprevalence by age group and year; Measles vaccination coverage by age group and number of dosages received.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: Only in- and outpatients of the university hospital were included in the study and may not be representative of the entire region. The vaccination coverage was determined solely based on voluntary data from persons who had visited the vaccination clinic, mainly for travel purposes; the results may therefore be skewed.
Study Design	Moderate	
Confounders	N/A	
Blinding	Moderate	The samples were collected anonymously; only year of birth and gender were known.
Data Collection Method	Strong	Comment: The immunization status data was collected by reviewing each participant's vaccination cards, and seroprevalence was determined using standardized methods with a high validity and reliability.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Ghebrehewet et al., 2013[125]

Topic	Measles
Study Design	Epidemiological report
Participants	147 suspected measles cases (67 confirmed, 23 probable, 14 possible, 42 excluded) were reported in Central and Eastern Cheshire, United Kingdom, between Oct. 2008 and Feb. 2009. A travelling community was disproportionately affected with 20% of all cases; most were among school-aged children. Genotypic analysis was performed for four confirmed cases.
Intervention/Data Collection	Data was obtained through routine and active surveillance, whereby health care workers were notified about the outbreak through letters. Molecular and phylogenetic analysis of measles strains occurred at the Health Protection Agency Reference Laboratory.
Outcomes	Outbreak description, including demographic variables and vaccination statuses of cases; Molecular and phylogenetic analysis of involved measles strains; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: All reported measles cases were included in the report; confirmed negative cases were excluded from the analysis. The four samples genotyped are not representative of the population infected with measles, however.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	

Data Collection Method	Strong	Comment: Case data collection occurred through local surveillance and confirmation was performed by IgM seroprevalence testing of oral fluid samples. The genotypes of involved measles strains were determined using standardized methods. Although validity and reliability are not reported, they are likely high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Hardelid et al., 2009[130]

Topic	Rubella
Study Design	Cross-sectional cohort study
Participants	Newborn screening blood spot samples of 18,882 infants in the Thames Valley region of England were collected randomly (by sample plate) in the spring and fall of 2004. The samples were also tested for HIV and repeats or HIV-positive samples, as well as those for which screening had been declined, were excluded.
Intervention/Data Collection	The samples were analyzed regarding the presences of maternal anti-rubella IgG antibodies using a commercial, standardized ELISA method. Rubella seronegativity was estimated using latent class regression finite mixture models. Demographic information about the mothers (such as residency and country of birth) was obtained by linking the newborn screening cards to birth registration records.
Outcomes	Rubella IgG seronegativity by maternal age, region of birth and current residence.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Quote: "We carried out a seroprevalence study among newly delivered women using residual dried blood spot samples from routine newborn screening. As coverage of screening is very high [nearly 100%], these samples provide a large and nearly unbiased sampling frame for serosurveys and eliminate the need for further sample collection....A random sample of 220 plates was taken, containing 19,781 of the approximately 55,600 samples.
Study Design	Moderate	
Confounders	Weak	Comment: A matching of the samples (accoring to maternal age, for instance) was not described in the comparison between native and immigrant women or between the various regions of residency, potentially leading to confounding.
Blinding	N/A	
Data Collection Method	Moderate	Quote: "The residual eluates from HIV testing were tested for rubella IgG antibody according to the manufacturersâĂŹ instructions using a commercial enzyme-linked immunosorbent assay (ELISA; Diesse, Siena, Italy), which has been validated for use on dried blood spot samples....The specificity of antibody assays may be compromised in serosurveys in which alternative specimens to serum are used, and cut-off values provided by the manufacturer to identify seronegative samples may therefore not be applicable. Instead, we constructed latent class regression finite mixture models to the distribution of rubella IgG levels to estimate the proportion of seronegative samples."
Withdraws/Dropouts	Strong	Comment: Due to concomitant HIV-testing of the newborn screening blood spots, 4.5% of the randomly selected samples were not included; all others were tested according to the study protocol.

Conflict of Interest	Weak	Quote: "This study was funded by the Medical Research Council.... This work was undertaken at the UCL Institute of Child Health which receives a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. In addition, The Centre for Paediatric Epidemiology and Biostatistics benefits from funding support from the Medical Research Council in its capacity as the MRC Centre of Epidemiology for Child Health."
Overall Rating	**Weak**	

Hegasy et al., 2012[137]

Topic	Measles
Study Design	Epidemiological report
Participants	216 measles cases in Hamburg, Germany, during an outbreak between Dec. 2008 and June 2009. Over half of the cases were reported among the local Roma community.
Intervention/Data Collection	Data was collected through enhanced electronic surveillance by the Robert Koch Institut (*SurvNet*). Demographic, epidemiological and clinical data was available for most cases. Genotyping of measles strains occurred through standardized methods at the National Reference Center for Measles, Mumps and Rubella.
Outcomes	Outbreak description, including demographic, geographic and epidemiologic case data; Laboratory case confirmation and epidemiological linking of cases; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: Although all confirmed and probable measles cases occurring in the city of Hamburg during the outbreak were included, demographic characteristics were mainly described for a sub-population living in one part of the city.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Data was collected using the national enhanced surveillance system. Molecular analysis of strains occurred using standardized methods. Although validity and reliability are not reported, they are likely high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Huoi et al., 2012[140]

Topic	Measles
Study Design	Epidemiological report
Participants	407 measles cases in Lyon, France, in 2010 and 2011. Among the cases were health care workers and 13 pregnant women.
Intervention/Data Collection	Data was obtained from the regional public health agency's notification system and four local hospitals belonging to the Lyon University, where the cases were diagnosed.

Outcomes	Demographic characteristics and vaccination status of cases; Characteristics of pregnant cases; Measles infection confirmation (laboratory or epidemically linked); Hospitalizations and complications; Outbreak control measures; Immune status of patients and health care workers.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Quote: "A prospective surveillance of measles cases was instituted in LUH [Lyon University Hospitals] from 1 January 2010....LUH form the largest group of public hospitals in the town of Lyon. Our data concerned the four main hospitals of the group...All patients and healthcare workers who had contracted measles were included."
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Quote: "For the present report, we analysed two different data sources: (i) surveillance of measles cases through all the mandatory notifications conducted by one of the LUH and (ii) virological surveillance through tested samples derived from patients and healthcare workers (HCW)." Comment: Validity and reliability of the data collection process are not reported, but are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Kaic et al., 2009[149]

Topic	Measles
Study Design	Epidemiological report
Participants	49 measles cases occurring during a 2008 outbreak in two regions of Croatia (Zagreb and Slavonski Brod).
Intervention/Data Collection	Data was obtained through national surveillance. Cases were either laboratory confirmed using standardized ELISA or PCR techniques or they were epidemiologically linked. Confirmed cases were interviewed and their medical records reviewed to determine vaccination status and demographic characteristics.
Outcomes	Outbreak description, including demographic characteristics and vaccination status of cases; Laboratory case confirmation and epidemiological linking rates; Hospitalizations and complications; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All cases occurring during the time of the outbreak were included; only cases without measles confirmation were excluded.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Comment: Case reports were obtained through mandatory surveillance. The validity and reliability of the data collection through interviews and medical records are not described, but are likely adequate.

Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Kakoulidou et al., 2010[151]

Topic	Rubella
Study Design	Cross-sectional cohort study
Participants	41,637 pregnant women of the Southern Stockholm region of Sweden were tested for rubella seropositivity between 2004 and 2006. For 97.2% of the participants, year of birth and country of origin where known; the remaining women were mostly recent immigrants and refugees.
Intervention/Data Collection	A standardized MEIA method was employed to determine anti-rubella IgG seroprevalence among the participants; additional demographic data were obtained through the Swedish personal identification numbers (if available), and the birth registry of the Swedish National Board of Health and Welfare.
Outcomes	Rubella IgG seroprevalence by birth year and nationality (if known) as well as among the recent immigrants and refugees (demographic data not available); Change in seropositivity over time in relation to changes in the national rubella vaccination plan; Effect of post-partum rubella vaccination, measured as seropositivity among primipara and multipara women.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: a very large regional sample was obtained using rubella screening methods during pregnancy. Although the testing occurred at the same Hospital, samples from the entire region were analyzed.
Study Design	Moderate	
Confounders	Weak	In regard to the sample comparisons between birth cohorts born before and after the introduction of the MMR vaccination, between primipara and multipara women, as well as between various countries of origin, a matching between the groups or controlling of confounders was not described.
Blinding	N/A	
Data Collection Method	Strong	Quote: "Sera were collected and assayed for rubella IgG antibodies employing the ABBOTT AxSYM procedure, which is based on the technology of Microparticle Enzyme Immunoassay (MEIA), upon arrival to the Division of Clinical Microbiology. The values obtained were quantitated by comparison to an international standard serum supplied by the WHO and, moreover, the assay was evaluated regularly utilizing external control panels from UK NEQAS. According to the manufacturer, the sensitivity of this test is 98.0% and the specificity 99.0%. In our hands, over the years the coefficient of variation was approximately 10%." Comment: In addition, negative or equivocal rubella antibody levels (<10 IU/ml) were confirmed through retesting.
Withdraws/Dropouts	N/A	
Conflict of Interest	Weak	Quote: "This study was supported financially by research grants from the Karolinska Institute and International Partners Limited."
Overall Rating	**Weak**	

Kalaycioglu et al., 2013[152]

Topic	Measles
Study Design	Epidemiological report
Participants	26 clinical samples (serum, urine, or throat swaps) were collected from suspected measles cases in Turkey between 2010 and 2011.
Intervention/Data Collection	The samples were collected by the Turkish National Public Health Agency and sequenced and genotyped using standardized methods.
Outcomes	Molecular and phylogenetic analysis of the clinical samples; Suspected sources of importation based on the identified viral strains.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: The number of confirmed measles cases included in the study was rather small and not representative for the national population. The total numbers of reported cases and tested samples were not described.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: standardized methods were employed by the National Public Health Agency Viral Reference Laboratory to sequence and identify the measles strains. Although the validity and reliability were not reported, they are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Quote: "Grant sponsor: Ministry of Health, Turkish National Public Health Agency" Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Karabulut et al., 2011[153]

Topic	Rubella
Study Design	Cross-sectional study
Participants	Serum samples of 1,268 pregnant women in their first trimester were tested to determine anti-rubella antibody seroprevalence in the Denizli province of Turkey between April of 2008 and April of 2009.
Intervention/Data Collection	Pregnant women attending the Denizil State Hospital for routine antenatal care during the study period were included. Serum samples were analyzed for anti-rubella IgG and IgM antibody seroprevalence using standardized, commercial ELISA techniques.
Outcomes	Seroprevalence of anti-rubella antibodies among the participants and comparison to related seroprevalence studies in Turkey.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: Although a large sample was obtained, all participants had attended the same hospital and may not be representative for the region.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Quote: "rubella IgM and IgG antibodies were assayed by the automated Vitros ECiQ system based on an immunometric technique (Vitrous ECIQB system Johnson & Johnson, New Brunswick, NJ, USA)....The assays were performed according to the manufacturer's instructions."

Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Karasek and Paradowska-Stankiewicz, 2013[154]

Topic	Rubella
Study Design	Epidemiological Report
Participants	4,290 rubella cases were reported in Poland in 2011.
Intervention/Data Collection	Quote: "Evaluation of rubella epidemiological situation in Poland was based on data from the newsletters: 'Infectious diseases and poisoning in Poland in 2011' and 'Vaccinations in Poland in 2011' (MP. Czarkowski, Warsaw 2012, NIPH-NIH, GIS). Classification of rubella cases was based on the definition of infectious diseases prepared by ECDC."
Outcomes	Rubella incidence by age group and gender; Comparison of incidence to previous year; Laboratory confirmation rate.

Quality Assessment	N/A	*Full text not accessible.*

Kasper et al., 2009[156]

Topic	Measles
Study Design	Epidemiological report
Participants	37 measles cases were reported in the Austrian region of Styria from March to May 2009; 25 of the cases were among an anthroposophic community.
Intervention/Data Collection	Case data regarding demographic characteristics, symptoms, contact to known measles cases and vaccination status were collected through telephone interviews.
Outcomes	Outbreak description, including demographic characteristics and vaccination statuses of cases; Molecular analysis of involved measles strains; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All measles cases occurring during the regional outbreak were included.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Weak	Comment: All case data were collected via telephone interviews of suspected measles cases. Validity and reliability of the interview process were not reported. Genotyping was performed by the Austrian National Reference Center for Measles using two case samples.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Kasper et al., 2010[155]

Topic	Rubella
Study Design	Epidemiological report
Participants	355 rubella cases (146 female, 247 confirmed) were reported in Austria between Oct. of 2008 and June of 2009.
Intervention/Data Collection	Case data collection occurred through active, enhanced surveillance reports to local health authorities and the Austrian Agency for Health and Food Safety (AGES). Demographic and clinical data were accessed through telephone interviews. Serological confirmation of cases was performed at the national rubella reference center using standardized methods.
Outcomes	Outbreak description, including case demographics and time of rash onset; Laboratory and epidemiological confirmation rates; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All reported cases that met the outbreak case definition were included in the analysis.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Cases were identified through active enhanced surveillance. Laboratory confirmation was performed using standardized methods. Although the validity and reliability are not reported, they are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Koksaldi-Motor et al., 2012[160]

Topic	Rubella
Study Design	Cross-sectional study
Participants	Rubella seroprevalence (next to Toxoplasmosis and Cytomegalovirus (CMV) seroprevalence) was determined among 746 women and children in the southern Turkish region of Hatay between Jan. and Dec. of 2009. All participants were patients in the Hatay Women and Children Hospital.
Intervention/Data Collection	Rubella IgG seroprevalence was tested using standardized Chemiluminescence Immunoassay (CLIA) kits.
Outcomes	Seroprevalence of rubella (and CMV, toxoplasmosis) according to age group, with a main focus on women of childbearing age (15-44 years old).

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: Although a large sample size was obtained, all cases were patients of the same hospital and may not be representative of the entire region.
Study Design	Moderate	
Confounders	Weak	Comment: Cases were grouped by age, but not stratified (sample sizes ranging from 9 to 528 people), making comparisons between the age-groups difficult. Among the study sample older than 14 years, only women were included; among those under the age of 14 years, both girs and boys were included. Other possible confounders, such as patient health status or immunocompetence were not taken into consideration.

Blinding	N/A	
Data Collection Method	Strong	Comment: Standardized methods were used to determine seroprevalence. Although validity and reliability are not described, they are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Kurugöl et al., 2011[161]

Topic	Rubella
Study Design	Cross-sectional study
Participants	597 healthy individuals (221 male, 376 female), aged 1 to 70 years, living in the Izmir region of Turkey in March of 2008. Participants were grouped by age.
Intervention/Data Collection	A random cluster sampling design was employed to recruit participants: 30 clusters of urban and rural areas were selected randomly and a total of 600 participants included in the study (of which three were excluded due to insufficient sera samples). Sociodemographic data and vaccination/disease history were obtained through a questionnaire. Serum samples were analyzed for anti-rubella IgG antibody seroprevalence using standardized, commercial EIA kits.
Outcomes	Proportion of susceptible participants and mean anti-rubella IgG antibody levels by age group, gender, residence (urban/rural), socioeconomic status and number of household members.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Quote: "A cluster sample design developed by EPI of the World Health Organization for the surveys of immunization was performed for the selection of the study population." Comment: The sample chosen is likely representative of the local population.
Study Design	Moderate	
Confounders	N/A	Comment: possible confounders are among the sociodemographic factors that were analyzed as part of the study.
Blinding	N/A	
Data Collection Method	Strong	Quote: "Rubella-specific IgG antibodies were screened quantitatively using commercial enzyme immunoassay kits (Biokit, S.A., Barcelona, Spain)." Comment: Both the sensitivity and specificity of this EIA method are high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Lashkari and Bashir, 2010[163]

Topic	Measles, Mumps, Rubella
Study Design	Retrospective cohort study
Participants	Students in a school district of London in their last year of school; average age: 14.7 years.
Intervention/Data Collection	The vaccination status of 400 randomly selected students were determined before (retrospectively) and after a regional "school leaver's" MMR catch-up vaccination intervention was performed. Vaccines were provided to those students who had received no or only one MMR-dosage and whose parents provided consent.

Outcomes	Number of students who had received zero, one or two doses of an MMR vaccine before and after the intervention.

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Strong	Comment: The intervention was provided for all students in the school district. The vaccination status of 400 randomly selected students were analyzed as part of the study.
Study Design	Moderate	
Confounders	N/A	Comment: The same sample group of 400 students was analyzed regarding their vaccination status before and after the intervention.
Blinding	Moderate	Comment: Blinding was not described.
Data Collection Method	Strong	Comment: Data was collected using electronic immunization records. For accuracy validation, the students' school health records were reviewed as well.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Lo Giudice et al., 2009[165]

Topic	Rubella
Study Design	Cross-sectional study
Participants	1,000 women of childbearing age (15-45 years) residing in the Messina province of Italy were tested for rubella seroprevalence between July 2006 and Dec. 2007.
Intervention/Data Collection	Anti-rubella IgG and IgM titers were determined using standardized, commercial MEIA kits. A questionnaire was provided to ascertain each participant's knowledge about CRS, sociodemographic factors (such as level of education), and rubella vaccination and disease history. Vaccination coverage by birth cohort data was obtained from the local health authority.
Outcomes	Number of seropositive and seronegative (susceptible) participants in each age group; Knowledge about CRS and sources of information; Regional MMR vaccination coverage according to birth cohorts (1993-2006).

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Strong	Comment: A large sample of women was included in the study. The sample is likely representative for the region.
Study Design	Moderate	
Confounders	Moderate	Comment: Participants were grouped, but not matched, by age. All participants were women. In regard to knowledge about CRS and source of information, the educational level of the participants was considered, but not confounder controlled. Vaccination coverage data were analyzed according to birth cohort.
Blinding	N/A	
Data Collection Method	Strong	Comment: Seroprevalence (both IgG and IgM) was determined using standardized methods with high validity and reliability.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

López Hernández et al., 2010[167]

Topic	Measles
Study Design	Epidemiological report (preliminary)
Participants	25 measles cases, reported during an outbreak in Grenada, Spain, between Oct. and Nov. of 2009.
Intervention/Data Collection	Data was obtained through enhanced regional surveillance.
Outcomes	Description of outbreak, including demographic characteristics, vaccination statuses, and complications among cases; Genotypic analysis of involved measles strain; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: The presented data is preliminary. More measles case were reported to have occurred at a later time. The measles genotype was assessed among only two cases.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Data was collected through the enhanced surveillance system of the Andalucian region. Although the validity and reliability are not reported, they are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Maduma-Butshe and McCarthy, 2013[169]

Topic	Measles
Study Design	Epidemiological report
Participants	142 measles cases, reported in the Thames Valley of England, UK. A large proportion of the cases were among Roma/Sinti travelers.
Intervention/Data Collection	Data collection occurred through surveillance of suspected measles cases and interviews with health-care staff, cases or parents of cases.
Outcomes	Outbreak descriptions, including demographic characteristics of the cases and whether they are members of a Roma/Sinti traveler population; Vaccination status of cases; Reasons provided by study participants for not seeking medical care.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: All confirmed measles cases occurring in the region between 2006 and 2009 were included. The number of Roma/Sinti measles cases is likely under-reported, however. Quote: "A possible bias in our study is that case ascertainment may have varied between the Gypsy-Traveller and non-Gypsy-Traveller communities. Reluctance to present measles to GPs by the Gypsy-Traveller communities may have decreased the probability of identification and reporting."
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	

Data Collection Method	Weak	Comment: Case data was collected through surveillance and interviews with health-care staff and the patients or parents of patients. Validity and reliability of the interview process were not reported. Data on the vaccination status of the cases was validated, when available.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Magurano et al., 2012[171]

Topic	Measles
Study Design	Epidemiological report
Participants	Clinical samples (urine or saliva) were obtained from 414 suspected (199 confirmed) measles cases in Italy. 179 samples were sequenced for genotypic analysis.
Intervention/Data Collection	Samples were collected between May of 2002 and Dec. of 2007 by the Italian National Institute of Health Reference Laboratory. Viral RNA isolation, sequencing and genotyping was performed using standardized methods.
Outcomes	Phylogenetic analysis of strains circulating in Italy between 2002 and 2007.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: Although a large number of samples was included, the proportion is very small compared to the case numbers reported during the time period and may not be representative for the entire nation.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Quote: "The tests on urine and salivary samples were performed under the indications of the 'National Plan of Elimination of Measles and Congenital Rubella'. The Plan has been elaborated by the Ministry of Health according with the WHO indications, and approved by all Regional Health Authorities. Our laboratory belongs to the WHO European Regional Network of National Measles and Rubella Reference Laboratories." Comment: The method validity and reliability are not described, but are likely high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Quote: "This work was partly supported by a grant from Italian Ministry of Health..." Comment: No conflict of interest has been declared.
Overall Rating	**Moderate**	

Magurano et al., 2013[170]

Topic	Measles
Study Design	Epidemiological report
Participants	Clinical samples (urine or saliva) were obtained from 203 confirmed measles cases of 4,177 total reported cases in Italy in 2008.
Intervention/Data Collection	Samples were collected between Jan and Dec. of 2008 by various local Italian health authorities and some of them laboratory confirmed. The Italian National Institute of Health Reference Laboratory retested the samples and determined their genotypes. Viral RNA isolation, sequencing and genotyping was performed using standardized methods.

Outcomes	Phylogenetic analysis of strains circulating in Italy in 2008.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: Only 37% of the reported cases were confirmed and of these, only 13% were sequenced and genotyped. The data are therefore likely not representative for the entire nation.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: As stated in a previous study,[171] the laboratory that performed the genotypic and phylogenetic analyses belongs to the WHO European Regional Network of National Measles and Rubella Reference Laboratories and follows the standards conveyed by the WHO.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Quote: "This work was partly supported by a grant from Italian Ministry of Health..." Comment: No conflict of interest has been declared.
Overall Rating	**Moderate**	

Mankertz, Mihneva et al., 2011[173]

Topic	Measles
Study Design	Epidemiological report
Participants	European affected by the D4-Hamburg measles strain.
Intervention/Data Collection	Genotyping of specimens collected from measles patients throughout Europe was performed at the WHO Regional Reference Laboratory in Berlin, Germany, using standardized methods. Data obtained from the WHO measles sequence database, *Measles Nucleotide Surveillance* (MeaNS), was also included.
Outcomes	Outbreak descriptions of the D4-Hamburg strain spread throughout Europe.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: Efforts were made to include all available epidemiological data regarding the D4-Hamburg strain and affected individuals.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Standardized, WHO-recommended methods were applied for the molecular and phylogenetic strain analysis.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Mankertz, Mulders et al., 2011[174]

Topic	Measles
Study Design	Epidemiological report

Participants	Measles outbreaks occurring in the WHO European Region between 2007 and 2009.
Intervention/Data Collection	Analysis of the measles genotypes detected by various national and regional laboratories in Europe.
Outcomes	Detected genotypes in Europe (endemic, introduced, and terminated); Outbreak descriptions, including reported measles cases and incidences.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All measles outbreaks occurring the European region were included.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Epidemiological data was obtained through routine monitoring systems (including data reported to EUVAC.NET and the WHO Regional Offices for Europe). Molecular data of the various genotypes was obtained using standardized methods, with high validity and reliability, as recommended by the WHO.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Martínez-Torres et al., 2009[176]

Topic	Rubella
Study Design	Epidemiological report
Participants	40 rubella cases from an outbreak involving 460 cases (mostly immigrants) were recruited between 2004 and 2005 in Madrid, Spain. The sample was distributed as follows: (quote) "10 local Spanish people, 21 immigrants, seven individuals of unknown origin, and two persons with CRS."
Intervention/Data Collection	Rubella viral RNA from the clinical samples (urine, serum, blood, saliva or pharyngeal exudates) was isolated, sequenced and analyzed using standard methods, as recommended by the WHO.
Outcomes	Genotypic and phylogentic analysis of rubella strains; Sequence analyses of clustered and isolated viral sequences.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: Clinical specimens from 40 (8.7%) out of 460 total rubella cases were collected in a clinical setting. Although many cases are likely linked, the small percentage of included samples may not be representative and other imported rubella strains may have been missed.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Quote: "Specimens were collected and processed in accordance with WHO recommendations." Comment: the described methods have been previously shown to be valid and reliable.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Quote: "This work received financial support from the fellowship for Ph.D. study by the Republic of Panama and Acuerdo de Encomienda de Gestión entre la Dirección General de Salud Pública del Ministerio de Sanidad y Consumo and the Instituto de Salud Carlos III" Comment: A conflict of interest statement is not included.

Overall Rating	**Moderate**

Mayoral Cortés et al., 2012[178]

Topic	Measles
Study Design	Epidemiological report
Participants	1,759 measles cases in the Andalucian Region of Spain, infected during an outbreak between Jan. and Aug. of 2011.
Intervention/Data Collection	Case data were obtained through the Andalucian epidemiological suveillance system, SVEA, which includes laboratory diagnosed measles cases as well as clinical and epidemiological information. Molecular analysis of strains was performed at two national reference laboratories in Madrid, Spain.
Outcomes	Outbreak descriptions, including demographic characteristics and vaccination statuses of the cases; Measles incidences and comparison between areas with high (>100/10,000) and low (<100/10,000) incidences; Complications and hospitalizations; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All confirmed and probable measles cases occurring during the outbreak were included. Vaccination status was available for about 30% of the cases.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Laboratory and molecular analyses were performed using standardized methods. Although validity and reliability are not reported, they are likely high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Melidou et al., 2012[179]

Topic	Measles
Study Design	Epidemiological report
Participants	126 people involved in a measles outbreak in Greece between Jan. and July of 2010. Clinical samples of 24 confirmed cases were sequenced and genotyped.
Intervention/Data Collection	Cases were reported through the national surveillance system. The clinical samples (nasopharyngeal swaps) were collected among cases from both southern and northern Greece and were analyzed at the national Measles and Rubella Reference Laboratory of the *Hellenic Pasteur Institute* as well as the Microbiology Laboratory of the Aristotle University of Thessaloniki using standardized methods.
Outcomes	Outbreak description; Laboratory confirmation of cases; Molecular and phylogenetic analysis of involved measles strains.

Quality Assessment

	Author's judgment	**Support for judgment**

Selection Bias	Moderate	Comment: Samples from a small proportion of the reported cases (19%) were genotyped. Although these samples were obtained from persons of different populations (Bulgarian Roma, Greek Roma and non-minority Greek populations), they may not be representative.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Measles virus RNA extraction, sequencing and genotyping were performed at two seperate laboratories using standardized, valid and reliable methods, as recommend by the WHO.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: No conflict of interest was declared.
Overall Rating	**Strong**	

Mereckiene et al., 2012[180]

Topic	Measles, Mumps, Rubella
Study Design	Review
Aims	Identification and monitoring of hard-to-reach populations in regard to MMR vaccinations in the WHO European region. Challenges and strategies for improving vaccination rates among these populations are addressed.
Methods	Literature search using the PubMed database as well as reports by immunization professionals accessed through the VENICE project and ECDC. Google was searched to complete the research (including websites and unpublished studies and reports).
Outcomes	Identification of hard-to-reach populations and barriers to vaccination; measles, mumps and rubella vaccination coverage and outbreak reports among the identified populations.

Quality Assessment

	Author's judgment	**Support for judgment**
'A Priori' Design	Yes	Comment: The pre-defined aims of the research are stated.
Duplicate Study Selection/ Data Extraction	Yes	Quote: "[The project] involved regular meetings with the project team to discuss methodology and progress....the literature review was led by one expert and supported by another two experts."
Comprehensive Literature Search	No	Comment: The search strategy, including database and MESH terms, is provided and supplementary strategies (expert consultation, "grey literature" search) are described. However, only one electronic database was used, and some publications may have been missed.
Status of Publications	Yes	Quote: "We also included the literature, publications, reports and discussion points provided by experts through an e-forum organised by the VENICE network and ECDC (EPIS-VPD). Finally, selected keywords were used to search Google for unpublished reports (grey literature), studies, websites and European documents on human rights, socio-economic conditions, health status, access to public services and vaccination coverage among hard-to-reach groups."
List of Studies	Can't answer	Comment: Included studies, reports and websites are listed. However, excluded studies and reports have not been referenced.
Characteristics of Included Studies	Yes	Comment: The characteristics of each study, including year, country, participants, and relevant demographic data, are provided.

Study Quality Assessment	No	Comment: The scientific quality of included studies and reports is not described.
Study Quality Consideration	N/A	
Combining Methods	Can't answer	Comment: The study results are not combined. Heterogeneity is not described.
Publication Bias	No	Comment: Publication bias is not addressed.
Conflict of Interest	No	Comment: The report was commissioned by the ECDC. However, potential conflicts of interest are not addressed for the included studies.
Overall Rating	**Moderate (36%)**	

Mette et al., 2011[182]

Topic	Measles
Study Design	Epidemiological report
Participants	Measles cases reported in the federal state of North Rhine-Westphalia, Germany, in 2006 and 2007.
Intervention/Data Collection	Two different case reporting methods (national mandatory surveillance and statutory health insurance data) were compared to estimate the extend of underreporting in the surveillance system. Incidences were calculated based on the numbers of reported cases using each method.
Outcomes	Number of cases and general population incidence based on surveillance data; Comparison to the number of cases and incidence based on health insurance data; Age groups of affected individuals and time of diagnoses/reporting.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All regionally reported cases were included in the analysis.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Data were obtained through the mandatory surveillance system and billing data of statutory health insurance providers. The data were verified before being reported to the Robert Koch Institute.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Muscat et al, 2009[200]

Topic	Measles
Study Design	Epidemiological report
Participants	12,132 measles cases occurring in 32 European nations during 2006 and 2007, as reported on a national level to the *European surveillance network for vaccine-preventable diseases* (EUVAC.NET), now part of the *European Center for Disease Control and Prevention* (ECDC).
Intervention/Data Collection	National measles surveillance data, including cases reported, vaccination status, hospitalization and deaths, were collected by EUVAC.NET and statistically analyzed.

Outcomes	Number of cases reported by each nation and crude incidences; Laboratory-confirmed and epidemiologically-linked cases; Cases by age group; Vaccination status of cases; Complications, hospitalizations and deaths among the reported cases; indigenous and imported cases and common source nations for imported cases.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: 30 of 32 European nations provided case-based measles data from national notification systems (of which 97% were mandatory). Two countries provided aggregated data.
Study Design	N/A	
Confounders	Moderate	Comment: Two countries provided aggregated data and one country did not have a mandatory, but partially voluntary, reporting system, making a comparisons between these countries and the ones that did report mandatory case-based data more difficult. Comparisons between confirmed (through laboratories or epidemiological linking) and unconfirmed (clinical or suspected) cases should also be done with caution.
Blinding	N/A	
Data Collection Method	Strong	Comment: Data collection occurred through nation-based surveillance reporting to EUVAC.NET, which validates all reported data.[111] Reliability is not reported, but is likely high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: Funding was provided by the European Commission and the Statens Serum Institut of Denmark. No conflict of interest has been declared.
Overall Rating	**Strong**	

Muscat et al., 2012[201]

Topic	Rubella, CRI
Study Design	Epidemiological Report
Participants	(See below)
Intervention/Data Collection	Epidemiological data on rubella and congenital rubella cases between 2000 and 2008 was collected from 32 European countries through EUVAC.NET; 24 of these nations had mandatory rubella surveillance systems in place.
Outcomes	Analysis of rubella surveillance systems; Rubella cases and incidences reported by 24 countries with mandatory surveillance for the time period 2000-2008; CRS cases and incidence for all 32 included nations for the time period 2000-2008; Epidemiological assessment of rubella cases, incidence, age-distribution, vaccination dosage, and diagnostic confirmation for 28 countries with mandatory notification in 2008.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: Only those countries with mandatory rubella notification system were included in the analysis. Although these data are not representative for the entire European continent, they provide the best available data and allow for a comparison between the nations.
Study Design	Moderate	
Confounders	Strong	Comment: For better comparability between the nations, only countries with mandatory surveillance systems were included (see above).

Blinding	N/A	
Data Collection Method	Strong	Comment: Each nation included in the report provided data from their national surveillance systems to EUVAC.NET. The validity and reliability of these data are not reported, but are likely high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Quote: "*Funding*: EUVAC.NET was funded by the European Centre for Disease Prevention and Control and the Statens Serum Institut. Prior to February 2009, EUVAC.NET received funding from the European Commission (DG SANCO) and the Statens Serum Institut. *Role of Sponsor*: No funding organization or sponsor had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript."
Overall Rating	**Strong**	

Orlikova et al., 2010[207]

Topic	Rubella, CRI
Study Design	Epidemiological report
Participants	Local outbreak in Eastern Poland involving 41 cases (8 confirmed, 24 probable, 9 possible) between June and Aug. of 2009. The majority (85%) of cases were within a Roma community.
Intervention/Data Collection	Cases were registered through passive and active surveillance. Laboratory confirmation of cases was performed at the National Reference Laboratory of the Polish National Institute of Health using standardized methods (ELISA and PCR). Viral sequencing and genotyping was performed at the WHO Reference Laboratory in Germany.
Outcomes	Outbreak description; Laboratory confirmation rate of case; Molecular and phylogenetic analysis of involved rubella strains.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: Although all cases were included in the report, the confirmation rate was with 19% low and the genotyping with 5% extremely low. These data may therefore not be representative.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Active surveillances was employed to identify cases from the hard-to-reach population. All laboratory testing was performed using standardized methods. Although the validity and reliability are not reported, they are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Orsi et al., 2010[208]

Topic	Measles
Study Design	Epidemiological report

Participants	39 measles cases were reported in a local outbreak in Liguria, Italy. Of these case, 19 were confirmed and 18 sequenced for genotypic analysis.
Intervention/Data Collection	Data was collected through three seperate surveillance systems (a mandatory notification system, a laboratory reporting system, and a syndrome surveillance system). Laboratory analysis occurred using standardized methods.
Outcomes	Description of surveillance systems; Outbreak description; Molecular and phylogenetic analysis of measles strains.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All reported cases were included in the analysis; about half of the cases were confirmed. The genotyping occurred among nearly all confirmed cases and is likely representative.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Quote: "the Regional Reference laboratory for Measles and Rubella diagnosis, located at Department of Health Sciences, University of Genoa, [operates] in accordance with the international standards established by the global laboratory network."
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Paradowska-Stankiewicz et al., 2013[212]

Topic	Rubella
Study Design	Epidemiological Report
Participants	21,283 clinical rubella cases in Poland, reported between Jan. and Apr. of 2013
Intervention/Data Collection	Data were obtained through national surveillance, as reported by physicians.
Outcomes	Outbreak description, including incidences by region, demographic indicators and vaccination status of cases; Development of rubella trends in the past years.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	All notified rubella cases within the time frame of the study were included.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Data were collected through the national mandatory surveillance system.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Parent du Châtelet et al., 2010[75]

Topic	Measles
Study Design	Epidemiological report (preliminary)
Participants	Between Jan. 2009 and June 2010, 4,753 measles cases were notified in France (54% of them confirmed). Cases that were likely imported were excluded from the analysis.
Intervention/Data Collection	Data was obtained through mandatory national surveillance. Viral genotyping occured at the National Reference Center for Measles in France.
Outcomes	Outbreak description, including demographic analysis and vaccination statuses of cases; Molecular and phylogenetic analyses of involved measles strains; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: Cases that had been reported up to the time of the report were included; 99 presumably imported cases were excluded. The data are preliminary as the outbreak had not come to an end yet.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Information about cases was collected through the national mandatory notification system. Although validity and reliability of the molecular analysis are not reported, they are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Pasławska and Mrożek-Budzyn, 2013[214]

Topic	Measles
Study Design	Epidemiological report (preliminary)
Participants	Measles cases reported in Poland by the National Institute of Hygiene, Warsaw, and in the WHO European Region by the WHO between 2002 and 2012.
Intervention/Data Collection	Surveillance data were obtained for Poland and European Region, as described above. Vaccination coverage data were also obtained and compared between selected European nations.
Outcomes	Cases reported in Poland (2004-2011), by age group; Numbers of suspected and confirmed cases reported by various European countries (2002-2012).

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All reported cases in Poland and the selected European countries (as reported by the WHO) were included in the analysis.
Study Design	Moderate	
Confounders	Moderate	A comparison between the countries may be difficult due to various reporting strategies and case confirmation rates.
Blinding	N/A	

Data Collection Method	Weak	Comment: Data obtained through the national mandatory surveillance in Poland is likely accurate. However, the types of surveillance systems used in the other included countries were not addressed. Validity and reliability may therefore not be accurate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Pavlopoulou et al., 2013[215]

Topic	Rubella
Study Design	Cross-sectional study
Participants	3,399 children, aged 10-65 months, attending nurseries in Athens, Greece, during the 2010-2011 school year; 731 of these children were randomly selected for the collection of additional demographic data.
Intervention/Data Collection	All children attending nurseries in the local municipalities were asked to participate and those with available immunization records were included in the study. 731 children were selected using stratified sampling methods, and sociodemographic data were obtained from schools and through structured questionnaire-based telephone interviews with the parents or guardians of the children. Vaccination rates were estimated using weighted sample proportions.
Outcomes	Demographics of the sample; Parental immunization attitudes; Proportions of complete and age-appropriate vaccination rates for several immunizations; Factors influencing vaccination coverage.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Quote: "A cross-sectional study was undertaken using stratified sample design in all public nurseries of the Municipality of Athens, Greece during the school year 2010-2011....On the day of population recording, a total of 4,165 pupils were present, but only 3,399 were considered for further evaluation, those whose parents had presented a health booklet." Comment: The large sample is likely representative for the region and the participation rate was with 82% high; however, a large proportion of unvaccinated or not-sufficiently vaccinated children may have been among the group without available immunization records, thus skewing the results.
Study Design	Moderate	
Confounders	Strong	The study design included the stratification according to region and gender; other possible confounders were included in the analysis as potential factors influencing vaccination rates and are thus not applicable here.
Blinding	N/A	
Data Collection Method	Moderate	Quote: "A structured questionnaire completed by the investigators was used. Basic demographic data were collected from school registries on the day of school visit. Detailed vaccination history and use of combination vaccines were obtained from vaccination booklets. Parental/guardian attitudes towards immunization and additional information were gathered on a second occasion by telephone interview." Comment: Neither validity nor reliability of the data collection methods are described, but are likely sufficient.
Withdraws/Dropouts	N/A	

Conflict of Interest	Moderate	Quote: "This research was partially funded by Vianex/ Sanofi Pasteur MSD, Vaccine Unit, Greece." Comment: No conflict of interest has been declared. However, taking into account the type of sponsor, an unintentional conflict of interest may exist nonetheless.
Overall Rating	**Strong**	

Peña-Rey et al., 2009[216]

Topic	Measles
Study Design	Review
Aims	Description of measles outbreaks occurring in Spain between 2005 and 2007, and the identification of high-risk groups. Comparisons to outbreaks occurring in other European countries are made as well.
Methods	Outbreak data were obtained through the Spanish National Surveillance Network and a literature search using the PubMed database. Additional information was sought out regarding preliminary reports to include the final data. Immunization history data was obtained from the included nations' official web pages, EUVAC.NET, the WHO and the Spanish Ministry of Health.
Outcomes	Description of measles outbreaks in Spain and other European countries, including year, number of cases, age and gender distribution, outbreak setting, predominantly affected groups, measles genotype and origin in the case of importation; Vaccination statistics for each country, including year of MCV introduction, recommended immunization age, primary and secondary dosage vaccination coverages and recent measles incidences.

Quality Assessment

	Author's judgment	**Support for judgment**
'A Priori' Design	Yes	Comment: The pre-defined aims of the research are stated.
Duplicate Study Selection/ Data Extraction	Can't answer	Comment: The exact study selection and data extraction process is not described.
Comprehensive Literature Search	No	Comment: Only one electronic database was searched, and publications may have been missed.
Status of Publications	Yes	Quote: "As some of these published outbreak reports were preliminary reports based on initial research results, to complete this information an individual search was made to locate the final reports on such outbreaks."
List of Studies	Can't answer	Comment: The included studies and reports are listed. However, excluded studies have not been referenced.
Characteristics of Included Studies	Yes	Comment: The characteristics of each study, including country, year of outbreak, age and gender of cases, affected populations, outbreak setting, measles genotype and origin, are provided.
Study Quality Assessment	No	Comment: The scientific quality of included studies and reports is not described.
Study Quality Consideration	N/A	
Combining Methods	Yes	Quote: "One study limitation is that the information reported in the various scientific papers is not homogeneous and that not all papers provide case-distribution data stratified by age group. In view of this, comparisons between countries should be made with caution."
Publication Bias	No	Comment: Publication bias is not addressed.
Conflict of Interest	No	Comment: Potential conflicts of interest are not addressed.
Overall Rating	**Moderate (36%)**	

Pervanidou et al., 2010[218]

Topic	Measles
Study Design	Epidemiological report (preliminary)
Participants	126 measles cases reported in Greece between Jan. and July of 2010. The majority of cases (63%) were among members of Greek or Bulgarian Roma communities.
Intervention/Data Collection	Data was collected through mandatory national surveillance and reported by the Hellenic Center for Disease Control and Prevention. Viral genotyping for 19 cases occurred at the National Measles Laboratory at the Hellenic Pasteur Institute in Greece.
Outcomes	Outbreak description (preliminary) and demographic analysis of cases, including vaccination status and travel history; Complications and hospitalizations; Molecular and phylogenetic analysis of strains; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: All cases that had been reported up to the time of the report were included. The data are preliminary, however.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Case data were collected through the national mandatory notification system and are likely reliable. Although validity and reliability of the molecular analysis are not reported, they are likely adequate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Pezzotti et al., 2013[219]

Topic	Measles
Study Design	Epidemiological Report
Participants	2,956 measles cases, reported during an outbreak in the Lazio region of Italy between 2010 and 2011.
Intervention/Data Collection	Case data was obtained through the national infectious disease surveillance system as well as from local emergency departments and hospital clinics.
Outcomes	Outbreak description, including case demographics and vaccination statuses; Incidences, by region and age groups; Complications and hospitalizations; Impact on the health system in terms of emergency department and hospital visits as well as financial aspects.
Quality Assessment	N/A — *Full text not accessible.*

Pfaff et al., 2010[221]

Topic	Measles
Study Design	Epidemiological report
Participants	13 measles cases (mostly adolescents) in Germany; all had attended the same international mass gathering in France.
Intervention/Data Collection	Case notification occurred through national surveillance. All reported cases were contacted though local health authorities and interviewed.

Outcomes	Outbreak description, including case demographics and vaccination, disease and recent travel histories; Geographic distribution of cases; Genotypic analysis of measles strain and epidemiological linking.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All cases reported in Germany and traced back to the same mass gathering in France were included. All but two cases were confirmed and the remaining two epidemiologically linked to the confirmed cases. Viral genotyping occurred for the primary case and five secondary cases.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Case data was collected through mandatory notification as well as interviews with the patients. Case confirmation and molecular analysis were performed using standardized methods at the National Measles, Mumps and Rubella Reference Center. Validity and reliability are not reported, but are likely high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Plans, 2013[222]

Topic	Measles, Mumps, Rubella
Study Design	Cross-sectional study
Participants	N/A
Intervention/Data Collection	A seroepidemiolgical survey was conducted in Catalonia, Spain, to identify population groups who have not yet reached the necessary vaccination coverages to establish herd immunity.
Outcomes	Population gaps in herd immunity coverages by age groups; Necessary increases in vaccination coverages to reach the herd immunity threshold.
Quality Assessment	N/A — *Full text not accessible.*

Poethko-Müller, Kuhnert and Schlaud, 2007[226](KiGGS Study)

Topic	Measles, Mumps, Rubella
Study Design	Randomized cross-sectional study
Participants	17,641 children and adolescents, 8,985 male and 8,656 female, aged 0-17 years, from 167 representative German cities and municipalities were recruited between May of 2003 and May of 2006.
Intervention/Data Collection	Immunization records were obtained from 93.4% of the study participants and analyzed according to vaccinations received, time of immunizations and inoculants used. Other data collected: age, gender, place of residence, socioeconomic status, nationality/migration background.
Outcomes	Vaccination coverage of children and adolescents by age group, gender and number of dosages received for measles, mumps, rubella and other vaccine-preventable diseases; Differences in vaccination coverage according to place of residence, migratory background, and socioeconomic status, among others.

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Moderate	Comment: The study included a large sample size and participants were recruited randomly from 167 representative German cities and municipalities. The participation rate was 66.6%.
Study Design	Moderate	Comment: A follow-up is planned.
Confounders	Strong	Comment: Results were weighted with correction factors for age, gender, region of residence and nationality based on the German 2004 population structure.
Blinding	N/A	
Data Collection Method	Strong	Comment: Immunization records (medical documentation of vaccination) were obtained and analyzed from >93% of the included children and youths.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: The KiGGS study was funded by several German ministries (see Poethko-Müller and Mankertz, 2012[227]). A conflict of interest statement is not included.
Overall Rating	**Strong**	

Poethko-Müller et al., 2009[223](KiGGS Study)

Topic	Measles
Study Design	Randomized, cross-sectional study
Participants	(See Poethko-Müller, Kuhnert and Schlaud, 2007.[226])
Intervention/Data Collection	(See Poethko-Müller, Kuhnert and Schlaud, 2007.[226]) Insufficiently vaccinated population subgroups were identified using multivariate logistic regression analyses. Factors assessed: gender, age, place of residence, socioeconomic status, number of siblings, migration background, place of origin, and parental attitude towards vaccinations.
Outcomes	Measles vaccination coverage among the study participants; Factors associated with insufficient vaccinations.

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Moderate	(See Poethko-Müller, Kuhnert and Schlaud, 2007.[226])
Study Design	Moderate	
Confounders	Strong	(See Poethko-Müller, Kuhnert and Schlaud, 2007.[226])
Blinding	N/A	
Data Collection Method	Strong	(See Poethko-Müller, Kuhnert and Schlaud, 2007.[226])
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: The KiGGS study was funded by several German ministries (see Poethko-Müller and Mankertz, 2012[227]). A conflict of interest statement is not included.
Overall Rating	**Strong**	

Poethko-Müller and Mankertz, 2011[224](KiGGS Study)

Topic	Measles
Study Design	Randomized cross-sectional study
Participants	Blood samples were obtained from 13,977 children, aged 1-17 years, of 167 representative German cities and municipalities between May of 2003 and May of 2006.

Intervention/Data Collection	The blood samples were tested for anti-measles IgG seroprevalence using standardized ELISA methods. Focus Reduction Neutralization testing was done for negative ELISA sample of children with a known positive vaccination status. Other data collected: age, gender, place of residence, migration background, vaccination status, age at first measles vaccination, years since last measles vaccination, and history of measles infection, among others.
Outcomes	Seroprevalence of measles antibodies according to the sociodemographic factors and health/vaccination history described above; Seronegativity (susceptibility) among various age groups compared to WHO targets for measles elimination; Positive and negative predictive values of parental reports of measles infections in relation to seroprevalence.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Quote: "KiGGS survey is based on a nationally representative sample of children and adolescents 0-17 years of age with main residence in Germany." Quote: "A migration-specific approach was used and, thus, it was possible to include children with a migration background according to their proportion in the general population." Comment: The study includes a large, randomized sample size (see above); however, oversampling of populations with migratory backgrounds occurred because the response rate of this group was expected to be lower. Overall reported response rate: 66.6%.
Study Design	Moderate	
Confounders	Strong	Quote: "The overall response for eligible children and adolescents was 66.6% and showed little variation between age groups and sexes, but marked variation between children with and without migration background." Comment: In a 2007 article, Poethko-Müller, Kuhnert and Schlaud[226] descripte that the sample characteristics for age, gender, region of residence and nationality were weighted based on 2004 German population statistics (see above).
Blinding	N/A	
Data Collection Method	Strong	Comment: The seroprevelance analyses were performed with purchased Siemens Enzygnost anti-measles IgG test kits of the same lot number. The sensitivity of these kits has been shown to be 100% in other studies.[141]
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: The KiGGS study was funded by several German ministries (see Poethko-Müller and Mankertz, 2012[227]). A conflict of interest statement is not included.
Overall Rating	**Strong**	

Poethko-Müller and Mankertz, 2012[227](KiGGS study)

Topic	Measles, Mumps, Rubella
Study Design	Randomized cross-sectional study
Participants	Seroprevalnce testing of measles, mumps and rubella was performed for 13,977, 13,930 and 13,968 children, respectively, aged 1-17 years, of 167 representative German cities and municipalities. The samples were collected between May of 2003 and May of 2006.)
Intervention/Data Collection	Serum samples were tested for IgG seropositivity of measles, mumps and rubella using standardized ELISA methods. Demographic data, including age, gender, place of residence, migration background, parental education level and history of measles, mumps or rubella infection were obtained through a questionnaire. Pertinent data regarding immunization history, including the time and type of vaccination, were obtained from vaccination cards (those without vaccination information were excluded).

Outcomes	Seroprevalence of measles, mumps and rubella (and combinations thereof) according to the sociodemographic factors and infection/vaccination history described above; Multivariate odds ratios for demographic factors associated with seronegativity; Seronegativity and odds ratios for susceptibility dependent upon time since the last vaccination.

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Moderate	(See Poethko-Müller and Mankertz, 2011[224])
Study Design	Moderate	
Confounders	Strong	(See Poethko-Müller and Mankertz, 2011[224])
Blinding	N/A	
Data Collection Method	Strong	Comment: The seroprevelance analyses were performed using standardized ELISA methods and test kits of the same lot number. Both the validity and reliability of these tests have been shown to be high.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Quote: "The KiGGS study was funded by the German Federal Ministry of Health (http://www.bmg.bund.de/), the Ministry of Education and Research (http://www.bmbf.de) and the Federal Ministry of Food, Agriculture and Consumer Protection (http://www.bmelv.de). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript." Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Poethko-Müller and Mankertz, 2013[225]

Topic	Measles
Study Design	Summary report based on cross-sectional studies
Participants	Measles immunization coverage and factors influencing insufficient vaccinations are analyzed among German birth cohorts born between 1989 and 2008.
Intervention/Data Collection	Vaccination coverage data was obtained from the KiGGS study results (see above) and annual school-entry health examinations. Further data on the number of immunizations provided were obtained from statutory health insurance refund claims. The KiGGS study results were analyzed in regard to factors associated with insufficient vaccination in a multivariate analysis, including age, gender, migratory background, socioeconomic status, and parental attitude, among others.
Outcomes	Measles immunization rates (based on the data collection methods described above); Anti-mealses IgG seroprevalence (based on KiGGS study results); Factors linked to gaps in vaccination coverage.

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Strong	Comment: Efforts were made to include national vaccination coverage data from various sources in the analysis.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Comment: The included KiGGS study data and school-entry health examination data are valid and reliable.[227, 246] The health insurance data serve only as an estimate, however.[228]
Withdraws/Dropouts	N/A	

Conflict of Interest	Weak	Comment: One of the authors has declared a conflict of interest due to the coordination of a separate epidemiological study financed by the German federal ministry of health, the Paul Ehrlich Institute, Sanofi Pasteur and GlaxoSmithKline.
Overall Rating	**Moderate**	

Ramos et al., 2012[236]

Topic	Rubella
Study Design	Cross-sectional cohort study
Participants	1,627 immigrant and an equal number of native Spanish pregnant women attending the antenatal clinic of a Hospital in Elche, Spain were recruited between Feb. of 2006 and June of 2010. The migrant women originated from Latin America and the Caribbean (35%), Northern Africa and the Middle East (34%), Eastern Europe (16%), Sub-Saharan Africa (6%), Asia (5%) and Western Europe (3%); all women were in the gestation trimester of their pregnancies.
Intervention/Data Collection	Anti-rubella IgG antibody seroprevalence was tested among 88% of each sample group using standardized ELISA methods.
Outcomes	Rubella seropositivity among immigrant and native pregnant women; Geographic origin of immigrant women with a positive rubella antibody titer.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: A large sample of both immigrant and native Spanish pregnant women was obtained. However, all participants were recruited from the same hospital and may not be representative for the region.
Study Design	Moderate	
Confounders	Moderate	Comment: Both the immigrant sample and native sample had an equal number of participants, who were matched by age and recruited on the same day. All women were in the same trimester. Other possible confounders, such as health status and vaccination status were not addressed.
Blinding	N/A	
Data Collection Method	Strong	Quote: "The detection of IgG antibodies against rubella was performed by enzyme immunoassay (Enzygnost Anti-Rubella-Virus/IgG, Siemens, Marburg, Germany) according to the manufacturerâĂŹs instructions." Comment: The method employed is both valid and reliable.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Reiter et al., 2009[238]

Topic	Measles, Mumps, Rubella
Study Design	Summary report based on cross-sectional studies
Participants	General immunization coverage and factors influencing insufficient vaccinations are analyzed among German birth cohorts born between 1987 and 2007.
Intervention/Data Collection	Vaccination coverage data was obtained from the KiGGS study results (see above) and annual school-entry health examinations. Limited data from preschool-entry examinations was also assessed.
Outcomes	Immunization rates among children and adolescents; Gaps in vaccination coverage, particularly in regard to measles, pertussis, hepatitis B and booster immunizations.

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Strong	Comment: Efforts were made to include national vaccination coverage data from various sources in the analysis.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Comment: The included KiGGS study data and school-entry health examination data are valid and reliable.[227, 246] The very limited data from preschool-entry examinations are not representative, however.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared
Overall Rating	**Strong**	

Rogalska et al., 2010[251]

Topic	Measles
Study Design	Epidemiological report
Participants	164 measles cases reported in Poland between 2008 and 2009. The Roma population was with 77% most affected. One case of a traveler was excluded because of non-Polish residency.
Intervention/Data Collection	Case notification occurred through the national mandatory enhanced surveillance system. Laboratory confirmation was performed at the National Reference Laboratory at the Polish National Institute of Public Health. Molecular and phylogentic analyses were performed at the WHO Regional Reference Laboratory in Germany (Robert Koch Institut).
Outcomes	Outbreak descriptions, including case demographics and vaccination history of cases; Comparison of the outbreak effects on Roma and non-Roma populations; Importation status of cases; Genotypic strain analysis.

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Strong	Comment: All reported cases with the exception of one non-Polish resident were included in the analysis. All cases were either laboratory confirmed or epidemiologically linked to a measles outbreak.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Mandatory enhanced surveillance likely ensured the reporting of all suspected cases. Contact tracing was performed and all included cases could be confirmed. Quote: "Serological testing and detection of measles virus RNA are performed in the National Reference Laboratory at the National Institute of Public Health. Measles virus-containing samples are sent to the WHO Regional Reference Laboratory for Measles and Rubella (Robert Koch Institute, Berlin) for genotyping." Comment: These laboratories use standardized, valid and reliable, methods, as has been described elsewhere.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Roggendorf et al., 2010[254]

Topic	Measles
Study Design	Epidemiological report
Participants	71 measles cases were reported in Essen, Germany between March and June of 2011. Most cases were unvaccinated children at Waldorf schools or kindergartens.
Intervention/Data Collection	Case notification occurred through mandatory surveillance to the local district health office and enhanced active surveillance. Laboratory confirmation of 16 cases was performed; most of the remaining cases were epidemiologically linked. Molecular and phylogentic analysis of the virus genotype occurred at the National Reference Center for Measles, Mumps and Rubella, Robert Koch Institut, Berlin.
Outcomes	Outbreak description including case demographics and vaccination histories; Genotypic strain analysis; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: All reported cases linked to the outbreak were included. However, three patients could not be linked. Serological confirmation occurred for 23% of the cases and genotyping for only 3%. Alternate viral importation into the study population is unlikely but can not be ruled out.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Case data was collected through the mandatory notification system as well as through active surveillance to detect cases that had not been seen by a physician. Case confirmation and molecular analyses were performed using standardized methods at the National Measles, Mumps and Rubella Reference Center.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Roggendorf et al., 2011[252]

Topic	Measles
Study Design	Cohort study
Participants	Students attending the 6^{th} or 7^{th} grade (mostly 11-13 years of age) of all schools in the city of Essen, Germany, between 2001 and 2008 were included; during 2002, a control group of 9^{th} graders (mostly 14-16 years of age) from the same schools was included as well.
Intervention/Data Collection	Data was collected from vaccination record cards of those participants who submitted the cards. Obtained vaccination records were checked for completion according to national recommendations, and letters for the parents with a list of missing vaccinations were sent to the children's homes. Extensive information about the importance of vaccination (in form of videos, lectures and letters to parents) was provided to all students in the 6^{th} or 7^{th} grade. In 2002, a follow-up of the vaccination status of the 2001 group was performed and compared to 9^{th} graders of the same schools who had not received the vaccination information (control). In 2003, a 3-months follow-up of students who had received extensive vaccination consultations at one school was performed. In 2007, a random sample of ten 7^{th} grade classes were given incentives when turning in 100% of vaccination records (response rate: 98%).

Outcomes	Vaccination rates of students before and after the intervention and comparison to the control group (2001/2002); Vaccination rates among 7^{th} graders during different years (2003-2008); Vaccination rates of second MMR and Hepatitis B vaccines before and after extensive vaccination consultation of students at one school (2003); Comparison of vaccination rates among those students who provided immunization records and those who did not, based on the 2007 sample of ten classes with a nearly 100% response rate.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: The study included all 6^{th} or 7^{th} graders in the city of Essen, Germany, between 2001 and 2008 who turned in their vaccination records. Although the intervention was received by all 6^{th} and 7^{th} grade students, the annual response rate averaged only about 64%.
Study Design	Moderate	Comment: Follow-ups with a control group occurred only in 2002; follow-up of a smaller group at one school occurred in 2007.
Confounders	Weak	Comment: Differences between the intervention and control group (2002) were not reported; the control group consisted of students at the same schools who were two grade levels above the intervention group.
Blinding	N/A	
Data Collection Method	Strong	Comment: Data collection occurred through medical vaccination record cards, which are completed by physicians administering the vaccines.
Withdraws/Dropouts	Strong	Comment: In the instances in which follow-ups were performed, the same students resubmitted their vaccination cards. The exact number of follow-up respondents is not reported, however.
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Other	Moderate	Comment: Participating students may have received vaccinations for reasons other than the intervention.
Overall Rating	**Moderate**	

Roggendorf et al., 2012[255]

Study Design	Epidemiological report
Participants	86 measles cases reported in Essen, Germany, between March and July of 2011.
Intervention/Data Collection	(See Roggendorf et al., 2010.[254])
Outcomes	Secondary outbreak description comparing the outbreak described in Roggendorf et al., 2010[254] with another concurrent outbreak caused by a different genotype.

Quality Assessment	N/A	*Full text not accessible*

Rosenkotter et al., 2012[256]

Topic	Measles, Mumps, Rubella
Study Design	Cross-sectional study
Participants	2007 school-entry examination data of 52,171 children (51.5% male) from 17 districts of North Rhine-Westphalia (NRW), Germany, were included in the study.

Intervention/Data Collection	Data was collected at compulsory school-entry health screenings. Factors influencing general vaccination uptake (as well as participation in early recognition examinations and referrals due to detected health problems) were assessed in bivariate, stratified and multivariate analyses. The following factors were included: migratory background, parental educational level, siblings, preschool attendance, single parent household, place or residency (urban/rural), and participation in all early recognition health examinations.
Outcomes	Number of children with an incomplete immunization status at the time of the school-entry examination; Demographic factors (see above) associated with gaps in vaccination coverage in bivariate and multivariate analyses.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: Although a large study sample was included in the analysis, it comprised only 34% of all children attending school-entry examinations in NRW in 2007. The sample may therefore not be representative for the region.
Study Design	Moderate	
Confounders	Strong	Comment: The bivariate analyses were stratified according to the determinants included in the study.
Blinding	N/A	
Data Collection Method	Strong	Comment: Only children who had participated in a standardized school-entry screening (using the Bielefeld model) were included in the study.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Moderate**	

Sakou et al., 2011[259]

Topic	Measles, Mumps, Rubella
Study Design	Cross-sectional study
Participants	1,005 adolescents, aged 11 to 19 years, who visited an adolescent health center in Athens, Greece, between Jan. and Dec. of 2009 and met the following inclusion criteria: "1) birth cohorts of 1990-1998, (2) first-time visitors (as they are typically accompanied by a parent/guardian), and (3) were holding the Child Health Booklet". Half (51%) of the participants were girls, 85% lived in an urban area and 96.7% had a Greek nationality.
Intervention/Data Collection	Vaccination history was recorded based on each participant's health booklet. Demographic data (gender, year of birth, parental nationality, parental educational level and marital status, urban or rural residency) was obtained through the completion of a questionnaire, whereby parents/guardians of the participants were interviewed.
Outcomes	Vaccination rate of completed immunization schemes against various diseases; Demographic factors influencing the overall complete vaccination status.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Quote: "An important limitation of this study is our population recruitment from a university-affiliated adolescent health unit, thus limiting the extent to which the sample is representative. In addition, the under-representation of non-Greeks/immigrants in our sample may have contributed to over-estimated coverage rates, thus raising bias concerns."
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	

Data Collection Method	Moderate	Comment: The validity and reliability were not described but are likely high for the child vaccination records. Correctness of answers given by parents during the interview could not be verified, however.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Santibanez and Mankertz, 2013[261]

Topic	Measles
Study Design	Summary report based on epidemiological data
Participants	Measles cases with known genotype in Germany from 2005 onward.
Intervention/Data Collection	Summary of studies and reports on measles outbreaks in Germany. Data of involved measles strains were obtained from the WHO *Measles Nucleotide Surveillance* database (MeaNS).
Outcomes	Transmission patterns of measles strains, including endemic circulation; Importation and exportation of measles viruses

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: The literature selection process was not described. Cases not reported or reported elsewhere may be missing.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: The genotypic data collection process occurred through molecular and phylogenetic analyses of measles strains using standardized methods, as recommended by the WHO.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Moderate**	

Schmid et al., 2010[262]

Topic	Measles
Study Design	Epidemiological report
Participants	394 measles cases among Austrian residents during an outbreak between March and July of 2008. Of the cases, 168 (43%) belonged to an anthroposophic community. (An additional 21 reported measles cases were not associated with the outbreak and excluded from the analysis.)
Intervention/Data Collection	Case data was obtained through mandatory reporting to the Austrian Agency for Health and Food Safety. All reported cases were interviewed by outbreak investigators, in person or per telephone, using a questionnaire. Demographic and clinical data as well as affiliation with an anthroposophic community, contact to a known measles case, and recent travel history were obtained through the interview process. In addition, vaccination records were checked and reasons for non-vaccination inquired. Laboratory confirmation of cases was performed using standardized methods, both by local laboratories and the Austrian National Reference Center for Measles. Molecular and phylogenetic analyses were also performed using standardized methods.

Outcomes	Outbreak description including spatial and temporal distribution; Report of case demographics, vaccination statuses and affiliations with an anthroposophic community; Comparison between cases among members of the anthroposophic community and the general population; Results of laboratory case confirmations and genotypic analyses; Outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All reported measles cases that met the outbreak definition were included in the analysis. 154 (39%) cases were laboratory confirmed and many of the remaining cases epidemiologically linked.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Comment: Case data obtained through mandatory surveillance and from vaccination records is likely accurate and reliable. Likewise, the laboratory confirmation and genotyping of samples was performed using standardized, valid and reliable, methods. Accuracy of the data obtained through interviews was not described, however, and may be insufficient, particularly regarding clinical signs and complications.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Schmid et al., 2010[262]

Topic	Measles
Study Design	Retrospective cohort study
Participants	340 students (aged 6-20 years, 44.1% male) attending an anthroposophic school in Salzburg city, Austria, were recruited. The school was affected by a measles outbreak in 2008 (see above).
Intervention/Data Collection	The students were interviewed in person by outbreak investigators to obtain data on demographic characteristics, vaccination history and history of measles before and after March 1^{st}, 2008. The source of the outbreak was also investigated. Vaccination records were analyzed and the immunization effectiveness calculated based on the attack rate among vaccinated and unvaccinated students.
Outcomes	Measles cases and attack rates by age group; Vaccination status of the participants, excluding those with a positive measles history prior to March 2008, and attack rates according to the number of measles-containing vaccine dosages received; newline Vaccine effectiveness among the unvaccinated, single-dosage vaccinated and fully vaccinated students.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: Participating students were included from all 13 classes of the school and the participation rate was 100%
Study Design	Moderate	
Confounders	Moderate	Comment: The students were stratified by age group and those with a past history of measles infection were excluded from the analysis. Other demographic factors, such as gender or place of residency (some of the students lived in Germany) were not controlled for, however.
Blinding	Moderate	Comment: Blinding is not described.

Data Collection Method	Moderate	Comment: The validity of vaccination records is not described, but is likely adequate. The validity and reliability of the data obtained through the questionnaire and interview process may be insufficient, however, as particularly young children may not have been able to correctly answer all questions.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Siedler, et al., 2011[267]

Topic	Measles
Study Design	Summary report based on epidemiological data
Participants	Measles cases reported in Germany between 2001 and 2009; vaccination coverage among children entering the school system.
Intervention/Data Collection	Report on measles elimination progress in Germany, as of 2010.
Outcomes	Measles epidemiology, including case numbers and incidences by year and region; National vaccination coverage based on school-entrance examinations; report of German measles cases between 2005 and 2010, including location, number of cases, genotype involved and molecular or epidemiologic link to the potential location of importation.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: Case data and vaccination coverage data was obtained from the Robert Koch Institute based on national surveillance and nation-wide school-entry health examinations. The literature selection process of other included sources was not described, however. Data not reported or reported elsewhere may be missing.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Weak	Case data and vaccination coverage data are likely accurate and reliable. The quality of the data from included studies is not described, however.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Moderate**	

Siennicka et al., 2011[268]

Topic	Measles
Study Design	Epidemiological report
Participants	278 serum samples of Polish patients with measles-like illness were assessed in 2006 and 2007 regarding seroprevalence of antibodies against measles and other diseases causing similar symptoms.
Intervention/Data Collection	Case data, including demographics and clinical and epidemiological information, were collected through routine surveillance. All samples were submitted to the Polish National WHO Measles/Rubella Laboratory. Standardized EIA methods were employed to determine anti-measles IgM titers; the presence of rubella, Parvovirus B19, Epstein-Barr virus, or Human Herpesvirus type 6 antibodies were also assessed (tested in that order if the previous test results were negative).

Outcomes	Seroprevalence of IgM antibodies against measles and the other tested diseases by age group, clinical symptoms, and measles vaccination status.

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Strong	Quote: "In Poland, measles-like illness cases (MLI) surveillance was established in 1998. Physicians are required to report suspect measles cases to Territorial Health Departments and to obtain samples for confirmatory testing....Confirmatory IgM testing is required for all MLIs." Comment: All reported cases were included in the analysis.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: The confirmatory testing was performed at the National WHO Reference Laboratory, which is subject to external quality assurance. Standardized, valid and reliable, methods were employed to determine the presence of the antibodies listed above.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Six et al., 2010[270]

Topic	Measles
Study Design	Epidemiological report (preliminary)
Participants	310 measles cases (28 among health care workers) reported in the Provence-Alpes-Côte dÁzur region of France in 2010. According to the authors, considerable underreporting is likely. An additional 74 notified cases were excluded due to insufficient data availability.
Intervention/Data Collection	Case data of clinical and laboratory confirmed cases were obtained through national surveillance systems and incidence was determined by region and year (2008-2010).
Outcomes	Outbreak description including case demographics (age, gender and geographic distribution) as well as vaccination statuses of cases; Complications and hospitalizations; Laboratory confirmation rate and measles strain genotyping; Outbreak control measures.

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Weak	Quote: "In our analysis, 74 of the 384 cases reported in 2010 were excluded because detailed data were unavailable." Quote: "...the number of measles cases reported is less than the true number of cases, for various reasons: cases were excluded from the analysis because of missing data, and clinicians and microbiologists did not report all cases to health authorities. InVS demonstrated that during investigations of measles outbreaks in 2008, cases reported through the national mandatory notification system represented only 10% of all detected cases." Comment: The data are therefore likely not to be representative for the region.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	

Data Collection Method	Weak	Comment: Data was collected through the national mandatory notification system; however, as the authors suggest, the reported case numbers may be inaccurate.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Weak**	

Stefanoff et al., 2010[279]

Topic	Measles
Study Design	Epidemiological report
Participants	377 individuals, estimated to belong to a Roma community in Pulawy, Poland, in 2009. The measles vaccination uptake was assessed among 102 children and adolescents (aged 0-19 years) from this population.
Intervention/Data Collection	A capture-recapture method was used to estimate the size of the local Roma community based on the number of registered persons and the number of individuals attending the mass vaccination. Demographic and vaccination history data were inquired during the campaign. Immunization records were obtained from general practitioners to verify the vaccination history statements.
Outcomes	Population size estimate among the local Roma community; Vaccination uptake according to year of birth and immunization history among participating children and adolescents.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: The capture-recapture method allows only for an estimation of the population size. Individuals opposed to immunizations likely did not attend the mass vaccination, and the sample included in the analysis may not be representative.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Comment: Demographic data for registered individuals is likely accurate and reliable. However, most of the data provided during the campaign is not verifiable. Vaccination history data, on the other hand, could be verified among the children and adolescents included in the vaccination uptake analysis.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Stronegger and Freidl, 2010[281]

Topic	Measles
Study Design	Randomized cross-sectional study
Participants	2,386 school-aged children attending the 1^{st}, 4^{th} or 7^{th} grade (6-13 years of age) in the Styria region of Austria.

Intervention/Data Collection	Parental questionnaires were used to receive information about the participating children, including vaccination status (vaccines received, dates of administration) and sociodemographic variables (grade level, gender, highest educational level of parents, number of children in family, employment status of parents, child care support through others, urban or rural place of residency). Data was analyzed using bivariate statistical analyses and recursive graphical models to explain the potential influence of the sociodemographic factors on the vaccination status of the children.
Outcomes	Correlation between the described sociodemographic factors (see above) and vaccination rate.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: A random cluster sample design was used and 7.3% of all children of the targeted age groups living in the Styria region of Austria were included. The study participation rate averaged 79.8%
Study Design	Moderate	Quote: "We used a stratified cluster sample design consisting of 176 randomly selected classrooms of primary schools and high schools as primary sampling units. All children in a selected classroom were included in the sample. The size of the clusters varied between 6 and 25 subjects."
Confounders	Strong	Quote: "To check for non-response bias, our analysis sample was compared with the sample of excluded subjects (n=651). The two groups did not differ in measles vaccination rates...and in demographic determinants." Comment: Demographic differences among the participants were the subject of this study and therefore not considered as confounders.
Blinding	N/A	
Data Collection Method	Moderate	Quote: "It has been shown that validity of parental recall depends on the number of shots of the vaccination and that recall is high for single dose vaccinations as is the MMR vaccination." Comment: Questionnaire surveys were used to ask parents about their child's vaccination status and the sociodemographic variables described. The reliability of this questionnaire was not reported, however.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: Funding was received by the local governmental health department (*Amt der Steiermärkischen Landesregierung, Fachabteilung für das Gesundheitswesen*). No conflict of interest is declared.
Other	Weak	The time (month or year) during which the study was conducted is not mentioned in the article.
Overall Rating	**Moderate**	

Takla et al., 2012[282]

Topic	Measles
Study Design	Epidemiological report
Participants	427 international residents of a shelter for asylum seekers in Germany were exposed during a small 2010 measles outbreak involving eight cases. Of the residents, 300 were serologically tested for anti-measles IgG antibodies.

Intervention/Data Collection	The eight cases were laboratory confirmed by determining measles-specific IgM and IgG antibodies or the presence of viral RNA; genotyping occurred at the National Reference Center for Measles, Mumps and Rubella. Serological samples of other participating residents were assessed regarding anti-measles IgG titers using standardized ELISA methods. Individuals found to be seronegative or with a borderline titer, as well as those who had not been tested, were offered a MMR vaccination, unless contraindications (pregnancy, age $\leq$6 months) existed. The containment strategy was evaluated in terms of cost, logistics and potentially avoided cases against a hypothetical mass vaccination of all residents eligible for vaccination according to the German immunization schedule.
Outcomes	Outbreak description including timeline, case demographics (age, gender, pregnancy) and hospitalizations; number of participants with seropositive, seronegative and borderline anti-measles IgG titers; age-distribution of seronegative individuals; attack rate; cost, logistic and case avoidance calculations for the actual and hypothetical outbreak control measures.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: All 427 residents were asked to participate in the study; the participation rate was about 70%.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Moderate	Comment: Standardized, valid and reliable, methods were used to confirm cases and determine seroprevalence among the participants. In terms of the hypothetical outbreak intervention analysis, several assumptions had to be made and the validity and reliability can not be determined.
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Tamer et al., 2009[283]

Topic	Rubella
Study Design	Cross-sectional study
Participants	Prenatal infection screening data of 1972 pregnant women in their first trimester, who visited a local university hospital in Koacaeli, Western Turkey between Mar. 2005 and Jan. 2007, were included.
Intervention/Data Collection	Serum samples had been taken of all participating women and were tested for seroprevalence of rubella antibodies (as well as *Toxoplasma gondii* and CMV antibodies). Standardized, commercial ELISA kits were used to determine IgG, IgM and combined IgG&IgM seroprevalence.
Outcomes	Seroprevalence of anti-rubella (and toxoplasma and CMV) IgG, IgM and combined antibodies among the participating women.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Quote: "Kocaeli is an industrial region and could be taken as a model for the general population of Turkey with its socioeconomic, cultural and ethnic diversity." Comment: While a large sample of pregnant women from the Kocaeli region was included in the study, all were screened at the same hospital and may thus not be representative for the region.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	

Data Collection Method	Strong	Comment: Standardized methods with high validity and reliability were employed to determine seroprevalnce.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Uysal et al., 2012[290]

Topic	Rubella
Study Design	Cross-sectional study
Participants	5,959 women in an early stage of pregnancy recruited from an out-patient prenatal clinic in Izmir, Turkey between 2001 and 2008.
Intervention/Data Collection	Seroprevalence of rubella (and CMV) IgG and IgM antibodies were determined using standardized Enzyme-Linked Fluorescent Assay (ELFA) techniques; rubella IgM-positiv women were followed up regarding pregnancy outcome.
Outcomes	Anti-rubella IgG and IgM seroprevalence; follow-up results of pregnancy for rubella IgM-positive women (termination or health status of fetus and newborn).

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: Although a large sample of pregnant women from the region was included, all were recruited from the same out-patient clinic and may thus not be representative for the region.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Standardized methods with high validity and reliability were employed to determine seroprevalnce.
Withdraws/Dropouts	Weak	Quote: "Pregnancy of the 8 of 12 pregnant women of which Rubella IgM antibody was found as positive in the first trimester was terminated with the decision of perinatology committee. The remaining four pregnant women did not come to follow-up....Three of the pregnant women maintaining their pregnancy [out of 10 with positive IgM titers in the 2^{nd} or 3^{rd} trimester] did not come to their follow-up regularly." Comment: The drop-out rate from the follow-up group was 32% (7 out of 22 participants).
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Vauloup-Fellous et al., 2010[292]

Topic	Rubella
Study Design	Epidemiological report
Participants	Clinical samples were obtained from a total of 106 cases of congenital rubella infection (Amniotic fluid from 80 infected pregnant women and clinical specimens from 26 children with congenital rubella syndrome) between 1995 and 2009; 104 of these samples were from France (including West Indies), 1 from Portugal and 1 from Tunisia.
Intervention/Data Collection	56 of the samples with sufficiently available RNA (others likely degradated during storage) were extracted, sequenced and phylogenetically analyzed using standardized methods.

Outcomes	Genotypes of all sequenced samples; clustering of samples; comparison to other known rubella virus sequences.

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Strong	Comment: A large percentage (88.6%) of the total CRI cases reported in France during the study period were included.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Standardized, valid and reliable, methods were employed in the sequencing and genetic analysis of the rubella virus samples.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Quote: "This work was supported by the Ministry of Health and the Centre de Recherche Public de la Santé, Luxembourg." Comment: A conflict of interest statement is not included.
Overall Rating	**Strong**	

Vilibic-Cavlek et al., 2011[294]

Topic	Rubella
Study Design	Cross-sectional study
Participants	Serum samples of 502 women of childbearing age (16-45 years) were collected in Croatia between 2005 and 2009; 409 of the women were pregnant.
Intervention/Data Collection	Serological anti-rubella IgG and IgM antibodies were determined using standardized, commercial EIA methods; positive IgM results were additionally confirmed. (The seroprevalence of other (TORCH) infections was determined as well).
Outcomes	Seroprevalence of rubella (and other TORCH infections) among the study participants.

Quality Assessment

	Author's judgment	Support for judgment
Selection Bias	Weak	Comment: The participant selection process was not described.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Quote: "Serologic tests were performed using commercial EIA according to manufacturerâĂŹs recommendation". Comment: Standardized, valid and reliable, methods were employed to determine seroprevalence.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Quote: "This research was supported by the Ministry of Science, Education, and Sports of the Republic of Croatia". Comment: A conflict of interest statement is not included.
Overall Rating	**Moderate**	

Wadl et al., 2011[295](1)

Topic	Measles
Study Design	Epidemiological report
Participants	217 measles cases were reported in Bavaria, Germany between March and July 2008. They were linked to an outbreak in Salzburg, Austria. 25% of cases were confirmed and 85% were epidemiologically linked.
Intervention/Data Collection	Case data was collected through mandatory notification and active contact tracing was performed. A questionnaire (74% response rate) was used to assess reasons for non-vaccination and complications. Laboratory confirmation of infection and genotyping of 12% of the cases were performed using standardized methods.
Outcomes	Outbreak description including case demographics and vaccination and disease history; complications and hospitalizations; vaccination rate and reasons for not having received vaccines.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: Case information was collected through mandatory surveillance and active contact tracing as well as questionnaires (completed via telephone or mail). The response rate was with 74% moderately high.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Laboratory analyses were performed using standardized methods. Quote: "Laboratory confirmation using serology was performed by regional laboratories. The National Reference Centre for Measles, Mumps and Rubella in Berlin (NRC) used the Enzygnost Anti-Measles Virus IgM ELISA (Siemens, Germany) for the detection of anti-measles IgM in serum. A subset of samples was genotyped by the NRC according to the WHO recommendation for measles virus."
Withdraws/Dropouts	N/A	
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

Wadl et al., 2011[295](2)

Topic	Measles
Study Design	Retrospective cross-sectional study
Participants	85 measles cases in 10 of 59 clusters identified in the outbreak described above (*Wadl et al, 2011* (1)) were compared after two different case control interventions were enforced by local health authorities. Six educational institutions/clusters (28 cases) carried out intervention A and four (57 cases) intervention B.
Intervention/Data Collection	Compulsory control measures were implemented though exclusion of non-immune individuals from school or kindergarten for two weeks after either one case had been notified (intervention A) or two cases had been reported (intervention B).
Outcomes	Comparison between intervention A and B in regards to the total number of cases in the cluster, the duration of the outbreak and the attack rate.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: The educational institutions chosen to participate were from different regions of the outbreak area and are likely representative of the affected population. However, the intervention groups differed (see below) and compliance with the intervention was not controlled for.

Study Design	Moderate	
Confounders	Weak	Comment: The intervention groups varied in size (6 vs. 4 clusters), type of schooling (anthroposopic or regular), and geographic distribution. Furthermore, the intervention was changed in one region to match that of the others. Quote: "Three counties implemented solely intervention A. The fourth county used intervention B until calendar week 22 (12 weeks) and intervention A since calendar week 23 (7 weeks). Comment: The confounders were not described to have been controlled for or matched at base-line.
Blinding	N/A	
Data Collection Method	Weak	Quote: "Immune persons were those with at least one documented vaccination against measles a minimum of three weeks before disease onset, immunity confirmed by serology or anamnestic measles...Vaccination cards in schools and kindergartens were checked by staff from the LHAs [local health authorities] in three of the affected counties, and by staff from the respective school or kindergarten in the fourth county." Comment: The data collection and intervention performance were not standardized throughout the study process. Validity and reliability are questionable.
Withdraws/Dropouts	N/A	
Other	Weak	Comment: Subjects exposed to intervention B may have been influenced by other control measures. Quote: "The county using intervention B informed as early as the occurrence of the first incident measles case in a kindergarten or school all contact persons about the incident measles case and the necessity of protection by vaccination."
Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Weak**	

Waku-Kouomou et al., 2010[296]

Topic	Measles
Study Design	Epidemiological report
Participants	604 measles cases reported in France in 2008. Half of the cases (50%) were laboratory confirmed, the remaining cases epidemiologically linked.
Intervention/Data Collection	Case data was collected through routine surveillance. Confirmation of infection and molecular analysis for 19% of the cases occurred using standardized methods at local laboratories and National Reference Centers for Measles.
Outcomes	Outbreak description including case demographics; molecular and phylogenetic analysis of measles viral strains.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Moderate	Comment: All reported cases were included. Genotypic analysis was performed for only 19% of the cases, however.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	

Data Collection Method	Strong	Quote: "Measles-specific IgM was detected either in oral fluid samples using the microImmune test anti-IgM antibody capture EIA (MicroImmune, Brentford, United Kingdom) or in serum samples using the enzygnost anti-measles virus/IgM test (Dade Behring, Marburg, Germany). Assays were performed according to the manufacturer's instructions." Comment: Molecular and phylogenetic analyses were also performed according to standardized methods set forth by the WHO.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: Support and funding were provided by the *Institut de Veille Sanitaire* and the *Institut national de la santé et de la recherche médicale* (INSERM). A conflict of interest statement is not included.
Overall Rating	**Strong**	

Walker et al., 2011[297]

Topic	Mumps
Study Design	Epidemiological report
Participants	119 mumps cases (56 male) were reported in the Oban area of Scotland, UK, between Nov. of 2010 and Jan. of 2011. 18 cases were laboratory confirmed, the remaining diagnosed clinically.
Intervention/Data Collection	Case data was collected through active surveillance and notification through physicians. Vaccination status was collected by contacting the respective general practitioner practices. Case confirmations occurred using oral fluid testing kits and reconfirmation through the Centre for Infections of the Health Protection Agency in London.
Outcomes	Outbreak description including case demographics and vaccination status.

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Weak	Comment: All notified cases occurring in the area were included in the analysis. The case confirmation rate was with 15% extremely low, however, and errors in diagnosis can not be rule out.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Weak	Quote: "Once laboratory confirmation had been received on the first 12 of these cases, we suspended testing and recorded cases that had been notified on the basis of clinical diagnosis alone. The clinicians involved were confident of their diagnosis" Comment: The clinical diagnoses may nonetheless not be as reliable as laboratory confirmations would have been.
Withdraws/Dropouts	N/A	
Conflict of Interest	Moderate	Comment: A conflict of interest statement is not included.
Overall Rating	**Weak**	

Zimmerman, Rogalsky, et al., 2011[328]

Topic	Rubella
Study Design	Epidemiological Report

Participants	80,096 rubella cases reported in Poland between 2003 and 2008 and 18 CRS cases reported between 1997 and 2008. Overview of rubella incidence in Poland between 1966 and 2008.
Intervention/Data Collection	Data were collected through national mandatory surveillance, including case-based regional data of four provinces, and annual vaccination reports available through the Polish National Institute of Public Health and National Institute of Hygiene.
Outcomes	Incidence of rubella in Poland (1966-2008); demographic case distribution by gender and age-group (2003-2008); regional case data by birth cohort (2006-2008); CRS cases in Poland (1997-2008); Vaccination coverage (among 15-year-old girls, 1992-2006, and among children, 2005-2008)

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All rubella and CRS cases reported in Poland through the mandatory surveillance system were included.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Data were obtained through mandatory surveillance and mandatory vaccination notification, both of which are likely to be valid and reliable.
Withdraws/Dropouts	N/A	
Conflict of Interest	Weak	Quote: "Potential conflicts of interest. P. S. has accepted funding for research purposes from GSK Biologicals for a study of pertussis epidemiology in Poland. Supplement sponsorship: This article is part of a supplement entitled "Global Progress Toward Measles Eradication and Prevention of Rubella and Congenital Rubella Syndrome", which was sponsored by the Centers for Disease Control and Prevention."
Overall Rating	**Moderate**	

Zimmerman, Muscat, et al., 2011 [329]

Topic	Rubella
Study Design	Epidemiological report
Participants	All 53 member states of the WHO European region.
Intervention/Data Collection	A survey was conducted regarding national rubella and CRS surveillance systems and case reportings between 2005 and 2009.
Outcomes	Rubella and CRS surveillance methods in each included country; total number of annually reported cases and incidence of rubella (2005-2009); number of annually reported CRS cases (2005-2009).

Quality Assessment

	Author's judgment	**Support for judgment**
Selection Bias	Strong	Comment: All nations that are part of the WHO European region were included; the response rate was 85% (45 of 53 nations) and represented about 90% of the total European population.
Study Design	Moderate	
Confounders	N/A	
Blinding	N/A	
Data Collection Method	Strong	Comment: Data from official national surveillance reports to the WHO and UNICEF (joint reporting system) as well as EUVAC.NET were included; validity and reliability of these data are likely high.
Withdraws/Dropouts	N/A	

Conflict of Interest	Strong	Comment: No conflict of interest has been declared.
Overall Rating	**Strong**	

F. List of Websites and Reports Accessed

The following governmental and organizational websites and reports were accessed within the scope of this review. The last date of accession and data retrieval is provided for each reference, as shown.

Bundesministerium für Gesundheit
(BMG, Austrian Ministry of Health)
www.bmg.gv.at

- Jahresstatistiken meldepflichtiger Infektionskrankheiten seit dem Jahr 2000 [Annual statistics of notifiable infectious diseases since 2000].[62] *Accessed: Oct. 2013*
- Impfplan Österreich 2013[Vaccination Schedule Austria 2013].[24] *Accessed: Feb. 2014*

Bundesministerium des Inneren, Bundesamt für Migration und Flüchtlinge
(Germany)
www.bamf.de

- Migrationsbericht [Migration report] 2010[9] and 2011.[27] *Accessed: Nov. 2013*

Centers for Disease Control and Prevention
(CDC, USA)
www.cdc.gov

- Measles, Epidemiology and Prevention of Vaccine-Preventable Diseases.[73] *Accessed: May 2014*

Department of Health, Social Services and Public Safety
(United Kingdom)
www.dhsspsni.gov.uk

- Chief Medical Officer 2011-2012 Annual Report Facts and Figures, Table 12: Notifiable Diseases 1996-2010 for Northern Ireland.[16] *Accessed: Nov. 2013*

EpiCentro
(Italian National Center for Epidemiology, Surveillance and Health Promotion)
www.epicentro.iss.it

- Morbillo, Aspetti epdiemiologici [Measles, epidemiological aspects].[102] *Accessed: Oct. 2013*
- Rosolia, Aspetti epdiemiologici [Rubella, epidemiological aspects].[101] *Accessed: Oct. 2013*

European Center for Disease Prevention and Control (ECDC)
www.ecdc.europa.eu

- Annual epidemiological reports on communicable diseases in Europe, 2009-2013.[103,105,106,109,110] *Accessed: Apr. 2014*
- Factsheet for health professionals: Measles.[107] *Accessed: Jul. 2013*
- Factsheet for health professionals: Mumps.[108] *Accessed: Jul. 2013*
- Factsheet for health professionals: Rubella.[112] *Accessed: Sep. 2013*
- Measles and rubella monitoring, May 2013.[26] *Accessed: Jan. 2014*
- Measles and rubella monitoring, February 2014.[116] *Accessed: Apr. 2014*
- Measles surveillance data.[113] *Accessed: Oct. 2013*
- Migrant health: Background note to the 'ECDC Report on migration and infectious diseases in the EU'.[104] *Accessed: Jan. 2014*
- Review of outbreaks and barriers to MMR vaccination coverage among hard-to-reach populations in Europe.[180] *Accessed: Apr. 2014*
- Rubella surveillance data.[114] *Accessed: Nov. 2013*

	• Survey on rubella, rubella in pregnancy and congenital rubella surveillance systems in EU/EEA countries.[30] *Accessed: Dec. 2013*
	• Vaccine Schedule.[115] *Accessed: May 2014*
Eurostat Statistics Database www.epp.eurostat.ec.europa.eu	• Employment (main characteristics and rates) - annual averages.[23] *Accessed: Nov. 2013*
	• Nursing and caring professionals.[23] *Accessed: Nov. 2013*
	• Population on 1 January by age and sex.[23,34] *Accessed: Jun 2014*
	• Unemployment rate by sex and age groups - annual average, %.[23] *Accessed: Nov. 2013*
EUVAC.net (now part of ECDC) www.ecdc.europa.eu	• Measles surveillance annual reports, 2006-2010.[194–198] *Accessed: Sep. 2013*
	• Mumps surveillance annual reports, 2000-2007[190] and 2008- 2010.[48,49,189] *Accessed: Oct. 2013*
	• Rubella surveillance annual reports, 2000-2007[191] and 2008- 2010.[192,193,199] *Accessed: Oct. 2013*
Haut Conseil de la Santé Publique (French High Council of Public Health) www.hcsp.fr	• Vaccination contre la rougeole avant l'age de 12 mois. Recommandations [Vaccination against measles before the age of 12 months. Recommendations].[132] *Accessed: Oct. 2013*
Health Protection Agency (United Kingdom; now part of Public Health England) www.hpa.org.uk	• Annual Vaccine Coverage Statistics: England.[230] *Accessed: Jan. 2014*
	• Completed Primary Courses at Two Years of Age: England and Wales, 1966 - 1977, England only 1978 onwards.[12] *Accessed: Feb. 2014*

	• Confirmed cases of measles by region and age: 1996-2010.[13] *Accessed: Feb. 2014*
	• Confirmed cases of Measles, Mumps and Rubella 1996-2012.[233] *Accessed: Nov. 2013*
	• Measles notifications and deaths in England and Wales, 1940-2008.[231] *Accessed: Nov. 2013*
	• Rubella notifications (confirmed cases), England and Wales, 1995 - 2013 by quarter.[234] *Accessed: Nov. 2013*
Health Protection Scotland (United Kingdom) www.hps.scot.nhs.uk	• Annual Data 2009[134] and 2012.[135] *Accessed: Nov. 2013*
	• Annual trends in notifiable diseases, selected years from 1980-2012.[136] *Accessed: Dec. 2013*
Hellenic Center for Disease Control & Prevention (Greece) www2.keelpno.gr	• Monthly Data (Mandatory Notification System).[138] *Accessed: Mar. 2014*
	• Vaccine-preventable diseases: surveillance systems in Greece and epidemiological data.[123] *Accessed: Nov. 2013*
Hrvatski Zavod za Javno Zdravstvo (HZJZ, Croation National Institute of Public Health) www.hzjz.hr	• Croatian Health Service Yearbooks, 2011[41] and 2012.[22] *Accessed: Jan. 2014*
	• Kalendar kontinuiranog cijepljenja u Hrvatskoj u 2013. Godini [Calendar of continuous vaccination in Croatia in 2013].[25] *Accessed: Nov. 2013*
Instituo de Salud Carlos III (ISCIII, Spain) www.isciii.es	• Enfermedades de declaracion obligatoria - Series temporales [Notifiable diseases - Time Series].[142] *Accessed: Oct. 2013*

Institut de Veille Sanitaire
(InVS French Institute for Public Health Surveillance)
www.invs.sante.fr

- Rougeole, rubeole, oreillons [Measles, rubella , mumps].[144] *Accessed: Sep. 2013*
- Rubeole - Donnees epidemiologiques [Rubella - epidemiological data].[145] *Accessed: Oct. 2013*
- Donnees de declaration obligatoire de rougeole en France (anterieures au 1er Aout 2013) [Mandatory notification of measles in France (prior to 1st of August, 2013)].[143] *Accessed: Oct. 2013*

Ministero della Salute
(Italian Ministry of Health)
www.salute.gov.it

- Bollettino epidemiologico [Epidemiological Bulletin].[186] *Accessed: Oct. 2013*
- Calendario vaccinale [Vaccination Schedule].[184] *Accessed: Nov. 2013*
- Piano Nazionale Prevenzione Vaccinale (PNPV) 2012-2014 [National Plan for Prevention through Vaccination 2012-2014].[185] *Accessed: Nov. 2013*
- Vaccinazioni dell'eta pediatrica, in Italia: coperture vaccinali [Pediatric immunizations according to age in Italy: vaccination coverage].[187] *Accessed: Nov. 2013*

Ministerio de Sanidad, Servicios Sociales e Igualdad
(MSPSI, Spanish Ministry of Health, Social Services and Equality)
www.mspsi.gob.es

- Coberturas de Vacunacion. Datos estadisticos [Vaccination coverage. Statistical data].[21] *Accessed: Jan. 2014*

National Health Service
(United Kingdom)
www.nhs.uk

- The NHS vaccination schedule.[202] *Accessed: Oct. 2013*

Narodowym Instytucie Zdrowia Publicznego - Państwowym Zakładzie Higieny
(Polish National Institute of Public Health, National Institute of Hygiene)
http://www.pzh.gov.pl/

- Infectious diseases and poisonings in Poland, 2006-2012.[85–87] *Accessed: Nov. 2013*
- Szczepionki przeciw odrze w Programie Szczepien Ochronnych [Vaccines against measles as part of the immunization program].[35] *Accessed: Feb. 2014*
- Szczepionki przeciw rozyczce w Programie Szczepien Ochronnych [Vaccines against rubella as part of the immunization program].[31] *Accessed: Feb. 2014*
- Szczepionki przeciw swince w Programie Szczepien Ochronnych [Vaccines against mumps as part of the immunization program].[18] *Accessed: Dec. 2013*
- Vaccinations in Poland, 2006-2012.[88–94] *Accessed: Dec. 2013*

Öffentliches Gesundheitsportal Österreichs
(Austria)
www.gesundheit.gv.at

- Impfungen fur Schulkinder [Immunizations recommended for school-aged chrildren].[124] *Accessed: Nov. 2013*

Public Health England
(United Kingdom)
www.gov.uk/government/organisations/public-health-england

- Evaluation of vaccine uptake during the 2013 MMR catch-up campaign in England.[269] *Accessed: May 2014*
- The complete routine immunisation schedule 2013/14.[232] *Accessed: Dec. 2013*

Réseau Sentinelles
(France)
www.websenti.u707.jussieu.fr

- Bilan annuel, 2006-2012 [Annual review, 2006-2012].[2–4,8,14,15,20] *Accessed: Feb. 2014*

Robert Koch Institut
(RKI, Germany)
www.rki.de

- Aufgaben und Gesetzliche Grundlagen des Robert Koch-Instituts [Tasks and legal foundations of the Robert Koch Institute].[244] *Accessed: Nov. 2013*
- Empfehlungen der Standigen Impfkommission (STIKO) am Robert Koch-Institut/Stand: August 2013 [Recommendations of the Permanent Committee on Vaccination (STIKO) at the Robert Koch Institute, as of August 2013].[245] *Accessed: Nov. 2013*
- Impfquoten bei der Schuleingangsuntersuchung in Deutschland, 2007-2011 [Vaccination rates at the school entrance examination in Germany, 2007-2011].[240–243,246] *Accessed: Jan. 2014*
- Mumps (Parotitis epidemica), RKI-Ratgeber fur Ärzte [Mumps (Parotitis epidemica), RKI guide for physicians].[247] *Accessed: Jul. 2013*
- Röteln (Rubella), RKI-Ratgeber für Ärzte [Rubella, RKI guide for physicians].[248] *Accessed: Jul. 2013*
- SurvStat@RKI.[249,250] *Accessed: May 2014*

Smittskyddsinstitutet
(Swedish Institute for Infectious Disease Control)
www.smittskyddsinstitutet.se

- Measles (Data and Statistics).[273] *Accessed: Oct. 2013*
- Mumps (Data and Statistics).[274] *Accessed: Oct. 2013*
- Rubella (Data and Statistics).[275] *Accessed: Oct. 2013*
- The Swedish vaccination program[272] *Accessed: Oct. 2013*

- Vaccinationsstatistik från barnavårdscentralerna, insamlad januari 2010, gällande barn födda 2007 [The vaccination statistics from child care centers, collected in January 2010, regarding children born in 2007].[10] *Accessed: Jan. 2014*
- Vaccinationsstatistik från barnavårdscentralerna 2013, gällande barn födda 2010 [The vaccination statistics from child care centers in 2013, regarding children born in 2010].[32] *Accessed: Jan. 2014*
- Vaccinationsstatistik från skolhälsovården Elever iårskurs 6, läsåret 2008/09 [Vaccination statistics among school-aged children 2008/09].[7] *Accessed: Jan. 2014*
- Vaccinationsstatistik från skolhälsovården Elever iårskurs 6, läsåret 2011/12 [Vaccination statistics among school-aged children 2011/12].[19] *Accessed: Jan. 2014*

Socialstyrelsen
(Swedish National Board of Health and Welfare)
www.socialstyrelsen.se

- Vaccinations.[276] *Accessed: Nov. 2013*

Statistisches Bundesamt
(German Federal Statistical Office)
www.destatis.de

- Regionales: Bevölkerung im Dezember 2012 auf der Grundlage des Zensus 2011 [Regional population in December 2012 based on the 2011 Census].[278] *Accessed: Mar. 2014*

T.C. Milli Eğitim Bakanlığı
(Turkish Ministry of National Education)
www.meb.gov.tr

- Okul Aşılaması Bilgi Notu [Information on school-based vaccinations].[28] *Accessed: Nov. 2013*

T.C. Sağkık Bakanlığı
(Turkish Ministry of Health)
www.saglik.gov.tr

- Childhood Vaccination Schedule-Turkey.[28] *Accessed: Oct. 2013*
- Health Transformation Program in Turkey and Primary Health Care Services November 2002-2008.[37] *Accessed: Aug. 2013*
- Progress Report, Health Transformation Program in Turkey, January 2009.[38] *Accessed: Aug. 2013*
- Turkey Health Transformation Program, Evaluation Report (2003-2010).[39] *Accessed: Aug. 2013*

Vaccine European New Integrated Collaboration Effort (VENICE II)
www.venice.cineca.org

- Analysis of Determinants for Low MMR Vaccination Coverage In Europe, 2010.[205] *Accessed: May 2014*
- Participating Countries (Immunization programs).[293] *Accessed: Nov. 2013*

World Bank, The
www.databank.worldbank.org

- World DataBank: World Development Indicators.[285] *Accessed: Mar. 2014*

World Health Organization
www.who.int

- Biologicals: Measles.[305] *Accessed: Jul. 2013*
- Biologicals: Mumps Vaccines.[306] *Accessed: Jul. 2013*
- Centralized information system for infectious diseases (CISID).[326] *Accessed: Dec. 2013*
- Eliminating measles and rubella, Framework for the verification process in the WHO European Region.[303] *Accessed: Apr. 2014*
- Framework for verifying elimination of measles and rubella.[307] *Accessed: Oct. 2013*
- Global and regional immunization profile: European Region.[308] *Accessed: Jul. 2013*

- Global and regional immunization profile: Global.[309] *Accessed: Jul. 2013*
- Global Measles and Rubella Strategic Plan: 2012-2020.[304] *Accessed: Feb. 2014*
- Immunization standards: WHO prequalified vaccines: Measles, Mumps and Rubella.[325] *Accessed: Feb. 2014*
- Measles and Rubella Elimination 2015: Package for Accelerated Action: 2013-2015.[310] *Accessed: May 2014*
- Measles Fact sheet No. 286.[311] *Accessed: Jul. 2013*
- Measles vaccines: WHO position paper.[301] *Accessed: Aug. 2013*
- Mumps vaccines: WHO position paper.[300] *Accessed: Sep. 2013*
- Rubella vaccines: WHO position paper.[302] *Accessed: Sep. 2013*
- Reported Estimates of Vaccination Coverage, WHO/UNICEF Joint Reporting Form Coverage Series.[312] *Accessed: Mar. 2014*
- Summary: Global immunization coverage in 2012.[29] *Accessed: Aug. 2013*
- WHO/UNICEF coverage estimates for 1980-2012, as of July 2013.[324] *Accessed: Mar. 2014*
- WHO vaccine-preventable diseases: monitoring system. 2013 global summary - country profile: Austria.[314] *Accessed: Nov. 2013*
- WHO vaccine-preventable diseases: monitoring system. 2013 global summary - country profile: Croatia.[315] *Accessed: Nov. 2013*

- WHO vaccine-preventable diseases: monitoring system. 2013 global summary - country profile: France.[316] *Accessed: Nov. 2013*

- WHO vaccine-preventable diseases: monitoring system. 2013 global summary - country profile: Germany.[317] *Accessed: Nov. 2013*

- WHO vaccine-preventable diseases: monitoring system. 2013 global summary - country profile: Greece.[318] *Accessed: Nov. 2013*

- WHO vaccine-preventable diseases: monitoring system. 2013 global summary - country profile: Italy.[319] *Accessed: Nov. 2013*

- WHO vaccine-preventable diseases: monitoring system. 2013 global summary - country profile: Poland.[320] *Accessed: Nov. 2013*

- WHO vaccine-preventable diseases: monitoring system. 2013 global summary - country profile: Spain.[321] *Accessed: Nov. 2013*

- WHO vaccine-preventable diseases: monitoring system. 2013 global summary - country profile: Sweden.[322] *Accessed: Nov. 2013*

- WHO vaccine-preventable diseases: monitoring system. 2013 global summary - country profile: Turkey.[323] *Accessed: Nov. 2013*

- WHO vaccine-preventable diseases: monitoring system. 2013 global summary - country profile: United Kingdom of Great Britain and Northern Ireland (the).[313] *Accessed: Nov. 2013*

G. List of Excluded Studies

The excluded studies listed below were reviewed either by abstract or full-text version. Reasons for exclusion are provided after each reference, in italics, and are based on the pre-defined criteria listed in Appendix A. All exclusion considerations pertain to the relevance of the articles to the present systematic review and are in no way intended as criticism of the publications. The listed studies and reports were not included in the data abstraction process or literature analyses, but may have been referenced in the Introduction or Discussion sections.

Excluded Studies

Agergaard, J., Nante, E., Poulstrup, G., Nielsen, J., Flanagan, K. L., Ostergaard, L., Benn, C. S. and Aaby, P. Diphtheria-tetanus-pertussis vaccine administered simultaneously with measles vaccine is associated with increased morbidity and poor growth in girls. A randomised trial from Guinea-Bissau. *Vaccine*, 29(3):487–500, Jan 2011. *Reason for Exclusion: Different country: Guinea-Bissau.*

Ahlgren, C., Toren, K., Oden, A. and Andersen, O. A population-based case-control study on viral infections and vaccinations and subsequent multiple sclerosis risk. *Eur J Epidemiol*, 24(9):541–552, 2009. *Reason for Exclusion: Different disease: multiple sclerosis.*

Akmatov, M. K. and Mikolajczyk, R. T. Timeliness of childhood vaccinations in 31 low and middle-income countries. *J Epidemiol Community Health*, 66(7):e14, Jul 2012. *Reason for Exclusion: Different country: other.*

Akyar, I. Seroprevalence and coinfections of Toxoplasma gondii in childbearing age women in Turkey. *Iranian Journal of Public Health*, 40(1):63–67, 2011. *Reason for Exclusion: Different pathogen: Toxoplasma gondii.*

Allmendinger, J., Paradies, F., Kamprad, M., Richter, T., Pustowoit, B. and Liebert, U. G. Determination of rubella virus-specific cell-mediated immunity using IFN gamma-ELISpot. *J Med Virol*, 82(2):335–340, Feb 2010. *Reasons for Exclusion: Analysis of method; specific employment group: health-care worker/student.*

Allwinn, R., Zeidler, B., Steinhagen, K., Rohwader, E., Wicker, S., Rabenau, H. F. and Doerr, H. W. Assessment of mumps virus-specific antibodies by different serological assays: which test correlates best with mumps immunity? *Eur J Clin Microbiol Infect Dis*, 30(10):1223–1228, Oct 2011. *Reason for Exclusion: Analysis of method.*

Alp, E., Cevahir, F., Gokahmetoglu, S., Demiraslan, H. and Doganay, M. Prevaccination screening of health-care workers for immunity to measles, rubella, mumps, and varicella in a developing country: What do we save? *J Infect Public Health*, 5(2):127–132, Apr 2012. *Reason for Exclusion: Specific employment group: health-care worker/student.*

Andrews, N., Stowe, J., Miller, E., Svanstrom, H., Johansen, K., Bonhoeffer, J. and Hviid, A. A collaborative approach to investigating the risk of thrombocytopenic purpura after measles-mumps-rubella vaccination in England and Denmark. *Vaccine*, 30(19):3042–3046, Apr 2012. *Reason for Exclusion: Other: vaccine safety.*

Ansaldi, F., Orsi, A., Altomonte, F., Bertone, G., Parodi, V., Carloni, R., Moscatelli, P., Pasero, E., Comaschi, M., Oreste, P., Orengo, G., Durando, P. and Icardi, G. Syndrome surveillance and molecular epidemiology for early detection and tracing of an outbreak of measles in Liguria, Italy. *J Med Virol*, 81(10):1807–1813, Oct 2009. *Reason for Exclusion: Analysis of method.*

Antai, D. Inequitable childhood immunization uptake in Nigeria: a multilevel analysis of individual and contextual determinants. *BMC Infect Dis*, 9:181, 2009. *Reason for Exclusion: Different country: Nigeria.*

Arora, N. K., Lal, A. A., Hombach, J. M., Santos, J. I., Bhutta, Z. A., Sow, S. O. and Greenwood, B. The need for targeted implementation research to improve coverage of basic vaccines and introduction of new vaccines. *Vaccine*, 31(2):B129–B136, Apr. 2013. *Reason for Exclusion: Analysis of method.*

Atchison, C., Zvoc, M. and Balakrishnan, R. The evaluation of a standardized call/recall system for childhood immunizations in Wandsworth, England. *J Community Health*, 38(3):581–587, Jun 2013. *Reason for Exclusion: Analysis of method.*

Aypak, C., Bayram, Y., Eren, H., Altunsoy, A. and Berktas, M. Susceptibility to measles, rubella, mumps, and varicella-zoster viruses among healthcare workers. *J Nippon Med Sch*, 79(6):453–458, 2012. *Reason for Exclusion: Specific employment group: health-care worker/student.*

Aytac, S., Yalcin, S. S., Cetin, M., Yetgin, S., Gumruk, F., Tuncer, M., Yurdakok, K. and Gurgey, A. Measles, mumps, and rubella antibody status and response to immunization in children after therapy for acute lymphoblastic leukemia. *Pediatr Hematol Oncol*, 27(5):333–343, Aug 2010. *Reason for Exclusion: Subjects with specific disease/condition/comorbidity: leukemia.*

Bagna, R., Bertino, E., Rovelli, I., Peila, C., Giuliani, F., Occhi, L., Mensa, M., Mazzone, R., Saracco, P. and Fabris, C. Benign transient blueberry muffin baby. *Minerva Pediatr*, 62(3):323–327, Jun 2010. *Reason for Exclusion: Different disease: fetal anemia.*

Barrabeig, I., Torner, N., Martinez, A., Carmona, G., Ciruela, P., Batalla, J., Costa, J., Hernandez, S., Salleras, L., Dominguez, A. and Catalonia, R. S. G. Results of the rubella elimination program in Catalonia (Spain), 2002-2011. *Hum Vaccin Immunother*, 9(3, SI):642–648, MAR 2013. *Reason for Exclusion: Analysis of method.*

Bartz, H. and von Knebel-Doberitz, M. Acceptance and safety of vaccines. *Dtsch Med Wochenschr*, 134 Suppl 2:S71–76, Apr 2009. *Reasons for Exclusion: Different pathogen: other; vaccination attitude.*

Bernal-Gonzalez, P. J., Navarro-Alonso, J. A. and Perez-Martin, J. J. Computerised vaccination register for the Murcia region, Spain, 1991 to 2011. *Euro Surveill*, 17(16), 2012. *Reason for Exclusion: Analysis of method.*

Bhattacharyya, S. and Bauch, C. T. A game dynamic model for delayer strategies in vaccinating behaviour for pediatric infectious diseases. *J Theor Biol*, 267(3):276–282, Dec 2010. *Reasons for Exclusion: Analysis of method; vaccination attitude.*

Bolton-Maggs, D., Conrad, D., Keenan, A., Lamden, K., Ghebrehewet, S. and Vivancos, R. Perceptions of mumps and MMR vaccination among university students in England: an online survey. *Vaccine*, 30(34):5081–5085, Jul 2012. *Reason for Exclusion: Vaccination attitude.*

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