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Quality and composition of anthelmintic medicines available in Eastern and Western Africa: an *in-vitro* analysis of Albendazole, Mebendazole and Praziquantel

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Operational definitions

Substandard [medical products][1]

Also called ‘out of specification’, these are authorized medical products that fail to meet either their quality standards or their specifications or both.

Falsified [medical products][1]

Medical products that deliberately/fraudulently misrepresent their identity, composition or source.

Counterfeit [medical products][2]

A counterfeit medicine is one, which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging.

[1] Cited from: Appendix 3 to Annex, World Health Assembly document A70/23, 2017. http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_23-en.pdf [last access: 23rd July 2022].

[2] Cited from: World Health Organization. *Report of the Situation of Counterfeit Medicines Based on Data Collection Tool. WHO Regions for Africa and Eastern Mediterranean*. World Health Organization. 2010. http://apps.who.int/medicinedocs/documents/s18385en/s18385en.pdf [last access: 4th May 2018].

1 Introduction and motivation

Borne by low- and middle-income countries (LMICs) boasting with young new generations, the global population is still growing. It is, however, these nations that are more and more severely affected by environmental issues like deforestation, desertification, repeated droughts and humanitarian tensions – apparent in the Democratic Republic of the Congo (DRC), Yemen, Venezuela and numerous other countries. Unemployment, poverty and illness are spread to a further extent than in other parts of our planet. Tackling this vicious circle that many nations and people struggle to escape, United Nations (UN) member states had implemented eight Millennium Development Goals (MDGs) in September 2000 to eliminate global inequality and to enable peace, well-being and equal rights. Struggling to succeed with these goals by the targeted date, the MDGs were subdivided and extended by 17 Sustainable Development Goals (SDGs) in 2015 that were to proceed with the MDG aims for another 15 years [111]. A crucial target in both plans is the combat against communicable diseases. Infections highly affecting public health and productivity shall aggressively be fought. Of course, this includes the different forms of viral hepatitis and the human immunodeficiency virus with all its sequelae. However, as they are predominantly discovered in LMICs of tropical and subtropical regions, it is the Neglected Tropical Diseases (NTDs) that special attention must be drawn to. The World Health Organization (WHO) lists 19 different infections as well as snakebite envenoming under this term, of which most are considerably more frequently or even exclusively encountered in LMICs. Approximately one and a half billion people in 149 countries are potentially threatened by at least one of these NTDs [140, 145]. By addressing them, patients and doctors likewise heavily rely on drugs and medication that are of decent quality on the one hand and of reasonable price (or even for free) on the other. Albendazole (ABZ), Mebendazole (MBZ) and Praziquantel (PZQ) are three of these – by the WHO regarded as ‘essential’ – medicines in the combat against NTDs [137]. They are applied in the therapy of soil-transmitted helminthiases (STH) and schistosomiasis – two key players among the NTDs, which contribute a combined impact of about 7.957 million disability-adjusted life years (data from 2015) to global morbidity and mortality [77, 91, 92]. Since these anthelmintics are administered in large quantities in affected areas, such high demand creates flourishing drug markets, with a diverse range of producers and offering pharmaceutical companies. Not all of these locally available agents are manu-

factured with commensurable standards. Substandard and falsified (SF) medicine products are regularly detected, even though national and international drug authorities reckon their contribution to the supply chain to be considerably higher. Known as substandard / spurious / falsely-labelled / falsified / counterfeit until May 2017, the 70th World Health Assembly approved a new classification, concentrating this exhausting description to substandard, unregistered / unlicensed and falsified medical products [144]. The WHO estimates that approximately 10.5 % of all drugs fall under this definition [149] – from obviously counterfeit pills whose package already shows inadequate information about containing substances to medicines whose lacking standard is just discovered after elaborate chemical analysis.

The global trend for detecting SF medical products shows a steady increase; in the first four years of analysis (2013 – 2017), approximately 1,500 incidents were reported to the WHO Global Surveillance and Monitoring System (GSMS) [149]. Of course, the international community is aware of this trend. The WHO and the European Commission – just to name some bodies – have already implemented strategies and laws to promote, guide, strengthen and improve effective quality assessment (QA). Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) have been defined to ascertain high-quality medical products and a successful surveillance of their distribution, from a local up to an international level [17, 18, 129, 134]. When implementing the SDGs in 2015, goal 3.8 specifically addressed the achievement of universal health coverage, pointing out to '[…] access to safe, effective, quality and affordable essential medicines and vaccines for all' [146]. In countries with sufficient resources at avail, these strategies seem to work: the WHO regions Europe and America contributed with 21 % each to the reports received by GSMS – QA seems to be performed diligently enough to unveil such number of substandard and falsified (SF) medicines [149]. In poorer parts of the planet however, reaching or guaranteeing such diligence tends to be a more intricate challenge. Africa, for instance, is in the process of exhaustively implementing sufficient and continuous surveillance for pharmaceutical crime. As most nations cannot boast with ubiquitous resources to install such pharmacovigilance, these ambitions demand time, patience and often international investment or even aid. Moreover, weak law enforcement and confusing drug supply chains create conditions, under which effective QA for SF medication – having resulted in 42 % of all incidents reported to GSMS [149] – is barely possible by

government authorities on their own [50]. Countries though that are more stabilised and stronger in economic and social prosperity have been capable of implementing profound surveillance systems and strategies. Ghana and Tanzania are two of them that shall be scrutinised in the following. Both nations have experienced longer years of peace (compared to their neighbours), are well recognised by international investment and tourism and benefit from well-running National Medicine Regulatory Authorities (NMRAs), which regularly screen the local drug market for SF products. In contrast, countries emerging from troubled years or still stuck in conditions of humanitarian tensions also try to guarantee adequate QA to secure successful medical and pharmaceutical treatment. Burkina Faso and Côte d'Ivoire can further be illuminated as such nations: regular extensive findings of dozens of tons of SF medicines highlight the urgency of reliable and strictly enforced QA. Moreover, the quarter of Adjamé in Abidjan / Côte d'Ivoire is notorious for being a West African centre and transhipment point of SF drugs [30, 65].

Notwithstanding the efforts of African governments to enable a safe, reliable and cheap access to anthelmintic medicines fighting NTDs, globalisation and open markets permit a steady import of drugs from different countries, which is difficult to thoroughly control. Thence, not only original trademark products are disposable, but also a large choice of generics that tend to be cheaper and consequently more affordable for the vast majority of African people. Furthermore, ubiquitous distribution and constant coverage of even such important standard drugs like anthelmintics appear to be logistically difficult, so that larger containers with hundreds of tablets can be an attractive alternative to vendors owing to easier storage and less frequent re-orders. Tracing down SF medicines under the depicted conditions is growing more and more difficult as they can be manufactured so diligently these days that simple colour reactions or dissolution checks sometimes just do not deliver utilizable result, provided there are results whatsoever [149]. Dependable quality tests require time and high-standard test systems that cannot be found on a regular basis throughout the continent. Even foreign research teams need to bring along patience to discover SF products and to validate their findings, either taking local infrastructure into account or spending a lot of time on transferring potential forgeries back home to have them analysed there. In addition to that, technically advanced systems like a high-performance liquid chromatography (HPLC) are expensive by the standards of LMICs, which hence cannot be performed on a regular basis by government authorities.

Therefore, dispassionate (and internationally published) studies and reviews on the evaluation of the quality and the composition of ABZ, MBZ and PZQ have rarely been conducted so far. Li et al. [66] analysed two PZQ batches by two different Tanzanian companies, both not showing major hints of being SF medicines. A study analysing drugs against schistosomiasis and fascioliasis in both human and veterinary treatment – supposedly containing either PZQ or Triclabendazole – in the Lake Chad region revealed that none of the tablets screened showed any of the expected active pharmaceutical ingredient (API) but comprised of ABZ and MBZ instead [47]. Extensively analysing various drugs from Africa and Asia applying the Global Pharma Health Fund e.V. (GPHF) Minilab™, Petersen et al. [90] included several batches of ABZ, MBZ and PZQ, which resulted in two MBZ brands from the DRC presenting with inadequately low dissolution profiles. In Ethiopia, several studies on the quality of these three drugs were conducted (in which fourfold ABZ, twice MBZ and once PZQ samples had been tested), resulting in some deficiencies in terms of dissolution profiles but mostly containing a sufficient amount of API [5, 6, 97, 101]. Khan et al. [59] performed an assay on ABZ, MBZ and Metronidazole available in Cambodia, which revealed some insufficiencies in disintegration testing.

The Medical Mission Institute (MMI) of Würzburg has got various long-lasting collaborations with different partners in Africa. In cooperation with colleagues of the Catholic University of Health & Allied Sciences (CUHAS) at the Bugando Medical Centre (BMC) in Mwanza / Tanzania, several research projects are mutually carried out. Amongst them, within the framework of a proof-of-concept study, a program is conducted to control and perpetually eliminate schistosomiasis on Ijinga Island in Lake Victoria by an intensified treatment protocol in combination with public health interventions like information, education and communication (IEC) and enhancements in the quality of water, sanitation and hygiene (WASH) [81]. Tremendously significant as well, co-endemic STH are highly prevalent in the Lake Zone area around Mwanza where over 14 million people in eight regions live and are prone to these NTDs – obviously, there is relevant interest in deworming medicines of decent quality. In Ghana, the MMI has been supporting St. Martin de Porres Hospital in the small fishing village of Eikwe in the deep south-west of the country for more than 60 years, from the foundation of this regional reference clinic in 1959. Sought out and referred to by many patients from adjacent Côte d'Ivoire as well,

successful preventive and therapeutic agents against both impactful NTDs are paramount in both countries to combat schistosomiasis and STH as public burden of disease.

Despite the necessity of trustworthy anthelmintic medicines in affected regions, the fact has to be conceded that reliable and robust data on the quality and the composition of ABZ, MBZ and PZQ available in Tanzania, Ghana, Côte d'Ivoire and Burkina Faso (benefitting from the same market) is more than scarce, to say the least. Studies focussing on the content of API and galenic proportions of these drugs have apparently been neglected so far. The present research addresses this uncertainty by screening and performing an *in vitro* examination of multiple samples of ABZ, MBZ and PZQ to eventually determine the risk of coming across SF anthelmintic medicines. In the following chapter, this study gives an overview of the necessity of diligent QA for ABZ, MBZ and PZQ by presenting both schistosomiasis and STH as well as the burden of NTDs in Burkina Faso, Côte d'Ivoire, Ghana and Tanzania. Alongside the international approach towards this challenge, the deworming agents ABZ, MBZ and PZQ are illustrated. Chapter 3 explains the process of sampling and the testing locations in East and West Africa. Furthermore, the different analytical and pharmaceutical methods applied on-site in Mwanza, Tanzania and both at the MMI and the Department for Pharmacy and Food Chemistry of the Julius-Maximilians-University (JMU) in Würzburg / Germany are depicted. Chapter 4 presents the results of the assays and demonstrates the quality and the composition of ABZ, MBZ and PZQ in these four countries. Chapter 5 discusses the generated data by illustrating the role of local conditions in drug sampling and evaluating the aptitude of the Minilab™ as a screening tool in anthelmintic QA. Moreover, the significance of content and galenic characteristics encountered in this research shall be classified appropriately, pointing out on the peculiarities of dissolution assays of MBZ 100 mg gives. Limitations of this study, a prospect of the combat against NTDs, particularly in view of an ongoing coronavirus disease 2019 (COVID-19) pandemic, and a summary in both English and German language conclude this research.

2 Background to the research on the quality and the composition of anthelmintic medicines in Eastern and Western Africa

2.1 Schistosomiasis

Human schistosomiasis is caused by trematodes – blood flukes – that circulate between humans and specific fresh water snails. Five important different species (spp.) are known to induce an infection: *S. intercalatum*, *S. japonicum*, *S. mansoni* and *S. mekongi* prefer to reside in mesenteric venules and thus lead to intestinal inflammation and excretion of their eggs in the faeces. *S. haematobium* prefer to reside in venules of the lower urinary tract and hence provoke urogenital inflammation, excreting eggs in the urine. After reaching fresh water, miracidia (0.1 mm long larvae) emerge out of the eggs and enter the body of an appropriate snail (*Biomphalaria* snails for *S. mansoni*, *Bulinus* snails for both *S. haematobium* and *S. intercalatum*, *Neotricula* snails for *S. mekongi* and *Onchomelania* snails for *S. japonicum*). In these, the miracidia perform asexual replica-

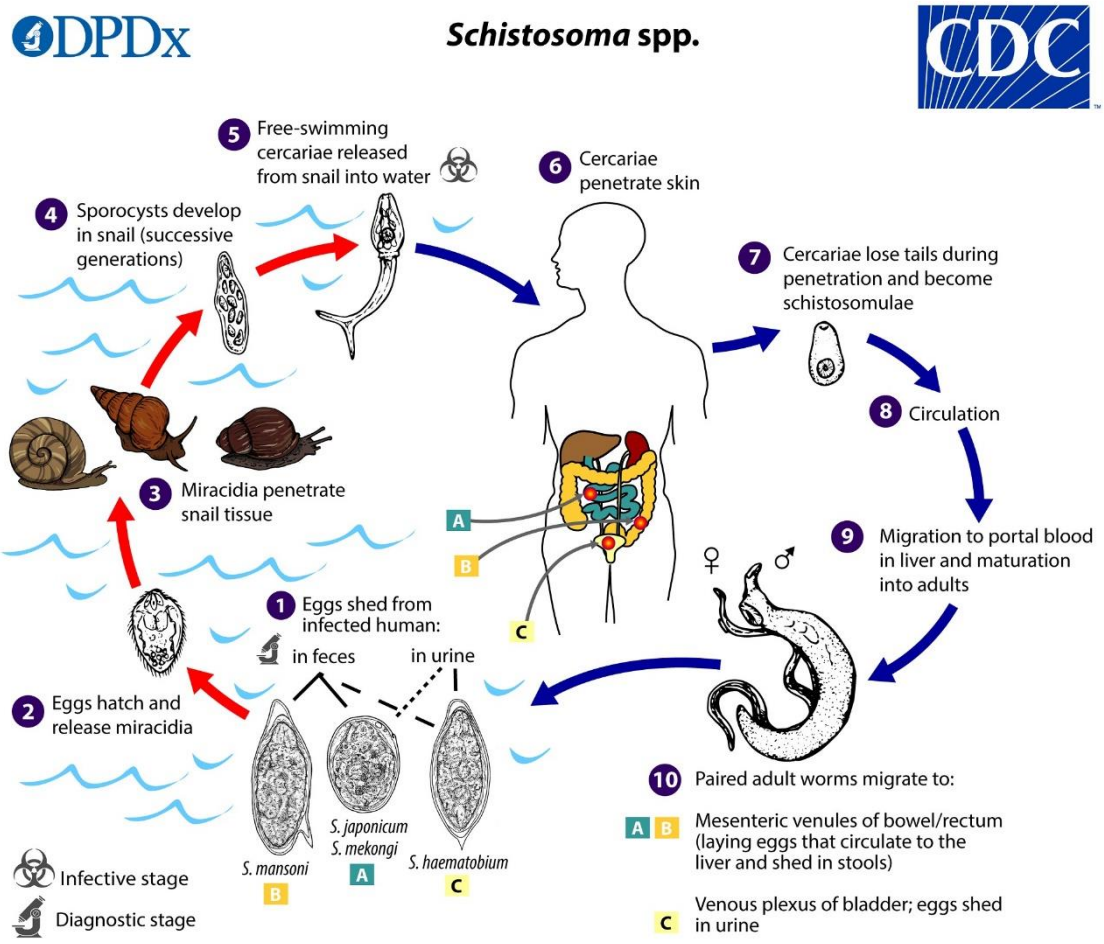
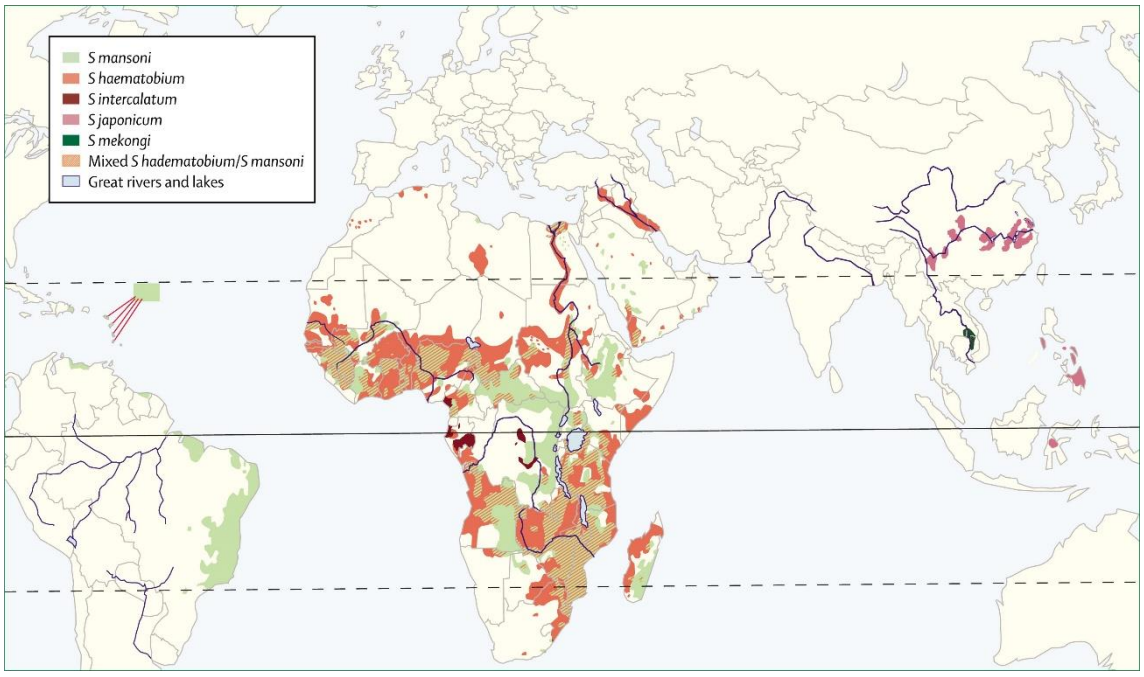


Figure 1: Life cycle of *Schistosoma* spp. between humans and fresh water snails. Resource: [15]

tion until, within four to six weeks, large numbers of motile, up to 0.2 mm long cercariae are released into the water to seek contact with human skin. Penetrating the skin in less than 15 minutes, they cast off their tails (then called schistosomulae) and make their way through lungs and heart towards the liver. Here they – now sexually – mature, copulate (when the name *schisto-soma*, Greek for 'split body', becomes obvious) and predominantly descend to their preferred venules (refer to Figure 1).

Schistosoma spp. are not equally distributed in tropical and subtropical regions; they, for instance, depend on the occurrence of the very species of snail (refer to Map 1). *S. haematobium* is spread across Africa (sub-Saharan West Africa, towards the coast of Equatorial Africa, along the river Nile, East and South-East Africa and Madagascar) and in the Middle East (e.g. in Yemen, Iraq or Syria). *S. intercalatum* is found to a lesser extent than *S. haematobium* in West and Equatorial Africa. *S. japonicum* is detected in East Asia (China, Indonesia and the Philippines) and can effectively persist in these regions as mammals like water buffaloes or pigs are natural hosts and thus sustain active life cycles and transmission. *S. mansoni* is globally distributed across three continents: South and Central America are infested especially in Brazil and several Caribbean islands. In Africa, *S. mansoni* is distributed comparably to *S. haematobium* (but also in the Congo basin, Ethiopia and Angola). In the Middle East, *S. mansoni* is found on the Arabian Peninsula. The occurrence of *S. mekongi* is limited to a small region along the Mekong River.



Map 1: Global distribution of *Schistosoma* spp. Resource: [48]

Clinically, a first cue on a possible infection with schistosomes can be a cercarial dermatitis, a local hypersensitivity reaction to cercariae penetrating the skin accompanied by a transient rash and prurigo, which is also called ‘swimmer’s itch’. An acute schistosomiasis is called Katayama Fever and defines the systemic spreading of the hypersensitivity reaction. It usually starts a few weeks after the infection and can present with flu-like symptoms, (bloody) diarrhoea, hepatosplenomegaly (hepatomegaly rather encountered in chronic cases due to periportal fibrosis), dyspnoea and coughing. Blood eosinophilia is widely discovered, related to the severity of symptoms, and may contribute to neurologic deficits. Growing to chronic forms, an intestinal and a urogenital type of schistosomiasis can be distinguished. *S. haematobium* provokes micro- and later macrohaematuria and triggers granulomatosis, fibrosis and calcification in the bladder leading to possible reflux and hydronephrosis. In the long run, this can result – especially when not treated – in squamous cell carcinoma. Women infected with *S. haematobium* show a significantly increased vulnerability to acquiring coinfections as human immunodeficiency virus or other sexually transmitted diseases. Intestinal schistosomiasis may lead to chronic inflammation and hence provoke melaena, haematochezia and ulceration. All spp. of schistosomes place their eggs into the vessels they dwell; those (especially of *S. japonicum*, *S. mansoni* and *S. mekongi*) can be transported back to the liver and uphold chronic hepatic / hepatosplenic inflammation with subsequent fibrosis, cirrhosis and induce typical morbidity of hepatic impairment (like hypoalbuminaemia or impaired coagulation) and portal hypertension (e.g. oedema or gastro-oesophageal varices). Patients with a coinfection of hepatitis B or C or alcoholism are at increased risk. Via bypasses, eggs can also reach the lungs, the kidneys or the central nervous system (CNS) and lead to pulmonary hypertension, a glomerulonephritis or cerebral respectively spinal cord damage.

Haematuria or haematochezia in people living in affected regions or returning from such are often the first symptoms that actuate diagnostics. Microscopic stool and / or urine examination are simple and cost-effective methods to diagnose an infection but are limited by a low egg count or intermittent egg excretion. The Kato-Katz technique allows filtering eggs of not only schistosomes but also of other worms like *Ascaris* or *Trichuris* and can consequently be applied in areas of moderate risk of obtaining bilharzia. A point-of-care rapid test detects a circulating cathodic antigen regurgitated from a living worm’s gut in the urine. As this antigen is ubiquitous in schistosomes, it does not exclu-

sively indicate an active infection with *S. haematobium* but can also point out to an infection with *S. mansoni* (for which sensitivity seems to be highest) or *S. japonicum* – therefore a positive test result should be confirmed (e.g. by microscopy of the specific eggs). In western nations, serologic testing for antibodies by enzyme-linked immunosorbent assay or detection of schistosomic deoxyribonucleic acid by polymerase chain reaction may be performed as well – such methods are not appropriate in countries with limited resources. To evaluate the damage caused by the disease, diagnostic imaging depending on symptoms should follow (e.g. ultrasound of the lower urinary tract or the bowels).

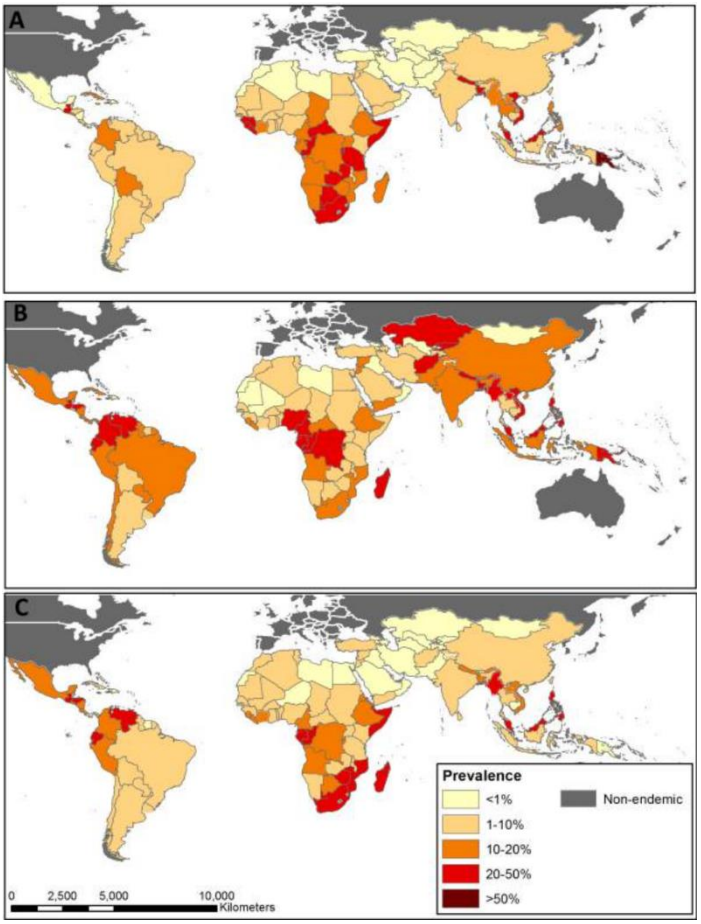
Even though *S. mansoni* is treated with Oxaminiquine in Brazil, too, PZQ is the treatment of choice in schistosomiasis:

- for *Schistosoma* spp. found in Africa (*S. haematobium*, *S. intercalatum* and *S. mansoni*), several regimes are recommended: a single dose of 40 mg/kg (WHO recommendation), a single dose of 60 mg/kg or 40 mg/kg for three consecutive days (all divided into two or three separate doses if required);
- for *Schistosoma* spp. found in Asia (*S. japonicum* and *S. mekongi*), a treatment with a single dose of 60 – 75 mg/kg divided into two to three separate doses is recommended.

However, in regions with a high prevalence of bilharzia or in patients with a severe form, a repetition of the adequate therapeutic regime should be considered. Patients suffering from a CNS affection should be treated with glucocorticoids as well to reduce the oedema around the dying worms and – in combination with an anticonvulsant when needed – prevent seizures. A steroid therapy may be complemented by Ivermectin (IVM) when suspecting simultaneous strongyloidiasis in patients from highly-endemic regions. In areas of high infestation, merely treating patients is not enough to obtain permanent cure of the disease, since reinfection rates were summarised to be substantial: 17.6 % (± 10.8 %) for urogenital schistosomiasis and even 43.9 % (± 20.6 %) for intestinal schistosomiasis [152]. Hence, control and prevention are paramount to ease the burden of this NTD from affected countries. Each citizen – particularly those from vulnerable social strata as children, pregnant or elderly – should be protected from sequelae that may deteriorate their quality of life. Not only the health of the patients themselves is at stake but also the conditions of their families when depending on the patient. Ways to intervene and combat schistosomiasis shall be discussed later on [15, 48, 69, 83].

2.2 Soil-transmitted helminthiases

The group of STH encompasses six major helminths: *Ancylostoma duodenale*, *Necator americanus* (both of which are hookworms / ancylostomatidae), *Ascaris lumbricoides*, *Trichuris trichiura*, *Strongyloides stercoralis* and *Enterobius vermicularis*. These have in common that they do copulate, hence have different sexes, and that eggs of these helminths need to dwell on soil before becoming infectious (thus known as geohelminths), too. This latter characteristic being mandatory for human infections with *Ascaris lumbricoides*, *Ancylostoma duodenale*, *Necator americanus* and *Trichuris trichiura*, both *Strongyloides stercoralis* and *Enterobius vermicularis* can also be transmitted directly from one person to another (*Enterobius vermicularis* only requiring exposure to oxygen and consequently leading to auto-infection as well). Strongyloidiasis and enterobiasis / oxyuriasis can be acquired globally (although *Strongyloides stercoralis* is preferably encountered in tropical regions). The other four helminthiases are bound to a warm and humid climate that includes moderate climate zones from spring to autumn (refer to Map 2) and shall be illustrated in the following [14, 53, 68, 83]. Interventions feasible in affected regions to control STH, to ease the burden of STH-caused morbidity and to promisingly approach SDG 3.3 ('By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases') [146] will be presented later on.



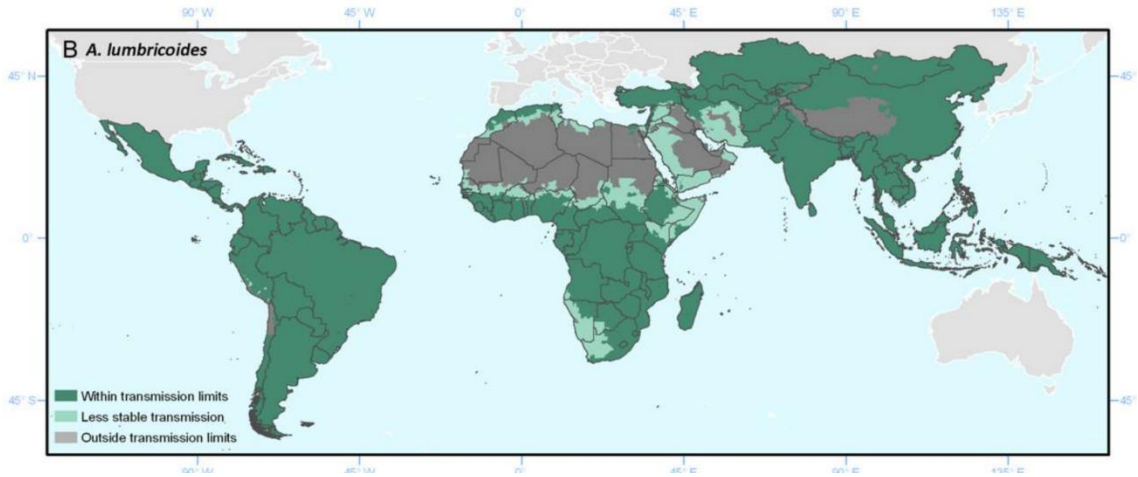
Map 2: Distribution of STH infection prevalence in 2010 by STH species. Resource: [92]
(A) Ancylostomatidae, (B) *Ascaris lumbricoides*, (C) *Trichuris trichiura*

2.2.1 Ascariasis

Ascariasis is estimated to be the helminthiasis with the highest prevalence worldwide (by 2013: about 804 million patients) [53]. Upon ingestion or inhalation of infectious eggs containing larvae (up to 0.25 mm in length), these are released in the small bowel, penetrate the intestinal wall and make their way via liver and heart to the lungs. Here, they pass through the pulmonary interstitial structures, invade alveoli and ascend the bronchial system. Swallowed and returning to the small bowel (preferably to the jejunum), they mature to adult helminths (with a maximal length of 35 cm), start egg production and live up to two years. The eggs are excreted and grow infectious within two weeks at 30 °C or within six weeks at 17 °C to possibly survive up to six years in favourable conditions (moist and warm soil).

The global distribution of roundworms is limited by extreme soil conditions. Soil that is too warm, too cold and too dry dramatically reduces the risk of transmission of infectious eggs to humans. As to be seen in Maps 2 and 3, deserts, high altitudes and regions beyond the influence of constant sun radiation, the Intertropical Convergence Zone and the trade winds pose unfavourable conditions for *Ascaris*. Peri-urban areas seem to be more affected by roundworms than urban or rural areas.

Most patients are infected with only a few worms and consequently remain asymptomatic. During the stage of pulmonary passage of the larvae, they may develop a hypersensitivity reaction with dry cough, fever and eosinophilia, that occasionally can extend to a Löffler's syndrome with dyspnoea and eosinophilic pneumonia. Abdominal



Map 3: Climatic suitability for *Ascaris lumbricoides* transmission, defined by land surface temperature and aridity. Resource: [91]
Less stable transmission is defined by infection prevalence < 2 %.

symptoms include mild discomfort, nausea or loss of appetite. The heavier the infestation, the more severe sequelae of this parasitosis can turn: malnutrition and both growth and mental retardation (in children) due to impaired absorption of nutrients and minerals, obstruction of the intestinal lumen leading to complications like appendicitis, ileus with perforation and peritonitis, blockage of the bile or pancreatic ducts with signs of cholestasis, exocrine pancreatic insufficiency and granulomatous hepatitis after oviposition.

Presentation at a medical facility may also be provoked by worms evading through mouth, nose, bladder or anus. Usually, the infection is verified by plain stool smears (in endemic regions, concentration may not be required due to high egg production) or ultrasound / radiography. In case of complications (ileus, duct obstruction or peritonitis), surgery can be necessary (computed tomography or endoscopic retrograde cholangiopancreatography are rarely available in tropical countries).

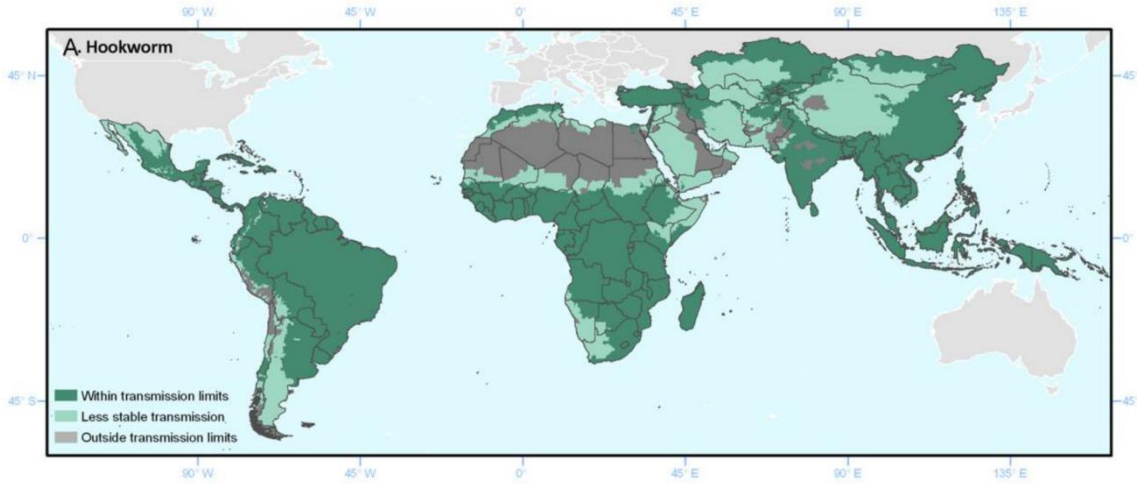
The treatment of choice in ascariasis are anthelmintic medicines. The following oral drugs are preferably applied in patients and show high efficacy:

- ABZ 400 mg as a single dose (tablet or suspension);
- IVM 150 – 200 µg/kg as a single dose;
- Levamisole 2.5 mg/kg as a single dose;
- MBZ 500 mg as a single dose (preferred in children under two years), or 100 mg twice daily for three days (both options possible as tablets or in suspended formulations as well);
- Pyrantel pamoate 11 mg/kg as a single dose (with a maximal dose of 1 g per day, usually as suspension for children) for up to three days.

Analgesic or rehydrating therapy may accompany anthelmintic use. Morbidity as malnutrition and growth retardation often requires compensation by nutrients, proteins and minerals.

2.2.2 Ancylostomiasis (*Ancylostoma duodenale* / *Necator americanus*)

Hookworms are, unlike ascariasis, not acquired by ingestion or inhalation of infectious eggs. Filariform larvae penetrate human skin swiftly via hair follicles or small lesions (larvae of *Ancylostoma duodenale* can be obtained orally likewise), invade venous blood vessels and circulate into the lungs. Here, they also pass through the pulmonary interstitium, invade alveoli and ascend the tracheobronchial system. Swallowed and



Map 4: Climatic suitability for hookworm transmission, defined by land surface temperature and aridity. Resource: [91]
Less stable transmission is defined by infection prevalence < 2 %.

returning to the small bowel into jejunum and ileum (not exclusively to the duodenum as the scientific name of this very *Ancylostoma* species would suggest), they attach to the intestinal mucosa, mature to adult helminths (with a maximal length of 13 mm), start egg production and live up to two (*Ancylostoma* spp.) respectively five (*Necator* spp.) years. The eggs are excreted and develop into infectious larvae within two weeks in favourable conditions (shady, moist and warm soil).

The global distribution of ancylostomiasis depends on the factors mentioned above. Temperatures ranging between 25 °C and 32 °C, protection from direct sun impact and sufficient rainfall are desirable prerequisites for hookworms to dwell and infect people, especially in rural areas of sub-Saharan Africa and South-East Asia lacking adequate sanitation. As for ascariasis, deserts, high altitudes and regions well beyond the Tropics of Capricorn and Cancer (refer to Maps 2 and 4) pose unfavourable conditions.

Most patients suffer from light infections and consequently remain asymptomatic. Predominantly after previous exposure to hookworms, a cutaneous hypersensitivity reaction with rash and pruritus on the site of helminthic penetration, which is called ‘ground itch’ may occur. Oral ingestion sporadically causes the Wakana syndrome (nausea, vomiting, pharyngeal and pulmonary irritation). During pulmonary passage of the larvae, patients may also develop an eosinophilic pneumonitis (less intense than in ascariasis). In chronic infections however – besides eosinophilia and abdominal discomfort – prevailing symptoms are caused by malnutrition and chronic loss of blood. The parasites lysate local mucosa to reach for capillaries and feed on erythrocytes (*Ancylostoma* spp. consume

0.3 mL per blood meal, *Necator* spp. just 0.04 mL). Consequences may be growth and mental retardation in children and a hypochromic, microcytic anaemia with pallor, lassitude and weakness leading to reduced productivity, heart failure and other sequelae.

Usually, the infection is verified by plain stool smears (concentration is merely required in light infestations with low egg production). Determination of the exact species by stool culture or polymerase chain reaction does not award any added value in practice.

The treatment of choice of hookworm infections are anthelmintic medicines. Herein, ABZ 400 mg once daily (tablet or as suspension) for up to three days shows the highest efficacy. The following drugs may be used, too (with decreasing cure rates and, in case of MBZ, a suspected increase in resistances):

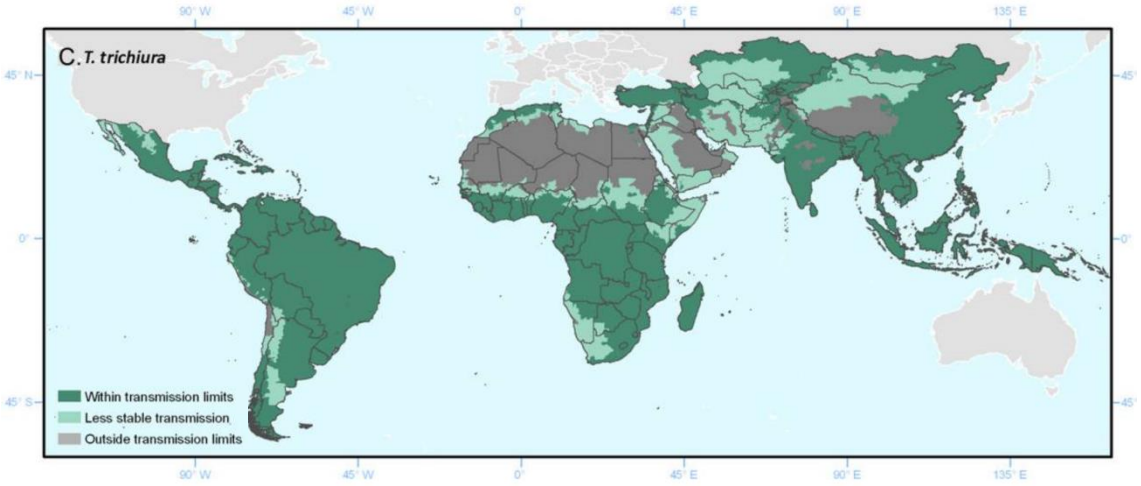
- MBZ 500 mg as a single dose or 100 mg twice daily for three consecutive days (both options possible as tablets or in suspended formulations, with the second option being more successful);
- repeated cycles of Pyrantel pamoate 11 mg/kg (with a maximal dose of 1 g per day, usually as suspension for children);
- Levamisole 2.5 mg/kg as a single dose.

Iron restoration and rehydration therapy as well as compensation of nutrients, proteins and minerals should accompany the use of anthelmintics to ease the listed morbidities.

2.2.3 Trichuriasis

The whipworm *Trichuris trichiura* is acquired by ingestion (or inhalation) of infectious eggs. Reaching the caecum, larvae emerge from the eggs and attach to the local crypt mucosa. Unlike *Ascaris lumbricoides* or hookworms, *Trichuris* larvae do not circulate through the pulmonary system. Within the crypts, larvae further mature to adult worms (approximately 4 cm long), then continue to spread through colon and rectum adhering to the epithelium, start egg production and live up to three years. The eggs are excreted and develop into infectious larvae within four weeks in favourable conditions (shady, moist and warm soil).

These ground conditions determine the global distribution of whipworms. Moderately warm temperatures, protection from direct sun impact and sufficient rainfall are prerequisites for eggs to embryonate, especially in rural areas lacking adequate sanitation. Children playing in contaminated soil appear to not only be most susceptible to *Trichuris*



Map 5: Climatic suitability for *Trichuris trichiura* transmission defined by land surface temperature and aridity. Resource: [91]
Less stable transmission is defined by infection prevalence < 2 %.

infections but also to heavy infestations. Following the two STH previously described, deserts, high altitudes and regions well beyond a tropical and subtropical climate (Central Asia still included; refer to Maps 2 and 5) pose unfavourable conditions for whipworms.

A majority of patients suffer from an asymptomatic disease, sometimes accompanied by blood eosinophilia. In chronic infections however, inflammation of the local mucosa (upheld by both parasites and invading macrophages) can lead to abdominal pain, a colitis with dysentery-like diarrhoea, hypochromic anaemia, hypoproteinaemia and rectal prolapse. Malnutrition, growth and mental retardation in children are often seen, too.

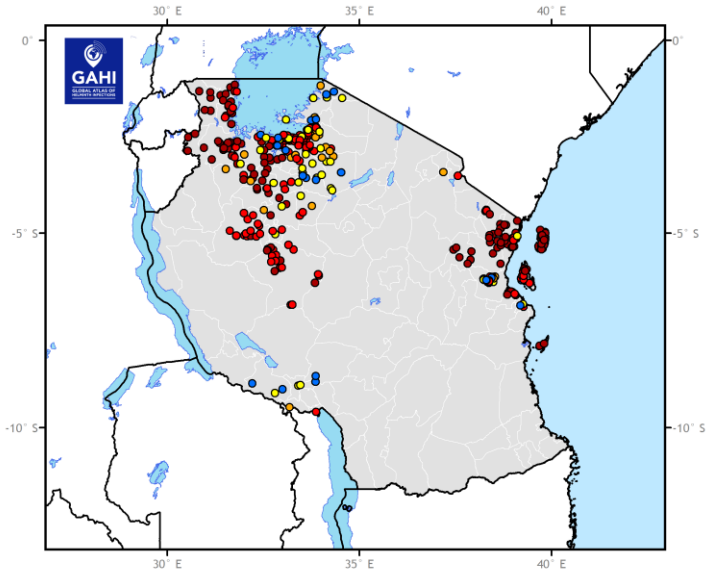
In general, microscopy of plain stool smears verifies the diagnosis (concentration is merely required in light infestations with very low egg production). Whipworms attached to the mucosa in case of a rectal prolapse and colonoscopy (difficult in a poor, rural setting) save the diagnosis likewise.

Treatment of trichuriasis is more cumbersome than of other helminthiases. A single dose of ABZ (400 mg), MBZ (500 mg) or Pyrantel pamoate does not exceed an efficacy of 50 % cure rate. Regimes of three consecutive days of ABZ or MBZ booster the anthelmintic effect. Combination therapies including ABZ, MBZ, Oxantel pamoate, Tribendimidine, Moxidectin (not officially approved yet) or IVM – successfully applied in the combat against lymphatic filariasis (LF) – seem to result in higher cure and egg reduction rates even in heavy manifestations [12, 58, 86, 99]. Besides, refeeding, rehydration and (if necessary) reposition of rectal prolapse are paramount for patients to overcome the sequelae associated with trichuriasis.

2.3 The need for effective quality assessment in Tanzania in view of a high burden of Neglected Tropical Diseases

The United Republic of Tanzania, an East African country of roughly 947,300 square kilometres [132] situated just south of the equator with more than 59.7 million inhabitants (calculated by 2020) [131], has been experiencing comparably more stable and calmer decades after its independence than neighbouring states like Uganda or the DRC. After starting in the early 1980s to slowly give up the national policy of the restrictive 'socialism with self-reliance', as it had been drafted in the Arusha Declaration of 1967 by the administration of president Nyerere, the Tanzanian markets opened up for international trade [56]. Following this influx of foreign products and a growing and liberalised competition for Tanzanian consumers, supervisory bodies had to be implemented to guarantee an effective and trustworthy QA. NMRAs as the Tanzania Food and Drugs Authority (TFDA) or the Fair Competition Commission were initiated in the early 2000s to control market dominance and to assure a high quality of the available goods. As this includes QA on the drug market likewise, it is worth having a look at the successes of these surveillance strategies for SF medication. Between 1999 and 2015, 24 products were discovered to not meet the required standards, of which 83.3 % contained at least one anti-infective API [49].

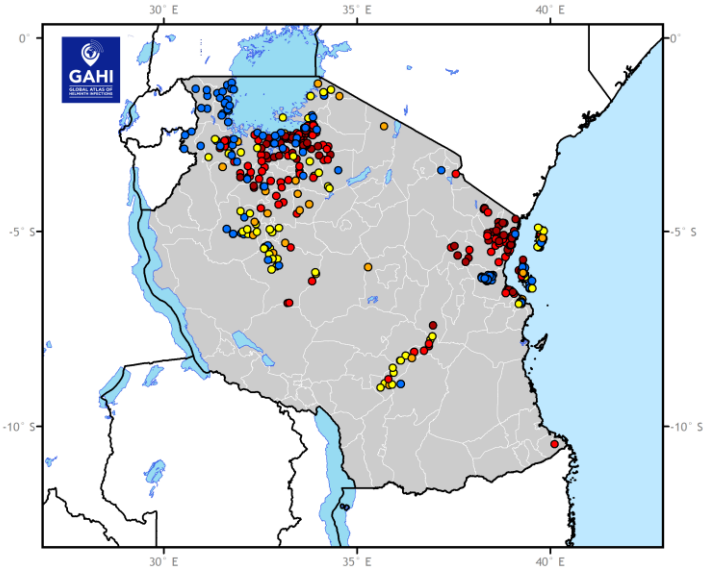
Despite Tanzania's socio-economic progress, NTDs are still highly prevalent in the country. Surrounded by three of the African Great Lakes and consisting of large rural areas, savannah and other original landscapes, a high hygienic standard and adequate sanitation cannot regularly be guaranteed nor maintained. Millions of people living there are prone to NTDs borne by mosquitoes, mammals, worms and snakes. As a consequence, the Tanzanian Ministry of Health, Com-



Map 6: Prevalence of STH in Tanzania. Resource: [39] Blue: prevalence < 1 %; yellow: < 10 %; orange: < 20 %; red: < 50 %; dark red: 50 % and beyond.

munity Development, Gender, Elderly and Children launched the integrated Neglected Tropical Diseases Control Programme in 2009, offering information about the NTDs prevalent in the country and different NTD-specific governmental sub-programmes that determine the extent of each NTD and the control mechanisms available [82].

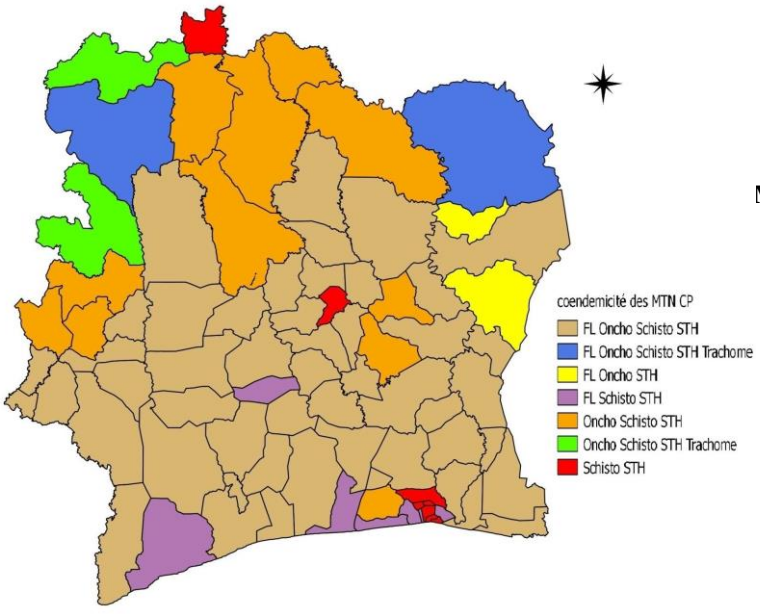
Eight out of those 20 entities are transmitted by helminths, with globally 24 % of the world's population being affected [140]. According to the Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN) and the Global Atlas of Helminth Infections (GAHI), data on STH in Tanzania is extensively available for the Lake Zone area, Tabora Region and the north-eastern regions of the country including Zanzibar. Here, STH prevalences up to 50 % and beyond can be observed in various testing sites (refer to Map 6) [24, 39, 81]. Consequently, not only IEC but also effective, available and cheap anthelmintic medication is imperatively necessary to treat local patients and to provide PC in high risk areas. The WHO highlights the significance of the following parasites: *Ascaris lumbricoides*, *Trichuris trichiura* and *Ancylostoma duodenale* respectively *Necator americanus*. To fight these parasites effectively, therapeutic as well as preventive use of the anthelmintics ABZ and MBZ is recommended [140, 145], accompanied by WASH [10, 67]. Tanzania's geographical features also permit large habitats for specific snails infected with *Schistosoma* spp. ESPEN and GAHI depict large areas around Tanga (in the north-eastern Coastal Region) and Mwanza (on the shores of Lake Victoria) with prevalences beyond 50 % for *S. haematobium* (refer to Map 7) [24, 43] and several locations in the Lake Zone Region and in the Manyara Region with equally high numbers for *S. mansoni* [44]. Properly combatting schistosomiasis, which is extensively found in the Great African Lakes, PZQ is the treatment of choice.



Map 7: Prevalence of *S. haematobium* in Tanzania. Resource: [43]
Blue: < 1 %; yellow: < 10 %; orange: < 20 %; red: < 50 %; dark red: 50 % and beyond.

2.4 The impact of schistosomiasis and soil-transmitted helminthiases on sub-Saharan West Africa

Burkina Faso, la République de Côte d'Ivoire and the Republic of Ghana are three West African nations encompassing approximately 835,220 square kilometres of land [132] and almost 78.4 million inhabitants (calculated by 2020) [131]. Climate zones gradually change from lush tropical rainforest in the southern parts of Côte d'Ivoire and Ghana to arid savannah of the Sahel in northern Burkina Faso. Numerous waterways drain the region, with Lake Volta (one of the world's largest artificial reservoirs) receiving extensive amounts of water from Burkina Faso, northern and eastern Ghana. Beyond that, large parts of the population live in very basic rural conditions with limited access to sanitation. Large numbers of internally displaced people in the region are seeking refuge in overcrowded and hygienically alarming camps (especially in northern and eastern Burkina Faso, under the threat of Islamist terror attacks). As a consequence, conditions like these provide perfect breeding grounds for many infectious agents. Malaria cases are still commonly seen and regularly treated in hospitals, dengue fever outbreaks repeatedly occur. High prevalences of NTDs continue to burden the region – of which many are co-endemically present (refer to Map 8). However, owing to extensive mass drug administration (MDA) rounds of PC in Mali and Burkina Faso, STH were effectively driven back so that ABZ or MBZ are not distributed any more for annual PC in these two countries [118, 119, 139].

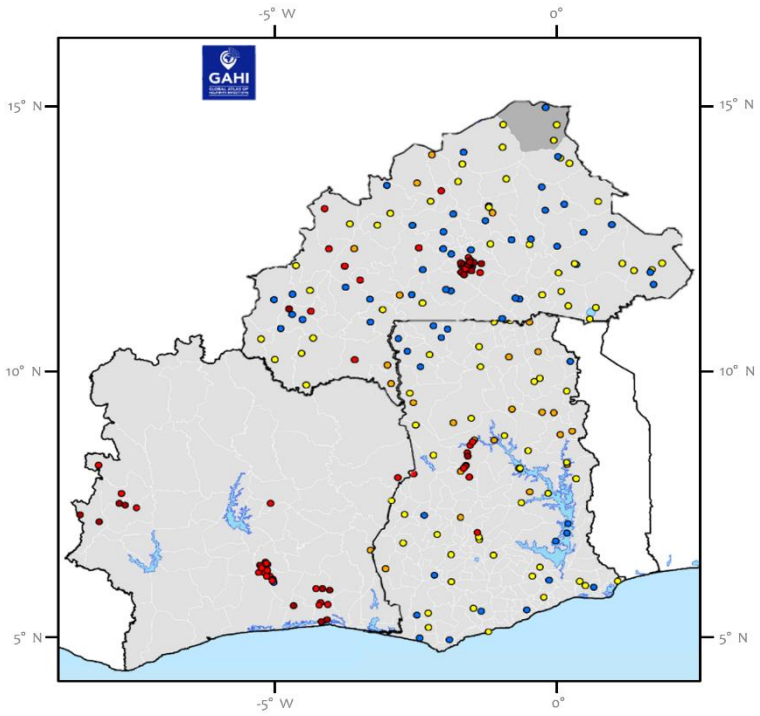


Map 8: Co-endemicity of different NTDs in Côte d'Ivoire addressed by PC. Resource: [73]

- FL: Lymphatic filariasis
- Oncho: Onchocerciasis
- Schisto: Schistosomiasis

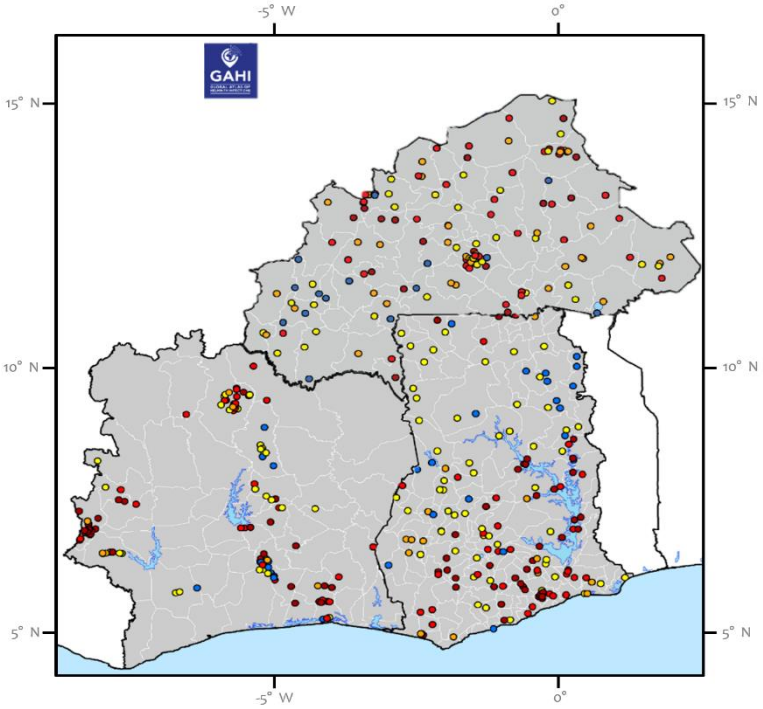
Overall, STH cases in Burkina Faso (ascariasis and ancylostomiasis with significantly higher prevalences than trichuriasis) [21] are predominantly detected around the capital of Ouagadougou, to a lesser extent in the north-west. In Côte d'Ivoire, scarce data reveal high prevalences up to 50 % and beyond between Abidjan and Yamoussoukro, and in the western highlands (high numbers of ascariasis) [22]. Ivorian figures suggest prevalences between 22 % and 46 % across the different regions of the country [73]. In Ghana, higher rates of STH (again ascariasis dominating) [23] are found in the centre and in the north-east of the country (refer to Map 9).

Apart from a few départements in the district of Zanzan in north-western Côte d'Ivoire, schistosomiasis is regularly encountered in all three countries (refer to Map 10). Burkina Faso faces high rates in most parts except for the west. The dominant spp. is *S. haematobium*; the prevalence of *S. mansoni* rarely exceeds 1 % [36]. Ivorian data illustrate severe manifestations of *Schistosoma* spp. from the western district of Montagnes across the country to the south-eastern district of Comoé [73]. GAHI distinguish the distribution of *S. haematobium* (extensively found between Abidjan and Yamoussoukro, and around Korhogo in the north) from the prevalence of *S. mansoni* (large numbers in the district of Montagnes, north of Abidjan and around Korhogo) [38]. Ghana suffers from bilharzia especially in the southern regions, along the shores of Lake Volta and at the border to Burkina Faso. Similar to its northern neighbour, *S. haematobium* provoke the vast majority of cases of schistosomiasis. Contrary to that, the prevalence of *S. mansoni* appears to rarely exceed 1 % [37].



Map 9: Prevalence of STH in Burkina Faso, Côte d'Ivoire and Ghana. Resources (modified): [40 – 42]
Blue: < 1 %; yellow: < 10 %; orange: < 20 %; red: < 50 %; dark red: 50 % and beyond.

Approaching the large burden and morbidity of NTDs, the governments of Burkina Faso, Côte d'Ivoire and Ghana responded to the endeavours of the WHO to conquer NTDs by MDA of PC, WASH, IEC and innovative and intensified disease management (IDM) [127, 133] and to ultimately reach SDG 3.3. The three nations implemented separate, country-specific strategic plans to tackle the different endemic NTDs (all yielding at a 5-year-period between 2016 and 2020) to gain control over their transmission and sequelae. Before starting any PC regime, mapping of the prevalences of each NTDs was paramount. Depending on the number of people affected and the likelihood of acquiring a specific NTD, variable therapeutic schemes were provided by the government and the international community, taking co-endemicities into account [33, 72, 73, 126, 128].



Map 10: Prevalence of schistosomiasis in Burkina Faso, Côte d'Ivoire and Ghana. Resources (modified): [36 – 38] Blue: < 1 %; yellow: < 10 %; orange: < 20 %; red: < 50 %; dark red: 50 % and beyond.

2.5 Strategies to combat Neglected Tropical Diseases

Challenging the tremendous impact of NTDs on health and well-being for millions of people on our planet, 20 internationally operating institutions – amongst these were pharmaceutical companies, donors, government partners and non-governmental organisations – joined the governments of endemic countries on a summit in January 2012 to sign the London Declaration on Neglected Tropical Diseases. Herein, they committed themselves to (inter alia) approach ten NTDs, which are addressed by the WHO strategies of WASH, PC (both shall be further illustrated later on) and IDM

- to eradicate dracunculiasis,
- to eliminate LF, leprosy, human African trypanosomiasis (HAT) and blinding trachoma
- and to control schistosomiasis, STH, American trypanosomiasis, onchocerciasis and visceral leishmaniasis

until 2020 [120, 133]. Up to now, more than 80 other organisations have joined to achieve these goals, which were reinforced by the Geneva Commitment in April 2017 [122].

Beyond WASH, PC and IDM, vector ecology and management as well as veterinarian public health services (fighting neglected zoonotic diseases) are performed in line to WHO strategic plans. Besides for the non-NTD cholera, which may be regarded as one, IDM particularly aims for the four NTDs Buruli ulcer, Chagas disease (American trypanosomiasis), HAT and leishmaniasis (yaws, traditionally approached by IDM, is now increasingly targeted by Azithromycin [94]). These infections cannot be fought efficiently by MDA of PC because patients are often difficult to detect. Cost-effective and reliable test systems are expensive, difficult to handle or just not available. Furthermore, treatment options sometimes require expensive drugs or are linked to severe adverse effects (e.g. a substantial ototoxicity and nephrotoxicity of Streptomycin in the WHO-recommended treatment of Buruli ulcer). Consequently, an intensified approach to and active case detection of patients is necessary to not only identify them and possible transmission foci but to also treat them with adequate medicine. Moreover, the development of cheaper and more effective diagnostic tools is promoted, and people in the affected regions are distinctively apprised by IEC (a strategy applied in the combat against other NTDs, too) [127]. Vector ecology and management addresses dengue and chikungunya virus infections, which are transmitted by arthropods and for which treatment options do not exist (yet). To successfully fight such infections (as it was attempted during recent outbreaks of zika, dengue or chikungunya), a rational use of pesticides especially in large urban areas is a promising strategy. Neglected zoonotic diseases, a sub-entity of NTDs, are transmitted by infected animals – whether it is livestock (transmitting foodborne trematode infections like fascioliasis or taeniasis / cysticercosis) or domesticated respectively wild animals (for echinococcosis, rabies and snakebite envenoming). Especially for livestock, effective therapeutics are available (like ABZ, PZQ or Triclabendazole), which do not only cure the infected animals but also prevent them from spreading such NTDs to

other animals or humans. Since animals play an important role in many developing countries because of culture, relationships or livelihood (with limited or no access to veterinary medicine), neglected zoonotic diseases are separately addressed by the WHO [141].

Despite the high social, medical and structural obstacles that have been appearing in the last years (civil uprisings in eastern DRC and western Cameroon, the Ebola virus outbreaks in West Africa and eastern DRC, religious and tribal tensions in Central Africa and Yemen), successes are already visible (just to name a few):

- blinding trachoma was eliminated in Oman (2012), Morocco (2016), Mexico, Laos and Cambodia (2017), Nepal and Ghana (2018), Iran and China (2019) and ultimately in Myanmar (2020) [120];
- dracunculiasis (guinea worm disease) has been pushed to the verge of elimination – from 3.5 million cases in 1985 to only 15 reported cases in 2021 (detected in Chad, Ethiopia, Mali and South Sudan) [133, 136];
- the number of confirmed cases of HAT dropped from 6,747 in 2011 to less than 1,000 today [120, 137]. By now, most cases are found in the DRC where, in 2017, 78 % of all infections with *Trypanosoma brucei gambiense*, the western and central African type responsible for 98 % of all HAT manifestations, occurred. Great efforts are under way in the DRC to achieve the 2020 goal. Promisingly, the lately rediscovered Fexinidazole seems to be an even more effective therapeutic agent to conquer west African HAT as a public health burden than the already highly effective Nifurtimox – Eflornithine combination therapy and has thence been added to the WHO List of Essential Medicines [16, 137, 147].

2.5.1 Water, sanitation and hygiene

A safe and reliable access to clean drinking water is paramount for all humans, regardless of origin, race or wealth. This tremendous value of water quality was highlighted by the international community in the SDG 6.1 ‘By 2030, achieve universal and equitable access to safe and affordable drinking water for all’ [111]. Most NTDs are directly linked to a lack of clean water – and to logical consequences of this: a shortage of proper sanitation and adequate hygiene, which the United Nations also dedicated themselves in the SDG 6.2 ‘By 2030, achieve access to adequate and equitable sanitation and hygiene for all and end open defecation, paying special attention to the needs of women

and girls and those in vulnerable situations' [111]. The WHO strategy of WASH addresses these targets, defined as one of five crucial pillars to combat NTDs in 2012 [133]. Supervising the implementation and progress of WASH, the Joint Monitoring Programme for Water Supply and Sanitation (JMP) by the WHO and the United Nations Children's Fund (UNICEF) supply extensive data of global developments towards SDG 6. The JMP emphasises the following aspects of WASH under the target 'Leave no one behind':

- [to end] open defecation;
- [to reduce] inequalities in basic water, sanitation and hygiene services;
- [to reduce] inequalities in safely managed water and sanitation services [114].

In all three aspects, Africa still seems to require intensified attention from the international community. The region shows high numbers of people living with not even basic drinking water service (436 million in 2017), open defecation (234 million in 2017) and a lack of basic handwashing facilities (600 million in 2015). Such numbers contribute to the large burden of NTDs still found throughout the continent. Especially schistosomiasis and STH rely on human contact to contaminated water, on excretion of eggs or larvae into habitats they can dwell in and on sparse hygiene after defecation and urination.

Compared to most other SDG regions, sub-Saharan Africa made slow progress in continuously improving the WASH conditions from 2000 to 2017. An exception to this is Oceania, where the situation on safely managed drinking water and sanitation appears to have deteriorated. Nonetheless, WASH contributed to an absolute increase in access to at least basic drinking water service of 15.2 %, being the largest leap forward compared

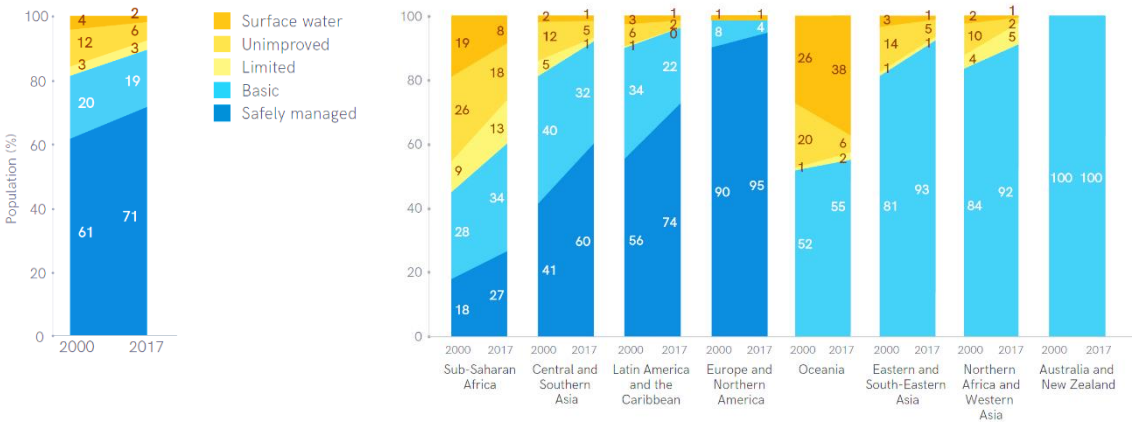


Figure 2: Drinking water coverage from 2000 to 2017, globally (on the left) and in the eight different SDG regions (on the right) (numbers within the graph in %). Resource: [114] The definition of the five categories is to be found in Figure 3.

to the other SDG regions (refer to Figure 2). Focussing on the countries of research, Tanzania exceeded this sub-Saharan average, improving by 29.5 % to 56.7 %. Ghana improved access to at least basic drinking water by 17.0 % to a total of 81.5 %. Although Côte d'Ivoire achieved slight increases, by 2.1 % to 72.9 %, the country was not able to reduce the dependence on surface water. Even though – among other steps – the national strategic plan to fight NTDs [72] focusses on the improving access to basic drinking water, Burkinabé people experienced a more aggravated access (reduced by 7.0 % to 47.9 %) to it (refer to Figure 3).

Analogous to the global progress, open defecation could be reduced by 13 % from 2000 to 2015. Herein, Burkina Faso took a major step forward by a 24.7 % absolute risk reduction (ARR). Both Côte d'Ivoire (10.4 % ARR) and Ghana (3.8 % ARR) were able

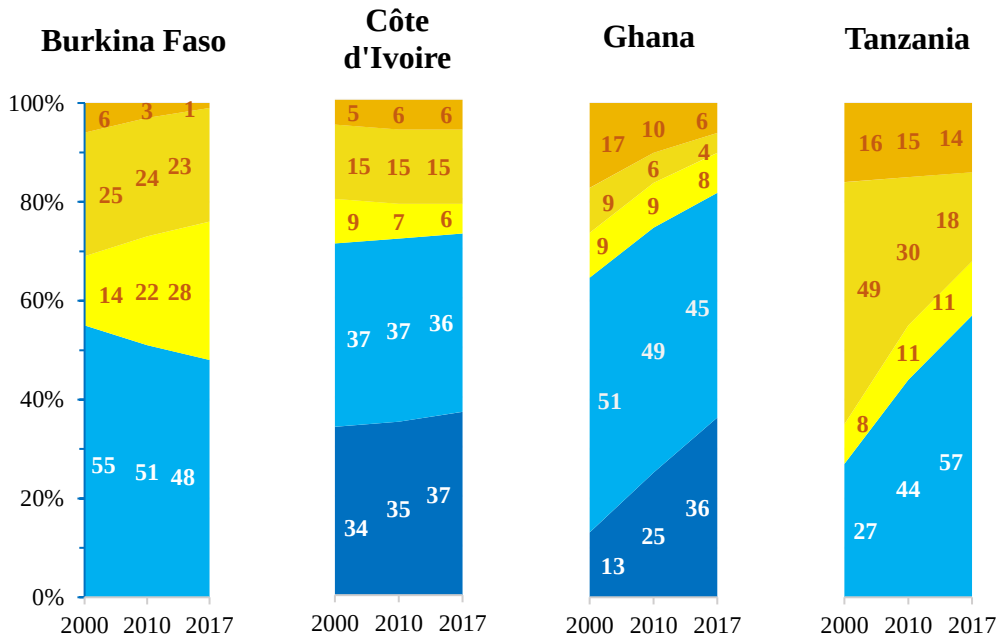


Figure 3: Access to drinking water in Burkina Faso, Côte d'Ivoire, Ghana and Tanzania from 2000 to 2010 to 2017 (population numbers within the graph in %). Resource: [112]

The following classification applies to all drinking water data of the JMP (Resource: [113]):

- *Surface water:* Drinking water directly from a river, dam, lake, pond, stream, canal or irrigation channel
- *Unimproved:* Drinking water from an unprotected dug well or unprotected spring
- *Limited:* Drinking water from an improved source where collection time exceeds 30 minutes for a roundtrip, including queuing
- *Basic:* Drinking water from an improved source provided collection time is not more than 30 minutes for a roundtrip including queuing
- *Safely managed:* Drinking water from an improved source, which is located on premises, available when needed and free from faecal and priority contamination (data were not always consistent and thus not always available)

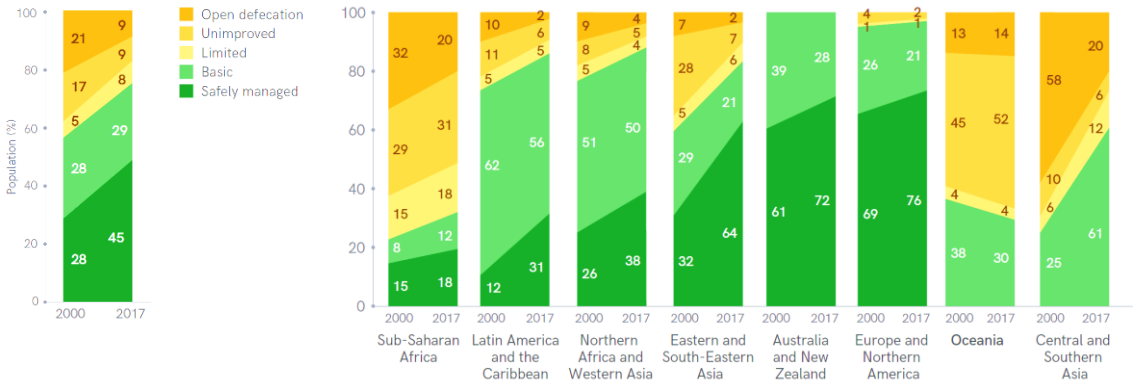


Figure 4: Sanitation coverage from 2000 to 2017, globally (on the left) and in the eight different SDG regions (on the right) (numbers within the graph in %). Resource: [114]
The definition of the five categories is to be found in Figure 5.

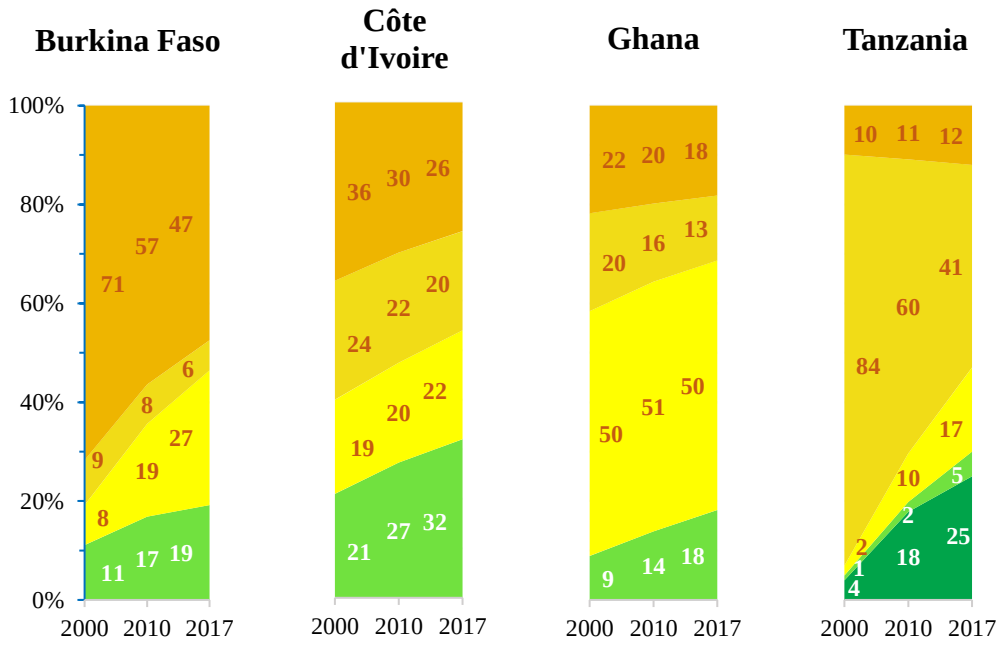


Figure 5: Access to sanitation in Burkina Faso, Côte d'Ivoire, Ghana and Tanzania from 2000 to 2010 to 2017 (population numbers within the graph in %). Resource: [112]

The following classification applies to all sanitation data of the JMP (Resource: [113]):

- *Open defecation:* Disposal of human faeces in fields, forest, bushes, open bodies of water, beaches or other open spaces or with solid waste
- *Unimproved:* Use of pit latrines without a slab or platform, hanging latrines and bucket latrines
- *Limited:* Use of improved facilities shared between two or more households
- *Basic:* Use of improved facilities, which are not shared with other households
- *Safely managed:* Use of an improved sanitation facility, which is not shared with other households and where excreta are safely disposed in situ or transported and treated off-site (data were not always consistent and thus not always available)

to lower the percentage of people practising open defecation. On the one hand, Tanzania experienced a slight increase in open defecation by an absolute 2.1 %. On the other hand, it significantly improved access to at least limited sanitation standard by 40.1 %. This approaches a fourfold improvement compared to the sub-Saharan average (refer to Figures 4 and 5). Despite the relative improvement in sanitation conditions, a growing population in Africa puts pressure on the sanitation infrastructure and results in more people being forced to practise open defecation (as to be seen in Figure 6: the tendency for sub-Saharan Africa unfortunately remained relatively stable over 15 years).

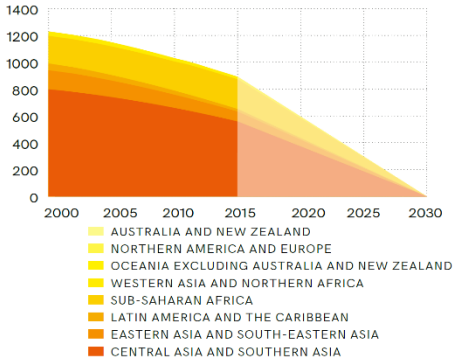
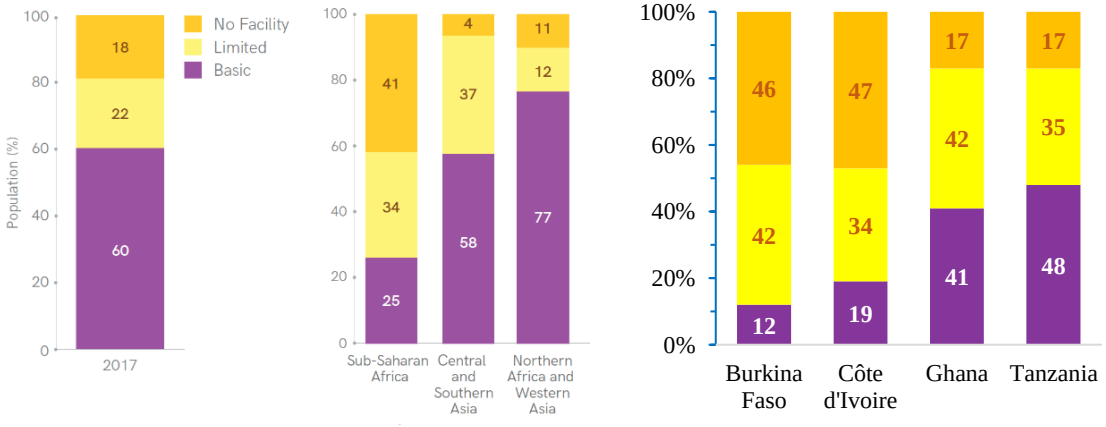
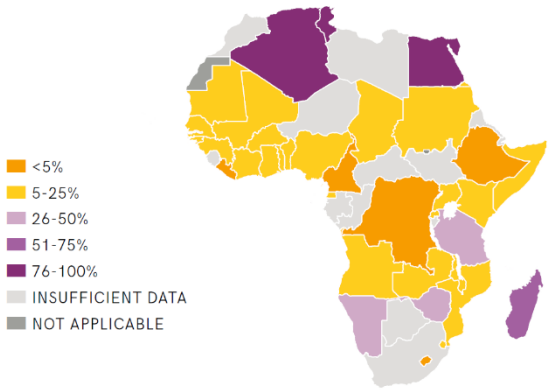


Figure 6: Global trend of reducing open defecation (2000 – 2015) and the prospect to the 2030 Agenda. Resource: [113]
Numbers are indicated per million.

The global availability of handwashing facilities shows a steep gradient: regions with insufficient water supply and obstacles in provision of adequate sanitation are clearly disadvantaged to industrialised nations. The global average of 60 % of the population having access to at least basic hygienic facilities is significantly undercut in sub-Saharan states (refer to Figure 7). This jeopardises health of inhabitants not only in terms of the fight against NTDs but also, for example, in development of extended drug-resistant bacteria. Within the region, disparities can be noticed (see Map 11). By 2017, Burkina Faso



Figures 7 + 8: Global (left), regional (middle) and local handwashing coverage (right) in 2017 (numbers within the graph in %). Resources: [112, 114]
The following classification applies to all sanitation data of the JMP (Resource: [113]):
No facility: No handwashing facility on premises
Limited: Availability of a handwashing facility on premises without soap and water
Basic: Availability of a handwashing facility on premises with soap and water



Map 11: African population with access to basic handwashing in 2015. Resource: [114]

and Côte d'Ivoire for instance were not able to provide people with the sub-Saharan average of 25 % of basic handwashing facilities – they even exceeded the proportion of inhabitants having no hygienic equipment at all. Compared to 2015, neither of them seemed to make progress in changing this: 16 % of the Burkinabé lost access to limited facilities, only 1 % of the Ivorians gained access to basic coverage. Ghana and Tanzania, on the other hand, have reached the global average of having no facilities at avail. Especially Ghana boosted handwashing hygiene, reducing the lack of amenities from 55 % (2015) to 17 % and increasing access to basic hygiene from 19 % (2015) to 41 %. Tanzania had started its WASH campaigns in the first decade of this millennium and performed well in enhancing the quality of hygienic infrastructure (refer to Figure 8) [112 – 114].

2.5.2 Preventive chemotherapy with anti-infective medicines

Up to 2019, Burkina Faso, Côte d'Ivoire, Ghana and Tanzania were making variable progress in providing the affected and threatened population with the support and medication needed (illustrated in Figures 9 and 10, as well as in Map 12). More recent data depicting the devastating consequences of COVID-19, as far as already available, were not taken into account.

Burkina Faso had early started with national campaigns to control NTDs. In 2001, MDA programmes to fight LF and STH were launched, followed by programmes against onchocerciasis and schistosomiasis in 2002 and action against blinding trachoma in 2007 [72]. Benefitting from them, the country achieved an advanced status in the combat against the five NTDs with validated PC (blinding trachoma, lymphatic filariasis, onchocerciasis, schistosomiasis in school-aged children – with an estimated prevalence of just 4.0 % in 2019 compared to 17.5 % in 2010 [60] – and STH in pre-school and school-aged children [142]). Blinding trachoma and STH were pushed back to such extent in the affected (and targeted) population that from 2018 onwards, a strategy of mere surveillance was considered sufficient. Onchocerciasis, continuously covered by more than 80 %,

dropped by 15 %. Schistosomiasis coverage was marginally decreasing – still beyond 80 % – while LF control, despite having reached just 80 % in 2019, turned more and more regions into a status of post-intervention surveillance [118]. As a result, the prevalence of schistosomiasis decreased by 77.9 % between the intervals 2000 – 2010 and 2015 – 2019 (78.5 % for *S. haematobium* and 70.7 % for *S. mansoni*), making Burkina Faso the (relatively) most successful country of sub-Saharan Africa in the combat against bilharzia [61].

Côte d'Ivoire began its fight against these five NTDs later than its north-eastern neighbour. Activities against onchocerciasis were resumed in 2002, effective MDA for LF, schistosomiasis and STH commenced in 2012. Blinding trachoma was not regarded as a public health issue for many years until a re-mapping of regional prevalence showed increased numbers. Hence, the successes in treatment coverage were not as remarkable as they were in Burkina Faso, but the country was catching up. MDA for blinding trachoma began in 2016 and reached 38 % of all threatened people by the next year. After plummeting to non-coverage, it recovered to 33 % in 2019. LF coverage almost trebled in two years (at 72 % in 2017), remaining stable then. Schistosomiasis coverage increased more than fivefold to 94 % before dropping to 54 % in 2019 – for this period, the prevalence dropped by 54.9 % (67.0 % for *S. haematobium* and 44.4 % for *S. mansoni*) compared to the years 2000 – 2010 [61]. Onchocerciasis was brought under almost full control in terms of MDA. STH treatment coverage dropped slightly (with a rogue result of 55 % in 2018), reaching 2.10 million out of an estimated 2.28 million affected children in 2019 [119]. Overall, Côte d'Ivoire fluctuates between 'progressing' and 'on track', with significant potential in improving MDA for blinding trachoma.

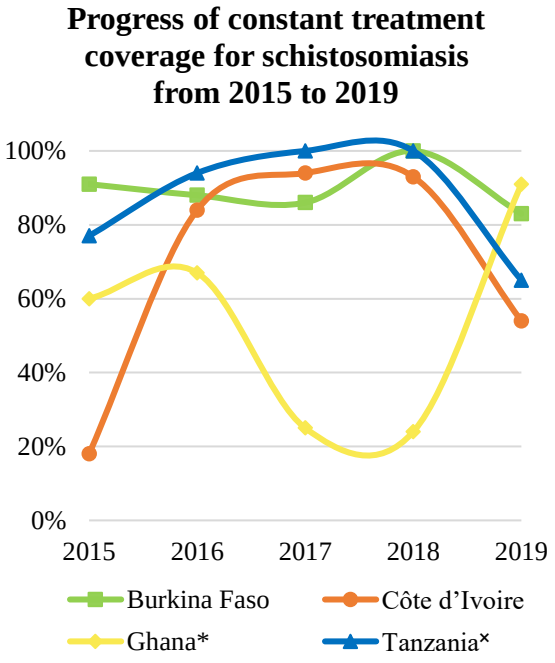


Figure 9: Progress of constant treatment coverage for schistosomiasis from 2015 to 2019. Resources: [118, 119, 121, 123]
(*): inconsistent data for 2018
(×): inconsistent data for 2016, thus average

Ghana implemented control programmes around the same time as the other two West African states (blinding trachoma and LF in 2001, STH in 2007 and schistosomiasis in 2008) – except for onchocerciasis programmes that date back to 1974. The strategies though were not making equal progress. The goals of the government were quite ambitious: elimination of trachoma, 92 % control over LF and 100 % control over onchocerciasis, schistosomiasis and STH by 2018 [33]. In reality, elimination of blinding trachoma was successfully reached in 2018. Constant treatment coverage of the four other NTDs had resurged by 2019 after an intermediate drop: LF from 49 % to 73 %, onchocerciasis from 55 % to 86 %, STH from 11 % to 37 %, and schistosomiasis from 24 % to an impressive 91 %. Ghana apparently put large focus on the WHO certification to be free of blinding trachoma but seems to temporarily have neglected MDA for the other PC NTDs [121]. By 2019 nonetheless, the country had accomplished to almost be 'on track'; the prevalence of schistosomiasis has decreased by 64.6 % (68.0 % for *S. haematobium*, 57.5 % for *S. mansoni*), above sub-Saharan African average, as well [61].

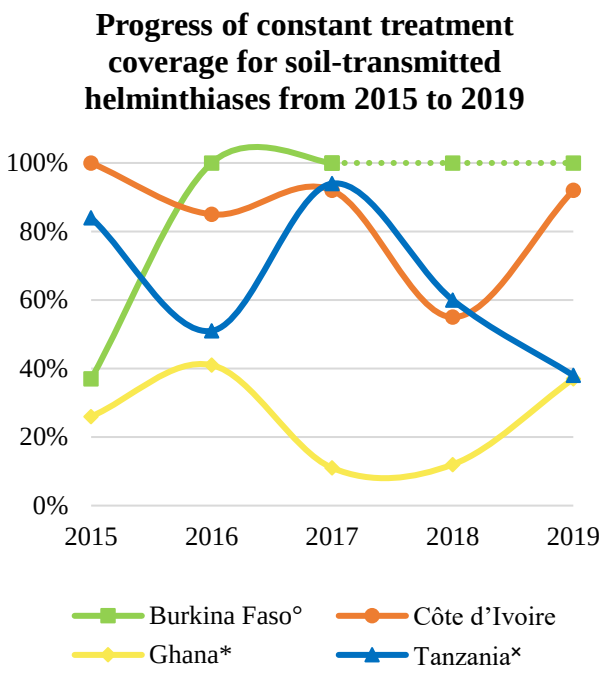
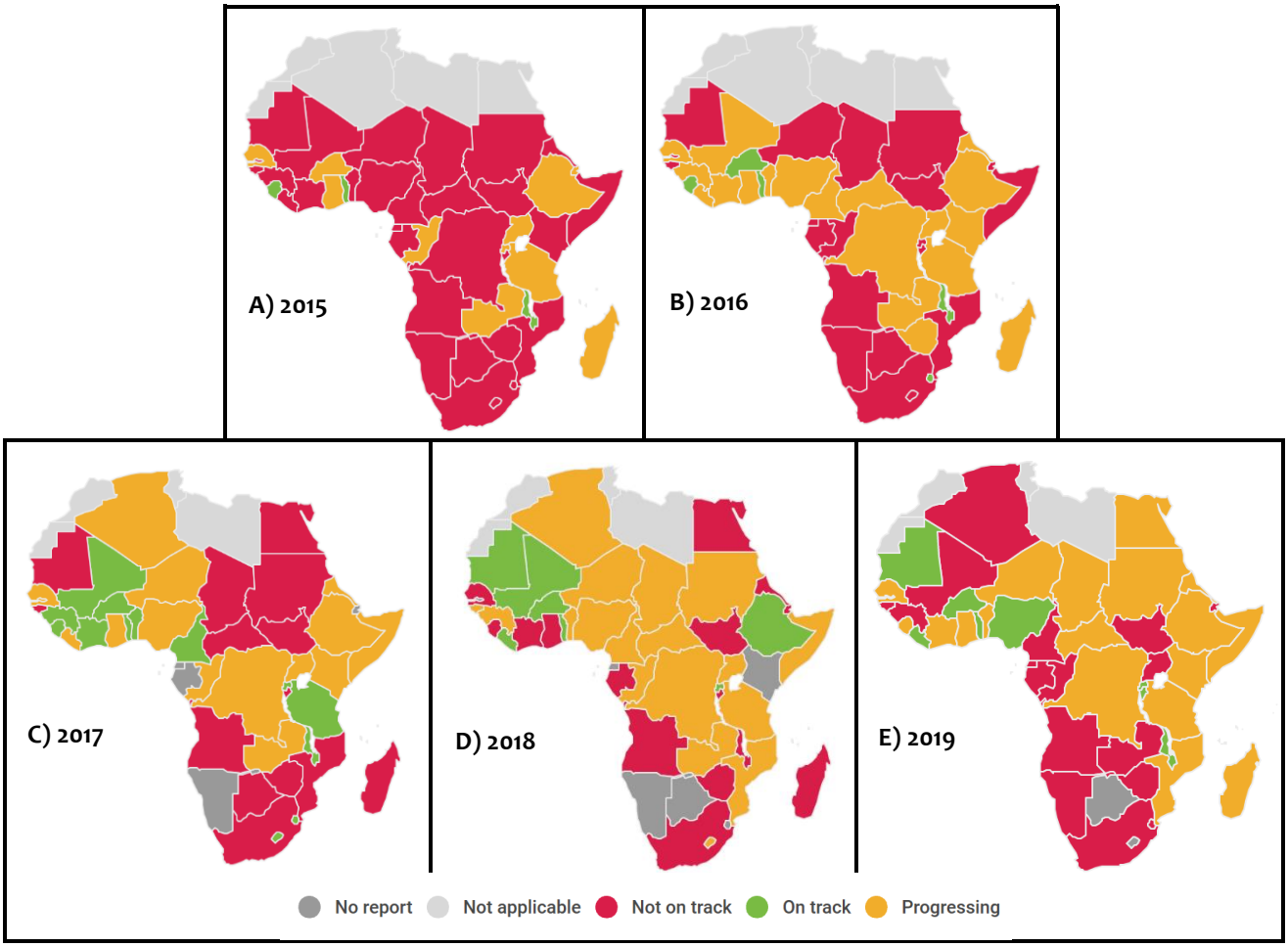


Figure 10: Progress of constant treatment coverage for soil-transmitted helminthiases from 2015 to 2019. Resources: [118, 119, 121, 123]
(°): from 2018 on surveillance status
(*): inconsistent data for 2018
(×): inconsistent data for 2016, thus average

Tanzanian authorities had soon realised the necessity of controlling NTDs. Steps against onchocerciasis were taken in 1994, followed by an enhancement in actions against blinding trachoma in 1994. National strategies against LF were put into practice in 2000, and schistosomiasis and STH were combatted as of 2004 [82]. Within the scopes of the WHO action plans however, the country's endeavours had to regain strength. In 2015 and 2016, the nationwide coverage of MDA for blinding trachoma was low (5 % and 7 %). Intensified efforts against this NTD resulted in a coverage of 41 % in 2019 (after a peak of 82 % in 2017). LF and onchocerciasis coverage rates climbed well above 80 % by 2018

before a sharp drop to 15 % set back LF control. Schistosomiasis coverage reached 100 % before decreasing by one third in 2019. Apart from an intermediate peak of 94 %, the approaches against STH gradually decreased to 36 %. As a result, the average treatment coverage with appropriate medicines merely passed 40 % [123]. The relative reduction in prevalence of schistosomiasis has not been as effective as in the three West African countries either: between 2000 – 2010 and 2015 – 2019, only a drop of 51.6 % (59.8 % for *S. haematobium* and 37.8 % for *S. mansoni*) could be reached, trailing well behind the sub-Saharan African average of 60.5 % (67.9 % for *S. haematobium*, 53.6 % for *S. mansoni*) [61].

Whatever progress one of these nations made: they have been administering PC depending on population groups, prevalences, co-endemicities and developments. Often these rounds of MDA of PC target not only one but more of the NTDs – especially when



Map 12: Progress of constant treatment coverage for the five NTDs blinding trachoma, LF, onchocerciasis, schistosomiasis and STH in Africa from 2015 (A) to 2019 (E). Resources: [117] Not on track: constant treatment coverage less than 25 %; Progressing: constant treatment coverage 25 % to 74 %; On track: constant treatment coverage 75% or above.

distributed in combination, which is highly desirable and thus supported by experts [67, 70]. When, for instance, issuing IVM and ABZ in a first round, LF, onchocerciasis and STH likewise are treated. Another round, e.g. PZQ and ABZ / MBZ, would cure schistosomiasis and take the high likelihood of a re-infection with STH into account. The following medicines are applied in specific regimes (donated under the London Declaration) [137]:

- Azithromycin is applied in blinding trachoma (and yaws [94]);
- LF is targeted by a combination of IVM and ABZ complemented by Diethylcarbamazine (DEC) (when ruling out co-endemicity of onchocerciasis) [71, 83];
- onchocerciasis is treated with IVM, which may be – as in LF – preceded by targeting bacterial endosymbiotic *Wolbachia* spp. with Doxycycline (in countries with co-endemic loiasis: initial therapy of loiasis with DEC, when necessary prior reduction of microfilaraemia beyond 1000/ml with ABZ) [83];
- schistosomiasis with PZQ;
- and STH with both ABZ and MBZ.

As effective as PC for schistosomiasis and STH may be in (pre-)school-aged children – the sub-Saharan African prevalence of schistosomiasis in this age group has significantly dropped from 23.0 % in 2010 to 9.6 % in 2019 [61]: the burden of disease reaches throughout the whole population. Patients beyond the target groups of the donation programmes (people at risk like pregnant women, fishermen or others) are jeopardised by escaping transmission control and developing chronic sequelae like anaemia or malnutrition [67]. They need to acquire the drugs of choice – ABZ, MBZ and PZQ – on the open market, where a wide range of products from different companies is offered.

2.5.2.1 Albendazole

ABZ is a synthetic nitroimidazole / benzimidazole that was first introduced in 1972 for veterinary use before being approved for human treatment in 1982. It is a broad spectrum anthelmintic drug, highly effective against nematodes like *Enterobius vermicularis*, *Ascaris lumbricoides* or *Ancylostoma duodenale* / *Necator americanus*. *Strongyloides* spp. or *Filaria* spp. as *Wuchereria bancrofti* or *Brugia malayi* are strongly targeted as well, even though IVM is regarded as the medicine of first choice. *Trichuris trichiura* responds inferior to ABZ than other nematodes. Helminthiases caused by *Echinococcus*

spp. are preferably treated with ABZ, too (higher doses in a prolonged regime are required, though – patients suffering from inoperable alveolar echinococcosis may just control and contain the infection by lifelong therapy). In patients suffering from clonorchiasis, neurocysticercosis (caused by *Taenia solium*, here concomitantly to PZQ and often glucocorticoids), opisthorchiasis, toxocariasis and trichinellosis, ABZ is also used.

ABZ irreversibly binds to the β-subunit of the nematodal tubulin molecule, leading to a blockage of the fluke's microtubule assembly. This causes immobilisation of the parasites, loss of the tegumental integrity, a certain ovicidity and a restriction of glucose uptake with the consequence of depletive glycogen and adenosine triphosphate (ATP) levels, which ultimately leads to the worms' death. In higher concentrations, a direct interference with the citric acid cycle is discussed, leading to a reduced production of ATP and the consequences mentioned before. Thereby, Albendazole itself is toxic to intraluminal intestinal flukes. Extraluminally situated helminths (*Ascaris* passing through the lungs, neurocysticercosis, *Echinococcus granulosus*) are affected most by Albendazole sulfoxide (ABZSO), the active compound ABZ is converted to during hepatic first-pass metabolism (refer to Figure 11).

ABZ is poorly absorbed when taking purely or together with; however, its bioavailability increases significantly (up to sixfold) when ingesting with high-fat foods. Simultaneous intake with Cimetidine, Dexamethasone or PZQ were reported to improve systemic concentrations of ABZ likewise. A concomitant intake of the anti-epileptics Carbamazepine, Phenobarbital and Phenytoin appears to cause a decrease in concentration. Relevant levels of ABZSO can be detected in serum (serum half-life between eight and 15 hours, depending on the dose), bile fluid, lung and liver tissues, cerebrospinal fluid (ABZSO passes the blood-brain barrier) and hydratid cysts of *Echinococcus granulosus*.

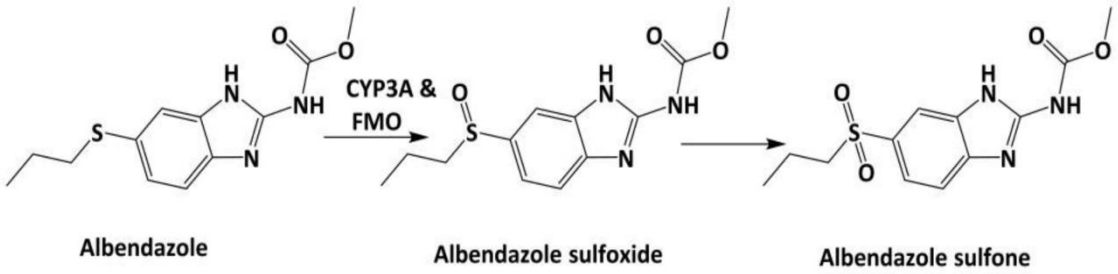


Figure 11: The steps of metabolisation from ABZ to ABZSO and further to ABZ sulfone. Resource: [34]
CYP3A: Cytochrome P 450 3A [enzyme]; FMO: flavin[-containing] monooxygenase

PC with ABZ is usually administered as an annual single dose of 400 mg (200 mg in children under two years of age). For proper treatment however, higher concentrations are sometimes needed (not exceeding 800 mg per day whatsoever), on extended regimes – ten to 14 days in strongyloidiasis; a second dose after two weeks in oxyuriasis; several years in alveolar echinococcosis. Side effects rarely appear when taking ABZ over a short period of time (allergic, gastrointestinal or central nervous symptoms). Despite suspected, significant embryotoxicity cannot be seen at a relevant scale. Under long-lasting therapy, hepatotoxicity and myelotoxicity must be mentioned, which is why a regular determination of serum concentrations of ABZSO may be recommended [64, 78, 83, 95].

2.5.2.2 Mebendazole

Like ABZ, MBZ is a synthetic nitroimidazole / benzimidazole that was introduced in the early 1970s. It is a broad spectrum anthelmintic drug, highly effective against intestinal nematodes like *Enterobius vermicularis*, *Ascaris lumbricoides* or *Ancylostoma duodenale* / *Necator americanus* (even though ABZ nowadays is preferred over MBZ). *Trichuris trichiura* responds inferior to MBZ, as it does to ABZ (either drug for several days or in combination with ABZ or IVM might ameliorate the efficacy). In patients suffering from echinococcosis or trichinellosis (here in combination with systemic glucocorticoids), MBZ can also be used.

Analogous to ABZ, MBZ binds irreversibly to the β-subunit of the nematodal tubulin molecule, leading to a blockage of the fluke's microtubule assembly. This causes immobilisation of the parasites, loss of the tegumental integrity, a certain ovicidity and a restriction of glucose uptake with the consequence of depletive glycogen and ATP levels, which ultimately leads to the worms' death. Mebendazole itself affects parasites intraluminally and extraluminally likewise, undergoing major hepatic first-pass metabolism. Contrary to ABZ, MBZ metabolites do not play a significant role as anthelmintic agents: out of the three existing polymorphic forms, polymorph C appears to be the clinically most active and effective one (refer to Figure 12).

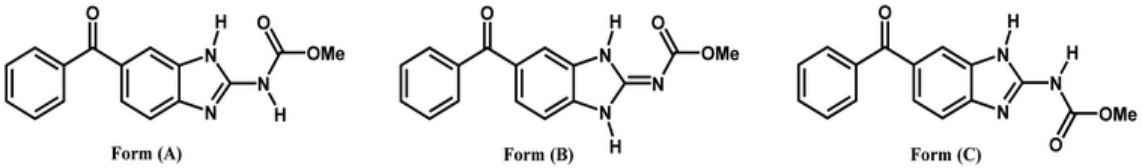


Figure 12: Chemical structures of the three Mebendazole polymorphic forms, with Form (C) being the clinically most active one. Resource: [2]

MBZ is poorly absorbed when taking purely or together with water; albeit its bioavailability increases by concomitant ingestion with high-fat foods, absorption rates do not exceed 10 %. Carbamazepine and Phenytoin seem to lower its concentration. Relevant MBZ levels can be detected in serum (serum half-life between 2.8 and nine hours, depending on the dose), bile fluid, liver tissue, cerebrospinal fluid (MBZ passes the blood-brain barrier) and cysts of *Echinococcus* spp.

Annual PC with MBZ is usually administered as a single dose of 500 mg. For proper treatment however, two regimes are possible (not exceeding 500 mg per day whatsoever): either a single dose of 500 mg, or 100 mg twice per day for three consecutive days. Adjuvant therapy of cystic echinococcosis takes up to 28 days (compare to ABZ). Side effects rarely appear when taking MBZ over a short period of time (gastrointestinal symptoms like diarrhoea or abdominal pain). Even though suspected (especially in the first trimenon), relevant teratogenicity has not been observed. Under long-lasting therapy, hepatotoxicity, myelotoxicity and CNS affection must be kept in mind [64, 78, 83, 130].

2.5.2.3 Praziquantel

PZQ is a synthetic pyrazinoisoquinoline that was developed in the early 1970s and first applied in human treatment in 1980 (Figure 13). It is a broad spectrum anthelmintic drug, highly effective against virtually all trematodes (except for *Fasciola hepatica*, which is treated with the narrow-spectrum benzimidazole Triclabendazole) and against cestodes like *Taenia* spp., *Diphyllobothrium latum* and *Hymenolepis nana.*

PZQ increases the permeability of the parasites' tegument, with the result of a calcium influx into the worms. Elevated calcium concentrations lead to tetanic contractions and subsequent muscular paralysis causing the helminths to lose adherence to the tissue they are dwelling in. Additionally, concealed antigens are exposed by the disruption of their tegument. Metabolites of PZQ do not show any relevant therapeutic effect. The drug (serum half-life up to 1.5 hours) is well absorbed in the intestines (bioavailability beyond 80 %, even better when ingested with foods rich in fats and carbohydrates) but reaches systemic circulation in

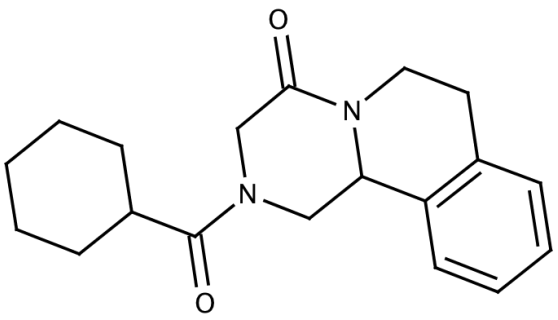


Figure 13: Chemical structure of Praziquantel. Resource: [35]

merely small concentrations due to extensive hepatic first-pass metabolism. As PZQ passes the blood-brain barrier, it should cautiously be administered in patients with neurocysticercosis (50 – 100 mg/kg body weight, twice daily for several weeks depending on the exact localisation, and combined with ABZ, glucocorticoids and – if needed – an antiepileptic to reduce an inflammatory reaction accompanying cysticercal lysis and to prevent potential seizure).

Annual PC for schistosomiasis with PZQ is usually administered as a single dose according to body size: one tablet of 600 mg from 94 cm, up to five tablets (3 g) for people taller than 177 cm [128]. The therapy of schistosomiasis (depicted in Chapter 2.1) and other flukes and cestodes depends on the species:

- *Clonorchis* spp., *Opisthorchis* spp. and *Paragonimus* spp. demand higher concentrations of PZQ: 25 mg/kg body weight thrice daily, for two (to three) consecutive days;
- for intestinal flukes, a single dose of 25 mg/kg body weight once is sufficient;
- cestodes are treated with 10 – 20 mg/kg body weight as a single dose.

PZQ is usually well tolerated, with mild forms of nausea, emesis and abdominal pain reported within 30 minutes after medication intake. The higher the infestation with parasites, the more distinct the symptoms present. However, besides taken with care in the first trimenon of pregnancy and in patients with hepatic impairment, PZQ is metabolised by the Cytochrome P450 3A4 system and thus interacts with other drugs like Rifampicin, Dexamethasone or Carbamazepine (all reducing the concentration of PZQ) [69, 78, 83].

3 Material and methodology

3.1 Ethics

Ethical clearance for publication in Tanzania had been granted by CUHAS in September 2018 before having started to analyse the samples in Mwanza (Research Clearance Certificate Number CREC/304/2018 – attached in the Appendix: IVa Ethical clearance from CUHAS) and was extended to August 2020. The ethical committee of JMU Würzburg regarded a separate ethical clearance for Germany as not necessary.

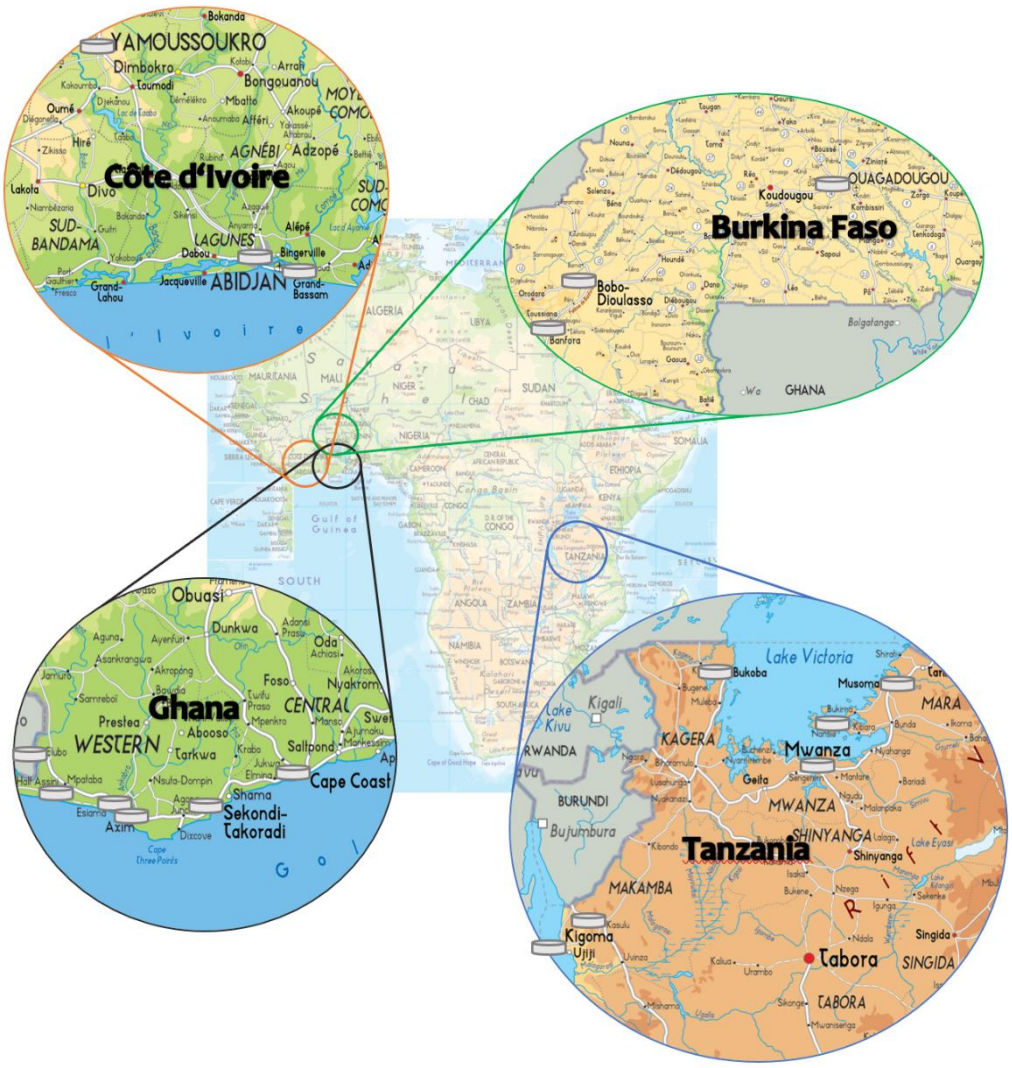
3.2 Trial design and survey area

To depict the current situation on the medicine market of ABZ, MBZ and PZQ in West Africa – choosing Ghana, with its health system still being influenced by the old English colonial ages, and Burkina Faso and Côte d'Ivoire, whose health systems have been developed out of the French health system – and East Africa on the example of the Lake Zone area in Tanzania, a cross-sectional study was purposed. This design suit best because of the interest in the status quo of the availability of different anthelmintic drugs, regardless of any changes in official licensing or customers' preferences.

3.3 Drug collection in West Africa

3.3.1 Sampling in Ghana

Due to the long-standing collaboration between MMI Würzburg and St. Martin de Porres Hospital in Eikwe, acquisition of ABZ, MBZ and PZQ samples in Ghana was coordinated from here. As the next larger city, Sekondi-Takoradi (SK-TK), is reached after a minimum of two hours of public transport, smaller towns in the closer vicinity of Eikwe were highlighted. Hence, samples were collected, from east to west, in Axim, in Essiama (a local hub for changing public transport towards SK-TK in the east and towards the Ivorian border in the west), in Eikwe itself and in Elubo (a border town along the important Abidjan – Lagos connection). On two occasions, travelling further to the east allowed to collect samples from SK-TK (more than 300,000 inhabitants) and Cape Coast with more than 150,000 inhabitants (Maps 13 and 14). An overt approach was chosen, as these three anthelmintics are usually available without having to hand in a prescription.



Map 13: Overview of the different sites of sample collection throughout Burkina Faso, Côte d'Ivoire, Ghana and Tanzania. Resources (adapted): [25 – 28]
A grey tablet does not indicate a certain quantity but the place of sample collection.

In only one wholesale pharmacy in SK-TK, a prescription for PZQ was demanded because a of shortage of PZQ – which was noticed throughout south-western Ghana: obtaining PZQ for treatment was difficult. In smaller towns, vendors were chosen randomly on advice of the local people. In both Cape Coast and SK-TK, most of the pharmacies are gathered around town centre (along Kotokuraba Road in Cape Coast and around the central market of Takoradi): here, the respective areas were visited and pharmacies to acquire samples from were randomly chosen. Most vendors sold different products of ABZ and MBZ; thence, particularly products that had not been acquired before were selected. Preferably, a minimum of 20 tablets per brand / batch were purchased, utilising them for Minilab™ testing and for HPLC analyses at the Institute for Pharmacy and Food

Chemistry of the JMU Würzburg as well. This complies with suggestions of Newton et al. [84] that a dosage size of 30 tablets may well be enough to perform physico-chemical analyses like an HPLC but sometimes be hard to obtain (especially in rural areas) and induce the sellers' alertness. According to them, a smaller number would be equally acceptable. It was the initial plan to reach this number in two steps (two times at least ten samples) to be able to screen different batches of a product. Unfortunately, this goal could not always be achieved – the large number of miscellaneous products was not distributed equally, and in the case of *Sequizol*, two different batches were handed out unnoticed. The number of tablets per batch collected in March and April 2019 varied between five (the ABZ product *Sequizol* by Prowill

Image 1: Choice of anthelmintic drugs from West Africa.

Map 14: Sites of sample collection in south-western Ghana. Resource (adapted): [26]

Pharmaceuticals Pvt. Ltd. / India) and 30 samples (*Praziquantel 600* by Ernest Chemists Limited / Ghana). Taking the difficulties of assaying suspensions with the Minilab™ into account, they were largely left aside (only one product was bought).

25 separate batches of anthelmintic drugs were obtained – three of them, batch number (B. No.) J8024 of *Tanzol* by Shalina Laboratories Pvt. Ltd. / India, B. No. 02 of *Trazole-500* by Trade Winds Chemist Ltd. / Ghana and B. No. 0109T of *Praziquantel 600*, were bought twice; one MBZ brand, *Minazol* by Pokupharma Ltd. / Ghana, could merely be obtained as a single give and was consequently not taken into consideration for assay. Two products, *Wormron 400* B. No. WA1801 by Ronak Exim Pvt. Ltd. / India (ABZ) and *Mentel* B. No. 1708100 by Danadams Pharmaceuticals Industry Limited / Ghana (MBZ), were donated by the hospital pharmacy of St. Martin de Porres. As to Figure 14, the 21 different batches resulted in 13 different brands of ABZ (72.2 %), four MBZ brands (22.2 %) and one PZQ product (5.6 %). As all batches considered were obtained at a quantity of at least five tablets, they could properly be analysed back in Germany.

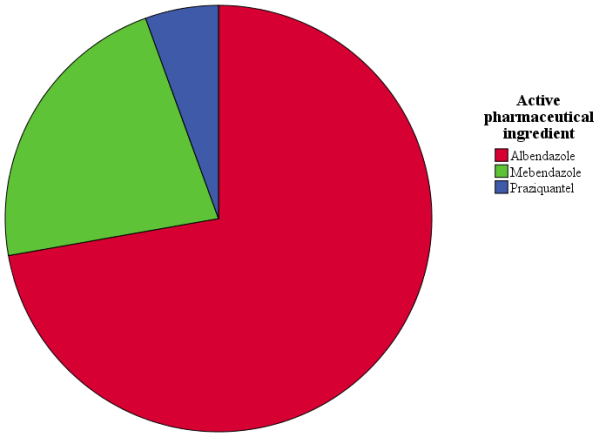
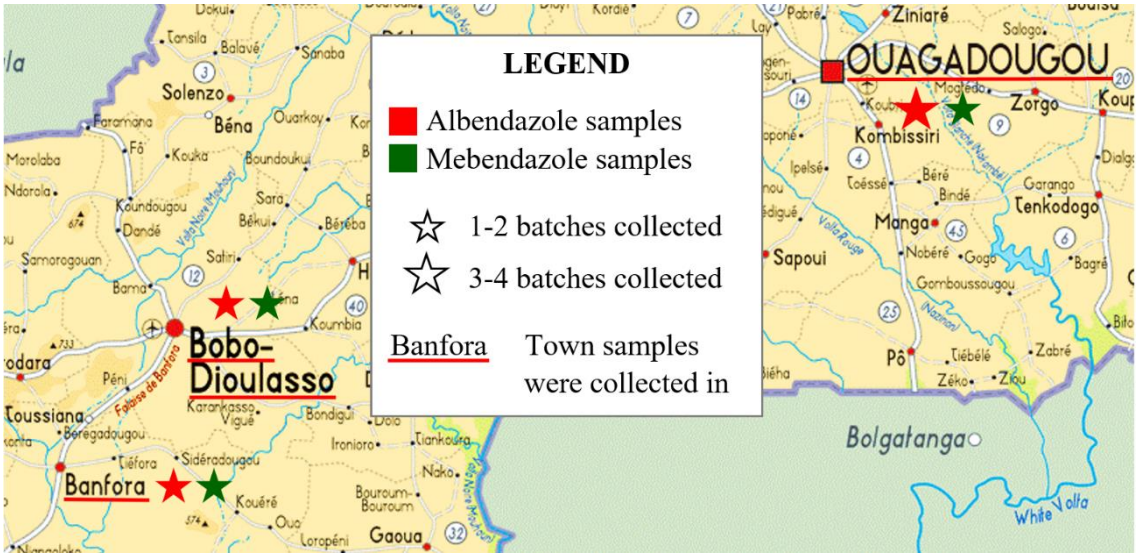


Figure 14: Distribution of API in the different brands collected throughout Ghana.

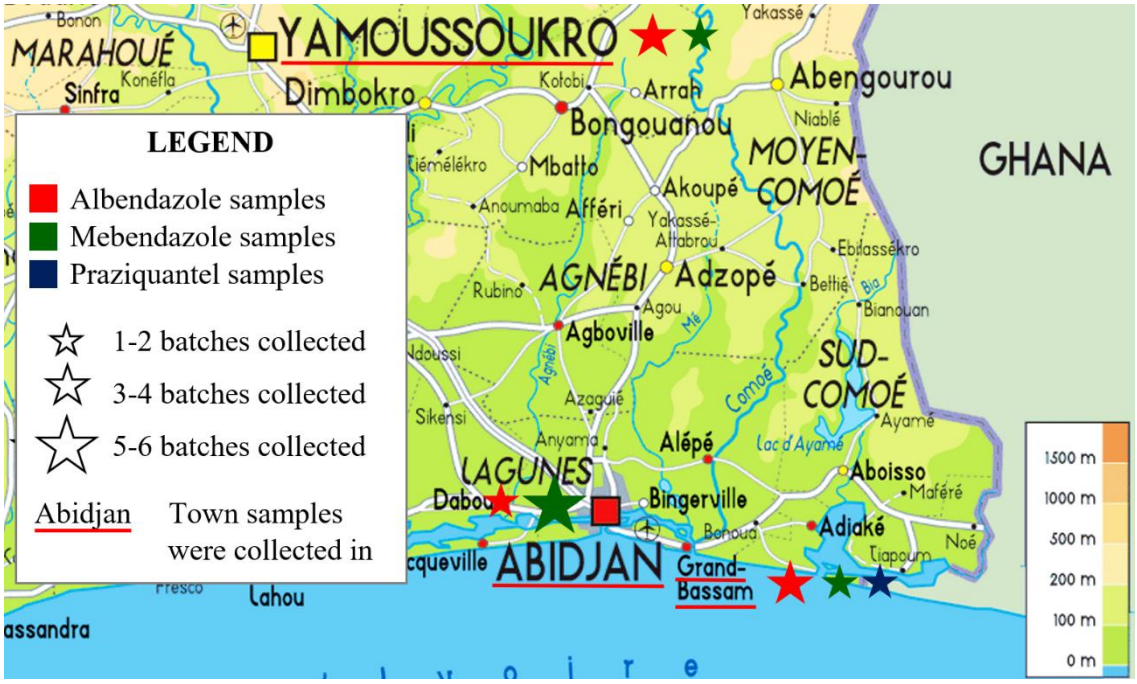
3.3.2 Sampling in Burkina Faso and Côte d'Ivoire

Samples in Burkina Faso and Côte d'Ivoire were gathered in larger cities than in Ghana. Focus was put on the large distribution centres, Abidjan and Ouagadougou, and on the more populous cities in between, such as Grand Bassam and Yamoussoukro in Côte d'Ivoire, and Banfora and Bobo Dioulasso in Burkina Faso (refer to Maps 13, 15 and 16). The overall range of different brands in both nations was very close to each other, owing to the same official language and Abidjan being the major port of entry for anything that is shipped to Côte d'Ivoire and Burkina Faso. Similar to Ghana, an overt approach was chosen: a prescription for anthelmintic drugs was not required either in both countries. The pharmacies to acquire ABZ, MBZ or PZQ from were randomly chosen when passing through the streets. In Burkina Faso, products were obtained from street



Map 15: Sites of sample collection in Burkina Faso. Resource (adapted): [25]

vendors in Banfora and Bobo Dioulasso as well – in contrast to the advice of some researchers, none of them seemed to care about foreigners buying drugs at their stalls. Newton et al. [84] recommend approaching especially anxious retailers and street vendors by an unbiased 'mystery shopper' to buy an adequate number of tablets without raising the counterpart's suspicion. The number of tablets to be obtained was calculated in reference to the Ghanaian procedure. It often occurred though that samples could not be bought in sufficient numbers because of not being in stock in quantities large enough. Consequent-



Map 16: Sites of sample collection in south-eastern Côte d'Ivoire. Resource (adapted): [27]

ly, the number of tablets per batch bought in April 2019 ranged between four (*Biltricide* by Bayer Pharma AG / Germany) and 60 units (a MBZ product from India, acquired at a street vendor in Banfora). Suspensions were not selected.

29 separate batches of anthelmintics were obtained – six of them, B. No. ABX1A83 of *ABZ* by Indoco Remedies Ltd. / India, B. No. 021217 of *Albendazole TM* by Tongmei Laboratoire / Togo, B. No. EC70059 of *Bendex-400* by Cipla Ltd. / India, B. No. 300191 of *Lyben* by Shandong Shenglu Pharmaceutical Co. / China (all ABZ), B. No. CB1015 of *Carben* by Bliss GVS Pharma Ltd. / India and B. No. TMZ9001 of *T-Medazol* by Sai Mirra Innopharm Pvt. Ltd. / India (both MBZ), were bought twice. As to Figure 15, the 23 different batches resulted in nine different brands of ABZ (50.0 %), eight MBZ brands (44.4 %) and one PZQ product (5.6 %). Except for *Biltricide* (only one jar with four tablets was acquired), all batches were considered for thorough assay in Germany – a quantity of at least five was obtained. *Biltricide* however is a PZQ originator brand that is also sold in Europe – these tablets were just prepared for disintegration, dissolution, thin-layer chromatography (TLC) and HPLC-UV (ultraviolet spectrophotometric detection of content).

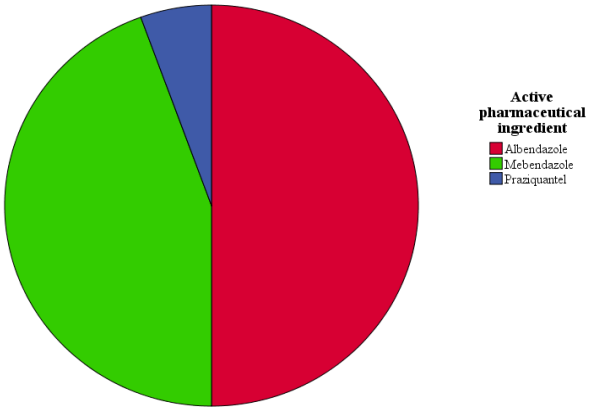


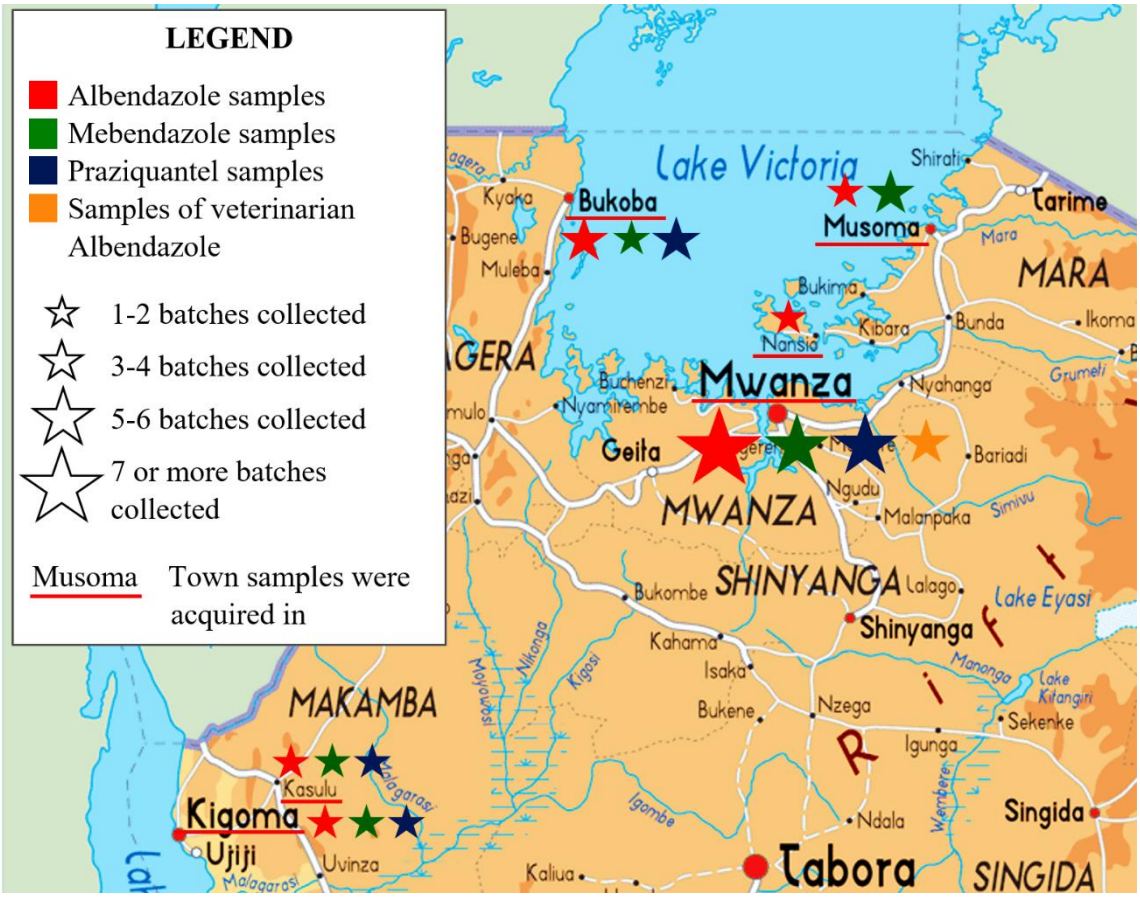
Figure 15: Distribution of API in the different brands collected throughout Burkina Faso and Côte d'Ivoire.

3.4 Drug collection in Tanzania

Drug collection took place in the city of Mwanza itself and, to obtain a better view on other local referral markets as well, in the cities of Bukoba, Musoma, Kasulu, Kigoma and Nansio on Ukerewe Island (refer to Maps 13 and 17). In collaboration with colleagues from BMC and CUHAS, a summary of local drug dealers in Mwanza was set up (concentrating around Nyerere Road in the city centre) and hence randomly chosen from. An overt approach was chosen as ABZ, MBZ and PZQ are available without handing in a prescription. These medicines as well as veterinarian ABZ (vetABZ) products were ob-

Image 2: Choice of anthelmintics from Tanzania.

tained by both local and German colleagues likewise. Outside Mwanza, a comparable strategy was applied: gathering information about the local pharmacies, dispensaries and smaller *duka la (ma)dawa muhimu* (Kiswahili expression for 'pharmacy of important medicines'), and then entering them and asking openly for different ABZ, MBZ or PZQ samples disposable. Correspondingly, the sources of acquisition covered hospitals' pharmacies (BMC Mwanza), pharmacies, dispensaries and *duka la (ma)dawa muhimu*. The idea of a 'mystery shopper' [84] was evaluated but then discarded. In Tanzania, TFDA – re-



Map 17: Sites of sample collection in north-western Tanzania. Resource (adapted): [28]

named Tanzania Medicines and Medical Devices Authority (TMDA) in 2019 – has done a lot to keep the sale of drugs under control. Street vendors have virtually disappeared, which is why a 'mystery approach' was not necessary while collecting the various samples. Just like in West Africa, the goal was to buy at least 20 tablets per brand / batch. Focus lay on tablets, which are sold more regularly than suspensions and of which ABZ, MBZ and PZQ samples can be purchased likewise (PZQ suspension are not available yet). Whenever retrievable, tablets openly sold out of larger containers were preferred over small sealed packages. In June, September and October 2018, a variable number of samples per batch was acquired, ranging from three tablets of *Vermox* (MBZ originator brand by Johnson & Johnson / South Africa) up to 50 tablets of *Albendafarm 1500* (a vetABZ drug by Chongqing Fangtong Animal / China).

Altogether, 47 separate batches of anthelmintics were collected (B. No. 180018 of *Alben* and B. No. 140007 of *Praziquantel-600*, both manufactured by Shelys Pharmaceuticals / Tanzania, and B. No. 256 of *Astazole* by Astra Lifecare / India were unfortunately bought twice), of which two – *Elyzole* B. No. 5I07 by Elys Chemical Industries Ltd. / Kenya and *Cesol* B. No. M74740 by Merck, S.A. de C.V. / Mexico – were received from CUHAS. As to Figure 16, these 44 batches could be classified into eleven different ABZ (39.3 %), eight MBZ (28.6 %; with *Astazole* being available as ten times ten tablets per blister and five times 20 tablets per two blisters sticking together), five PZQ (17.9 %) and four vetABZ brands (14.3 %). As explained before, 30 or more samples per batch could not always be bought. *Zentel* (by GlaxoSmithKline / GSK South Africa, four samples) and *Vermox* (three samples) were not bought in numbers large enough to fulfil the suggestion of Newton et al. to reduce the number of tablets acquired down to five to ten and thereby to at least bypass the problem of quantity of drugs per brand / batch [84]. All other products were gathered in numbers larger than five tablets per batch / brand.

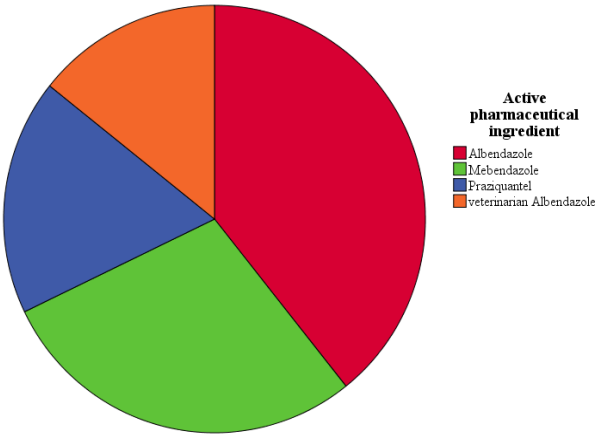


Figure 16: Distribution of API in the different brands collected in north-western Tanzania.

3.5 Physico-chemical analyses performed in reference to the Minilab™

Regardless of the evaluation of the API (either performed by TLC or HPLC-UV), non-destructive examination was conducted beforehand. In order not to alter the traits of the tablets, it was important to store them in closed containers protected from light at medium room temperature and controlled humidity. In West Africa, protection from light, humidity and dust was effectively realised as all samples purchased were sold in blisters (and packages). Transportation in moderate temperatures was difficult to achieve, owing to public overland transport through the region. In Tanzania, ambient conditions were mostly guaranteed by keeping the tablets in an air-conditioned (21 °C) sterile unit at the pharmacy of BMC. Shipping the samples from towns like Kigoma or Bukoba to Mwanza, temperature could not always be regulated equally – at least they were stored protected from sunlight and dust. Preliminary examination in terms of mass uniformity, disintegration profiles and TLC were carried out on-site in Mwanza. When buying several packages of one brand or batch (for example due to just one or two tablets per container), only a selected number was fully examined on-site – the rest of them were either brought to Germany and completely assayed in Würzburg before HPLC-UV testing or handed over to TMDA Mwanza for mutual Minilab™ QA. This portable laboratory incorporates the three analytical methods listed above (mass uniformity, disintegration times and TLC) and whose accessibility – more than 800 kits have been distributed and applied for QA in over 80 countries – contributes to its significance as an acknowledged method for especially rural quality control in LMICs [45, 49, 51, 90]. In terms of TLC, it is considered that the Minilab™ can only deliver semi-qualitative and negligible quantitative results.

Image 3: GPHF Minilab, applied at MMI Würzburg.

3.5.1 Appearance and packaging of samples

As soon as having acquired the tablets, a swift documentation of the packaging / the samples themselves (if received out of a dispenser merely in a sachet) was paramount. Photographs were taken of the containers, the blisters and the tablets to secure their condition before starting to analyse and compare them (camera used: Sony DSC-HX50V). Addressing the authenticity and genuineness of the tablets and their containers (wherever the respective samples can be bought in a packaging), the WHO has published a 'Tool for visual inspection of medicines' that thoroughly checks every possible aspect before actively altering a tablet's texture for analytical reasons [135]. An abbreviated form of this tool is to be found in the supplementary data (IVb Abbreviated 'Be Aware' tool: data form on the categorisation of the tablets' appearance and their packaging), which was routinely applied on-site. Herein, an inspection of the packaging and a characterisation of the physical aspects of a tablet are distinguished. Packages were checked for suitability of the container, an enclosed leaflet and adequate labelling indicating trade / brand name, name of the API, the manufacturer's name, logo and address, dosage form and statement, medicine strength, number of units per container, batch number, date(s) of manufacture (DoM) / date(s) of expiry (DoE) as well as storage information. Topmost aspects were the ones proposed in the checklist (incorrect labelling, missing or incoherent information about strength, dosage or DoE) as well as correctness of registration (according to the websites of the local NMRAs in Ghana and Tanzania and to trademark registration in Burkina Faso and Côte d'Ivoire). TMDA and Food and Drug Authority (FDA) Ghana publish and regularly update summaries of all registered products of every drug licensed in the respective country. TMDA reports refreshed around November 2018 [74 – 76] and FDA Ghana reports refreshed around January 2019 were taken into account [29]. Next, the tablets (not appropriate for suspensions) were screened for uniformity of colour, shape, size and texture, markings, breaks / cracks / splits, embedded surface spots or contamination and smell. When buying several packages of one brand or batch (for example due to just one or two tablets per container), only a selected number was fully examined on-site – the rest of them were either brought to Germany and completely assayed in Würzburg before HPLC testing or handed over to TMDA Mwanza for mutual QA.

3.5.2 Mass uniformity

Mass was determined using a calibrated analytical balance (in Mwanza: Kern CM Version 1.8, in Würzburg: Kern EMB 600-2; both by Kern & Sohn GmbH, Balingen, Germany), weighing ideally 20 tablets per batch / brand. The mass of at least 18 of these samples should not deviate by more than ± 5.0 % from the average mass, and of the remaining two tablets by not more than ± 10.0 % [107]. In case less than 20 tablets per batch or brand had been obtained, the respective proportions of 90 % (instead of 18 tablets) and 10 % (instead of two tablets) were calculated.

3.5.3 Disintegration times

Tests on disintegration characteristics were conducted according to the *Manual Accompanying The GPHF-Minilab*™, which are more simplified and easier applied on-site than the guidelines provided by the WHO [51]. The respective tablets were placed into a jar containing 100 mL of warm water (imitating body temperature at 37 °C). Times to complete disintegration were taken, which should remain under 30 minutes to pass the criteria (for all anthelmintics). When, after 45 minutes, tablets had not disintegrated at all or had poorly done so, tests were terminated. Samples not having disintegrated in time were continued beyond 30 minutes. The exact times of complete disintegration were collected and listed. Batches varying significantly from each other were regarded separately. Afterwards, mean, standard deviation (SD) and 95% confidence interval (CI) were determined. These, however, were not always determined for a single batch: whenever adequate, all disintegration times collected per product were summarised and afterwards statistically evaluated as mentioned before, to regard a sample size of at least six tablets.

Image 4: Disintegration test of a Ghanaian ABZ sample.

3.5.4 Thin-layer chromatography

TLC was realised referring to the manuals of the Minilab™ [51]. According to the manuals, up to three samples had to be tested before rejecting a batch. Satisfyingly,

analysing two units (as far as possible) with an internal repetition proved to suffice. Batches that had coincidentally been acquired twice were not assayed separately. TLC results of the five suspensions were left aside, as the Minilab™ method was not designed for this formulation. Reference standards were bought from GPHF, and prepared as working standard solution (WSS) to determine a lower specification limit (LSL) of 80 % label claim (l.c.) and a upper specification limit (USL) of 100 % l.c. All APIs could be detected under UV light of 254 nm. Both the intensity and the retention factor (RF) – the ratio of the distance the testing API proceeded divided by the distance the mobile phase proceeded – of a working sample solution (WSaS) compared to the WSS were evaluated. Photographs were taken of each chromatoplate to secure comparability and to avoid alterations on the chromatoplates caused by transportation, environment or carelessness. The following list of equipment was required for TLC assays:

1) pestle
2) aluminium foil
3) funnel
4) label tape
5) pencil, ruler and marker pen
6) 10 mL vials
7) set of straight pipettes (1 mL to 20 mL)
8) set of laboratory glass bottles (25 mL to 100 mL)
9) Merck TLC aluminium plates pre-coated with silica gel 60 F_{254}, size 5 x 10 cm
10) glass microcapillaries (2 µL filling capacity)
11) TLC developing chambers (500 mL jars)
12) hot plate
13) filter paper
14) pair of scissors
15) pair of tweezers
16) UV light of 254 nm
17) iodine chamber
18) GPHF reference standards for ABZ 400 mg (lot no. 6MF96; DoE 31st May 2019), MBZ 100 mg (lot no. 6MF143; DoE 31st May 2019) and PZQ 600 mg (lot no. M75474; DoE 31st December 2019)

The following reagents were needed for the three different TLC manuals:

- acetic acid 96 % solution
  - in Germany: Carl Roth GmbH + Co. KG, Karlsruhe, Germany
  - in Tanzania: dilution of acetic acid 100 % solution, see below
- acetic acid 100 % solution (glacial acetic acid)
  - in Germany: Merck KGaA, Darmstadt, Germany
  - in Tanzania: Carlo Erba Reagents, Val de Reuil, France
- acetone
  - in Germany: Merck KGaA, Darmstadt, Germany
  - in Tanzania: Labtech Chemicals
- ammonia 25 % solution
  - in Germany: Merck KGaA, Darmstadt, Germany
  - in Tanzania: Labtech Chemicals
- ethyl acetate
  - in Germany: Carl Roth GmbH + Co. KG, Karlsruhe, Germany
  - in Tanzania: LobaChemie Pvt. Ltd., Mumbai, India
- methanol
  - in Germany: Carl Roth GmbH + Co. KG, Karlsruhe, Germany
  - in Tanzania: Trust Chemical Laboratories
- toluene
  - in Germany: Merck KGaA, Darmstadt, Germany
  - in Tanzania: LobaChemie Pvt. Ltd., Mumbai, India

3.5.4.1 Thin-layer chromatography for Albendazole

TLC for ABZ tablets was prepared as follows: for the stock standard solution (SSS), an ABZ reference sample was wrapped in aluminium foil and crushed with a pestle to powder. 40 mL of acetic acid 96 % solution were added, and thus properly dissolved by vigorously shaking and settling down. The USL of the WSS was then prepared by taking 1 mL of this dilution and adding another 7 mL of acetic acid 96 % solution. The LSL was prepared by taking 1 mL of the dilution and adding another 9 mL of acetic acid 96 % solution. The stock sample solution (SSaS) was readied comparable to the SSS: crushing of one tablet and adding 20 mL (for a 200 mg give) respectively 40 mL (for a

400 mg give) of acetic acid 96 % solution, with vigorously shaking and settling down. The WSaS was readied analogous to the USL of the WSS, containing 1.25 mg of drug per mL. WSS and WSaS were then arranged on a silica aluminium plate (USL and LSL spots of 2 µL begirding two or three spots of WSaS) and developed in a solution of 14 mL of toluene, 4 mL of acetic acid 96 % solution and 4 mL of ethyl acetate.

Two special diluting approaches were undertaken for the vetABZ samples: either crushing the whole tablet (i.e. masses up to 10 g) and then diluting it step by step, or just taking one third (referring to *Ashialben* samples) respectively one fifth (referring to *Albendafarm* samples) of the mass of the respective crushed tablet and then diluting it with less volume in the jars.

3.5.4.2 Thin-layer chromatography for Mebendazole

Comparable adaptations were made for MBZ tablets: for the SSS, an MBZ reference sample was wrapped in aluminium foil and crushed with a pestle to powder. 1 mL of water was added to facilitate disintegration of larger granules followed by 39 mL of acetic acid 96 % solution, and thus properly dissolved by vigorously shaking and settling down. The USL of the WSS was then prepared by taking 2 mL of this dilution and adding another 2 mL of acetic acid 96 % solution. The LSL was prepared by taking 2 mL of the dilution and adding another 3 ml of acetic acid 96 % solution. The SSaS was readied comparable to the SSS: crushing of one tablet and adding 1 mL of water plus 39 mL of acetic acid 96 % solution (for a 100 mg give) respectively 2 mL of water plus 98 mL of acetic acid 96 % solution (for a 500 mg give), with vigorously shaking and settling down. The WSaS was readied analogous to the USL of the WSS, containing 1.25 mg of drug per mL. WSS and WSaS were then arranged on a chromatoplate (USL and LSL spots of 2 µL begirding two or three spots of WSaS) and developed in a solution of 14 mL of toluene, 4 mL of ethyl acetate and 4 mL of glacial acetic acid.

Further distinguishing ABZ and MBZ from each other, the chromatoplates were exposed to ‘Mobile Phase B’, which consists of 27 mL of ethyl acetate, 5 mL of ammonia 25 % solution and 3 mL of methanol, and then observed at UV light of 254 nm. ABZ would differ from MBZ by a larger RF (the manual suggests approximate RFs of 0.46 for ABZ and 0.42 for MBZ). Based on a possible replacement of the API ABZ by MBZ, Jähnke and Dwornik recommend to further verify samples containing either of these two APIs. ABZ samples can be distinguished from MBZ by exposing the chromatoplates to

iodine vapour and seeing the colour of the spots change to brownish-yellowish in daylight. MBZ samples on the contrary can be heated after exposing them to a mixture of methanolic sulfuric acid (190 mL of methanol and 10 mL of sulphuric acid 96 % solution, by Merck KGaA, Darmstadt, Germany) and observed at UV light of 365 nm, emitting bluish fluorescence.

3.5.4.3 Thin-layer chromatography for Praziquantel

TLC for PZQ tablets was prepared as follows: for the SSS, a PZQ reference sample was wrapped in aluminium foil and crushed with a pestle to powder. 20 mL of methanol were added, and thus properly dissolved by vigorously shaking and settling down. The USL of the WSS was then prepared by taking 2 mL of this dilution and adding another 2 mL of methanol. The LSL was prepared by taking 2 mL of the dilution and adding another 3 mL of methanol. The SSaS was readied comparable to the SSS: crushing of one tablet (600 mg per unit) and adding 20 mL methanol, with vigorously shaking and settling down. The WSaS was readied analogous to the USL of the WSS, containing 15 mg of drug per mL. WSS and WSaS were then arranged on a silica aluminium plate (USL and LSL spots of 2 µL begirding two or three spots of WSaS) and developed in a solution of 14 mL of acetone and 7 mL of toluene. Further verification was reached by exposing the chromatoplates to iodine vapour and seeing the spots' colour change to brownish-yellowish in daylight.

3.6 Methods applied at JMU Würzburg

A comparison of the respective dissolution profiles to standardised references did not take place in Mwanza itself since the equipment of the Minilab™ does not extend to this technique nor does the accompanying manual offer a practicable chapter. These tests were performed alongside the HPLC-UV analyses by colleagues of the Institute for Pharmacy and Food Chemistry at JMU Würzburg. In comparison to TLC assays, batches coincidentally obtained twice were analysed only once. The following reagents and standardised samples were applied:

- acetonitrile (HPLC grade) by VWR International GmbH, Darmstadt, Germany
- Albendazole reference samples by Fargon GmbH, Barsbuettel, Germany
- ammonium acetate by Sigma-Aldrich Chemie GmbH, Steinheim, Germany

- formic acid 99 % by Gruessing GmbH, Filsum, Germany
- hydrochloric acid (HCl) 37 % by Bernd Kraft GmbH, Duisburg, Germany
- Mebendazole reference samples by Sigma-Aldrich Chemie GmbH, Steinheim, Germany
- methanol (HPLC grade) by VWR International GmbH, Darmstadt, Germany
- Oxibendazole reference samples by Sigma-Aldrich Chemie GmbH, Steinheim, Germany
- Praziquantel CRS and Praziquantel for system suitability CRS by EDQM, Strasbourg, France
- sulfuric acid 95 – 97 % by Fisher Scientific, Loughborough, United Kingdom

Water for HPLC-UV was purified using a Milli-Q purification system by Merck Millipore, Schwalbach, Germany. The HPLC-UV experiments were performed on an Agilent 1100 modular chromatographic system (Agilent technologies, Waldbronn, Germany) consisting of a vacuum degasser (G1379A), a binary pump (G1312A), an autosampler (G1313A), a thermostatted column compartment (G1316A) and a diode array detector (G1314A). Data were processed on Agilent ChemStation® Rev B.03.02 software.

3.6.1 Dissolution profiles

Due to the limited number of samples, the dissolution profile of merely one tablet per batch was evaluated. Requirements were met if the quantity of API dissolved from a dosage form was equal to or larger than the minimal quantity (Q) listed in the corresponding monographs of the current pharmacopoeia. Q is defined as the specified amount of dissolved API expressed as a percentage of the labelled content. The different specifications are summed up in Table 1 and further described afterwards. VetABZ samples were not evaluated.

3.6.1.1 Dissolution profiles of Albendazole

Dissolution tests of ABZ complied with specifications of Ph. Int. 7 to release at least 80 % of the API within 30 minutes (applicable for both 200 mg and 400 mg gives) [104, 108]. A paddle apparatus was used at a spindle rotation speed of 75 revolutions per minute (rpm), with the dissolution medium equilibrated to 37 ± 0.5 °C. One randomly chosen tablet was placed into the apparatus containing 900 mL of 0.1 M HCl. A 5.0 mL

sample was regularly withdrawn from the vessel (after 10, 20 and 30 minutes) and replaced by dissolution medium. Cooled to room temperature, 200 mg gives were not further diluted before passing them through a cellulose acetate membrane (diameter 25 mm, pore size 0.45 µm; VWR International GmbH, Darmstadt, Germany); 400 mg samples were equally diluted (1:1). The content of ABZ was then determined by HPLC-UV (refer to chapter 3.6.2.1).

3.6.1.2 Dissolution profiles of Mebendazole

Dissolution tests of MBZ were performed according to two different pharmacopoeiae: 100 mg gives were initially tested in reference to Ph. Int. 7 monographies before they were re-evaluated (as far as possible) by USP-NF 41 criteria. 500 mg gives were thoroughly tested according to the respective Ph. Int. 7 chapter. Unanimously, a paddle apparatus was used at a spindle rotation speed of 75 rpm, with the dissolution medium equilibrated to 37 ± 0.5 °C.

Ph. Int. 7 sets the standard of Q ≥ 60 % for a 100 mg MBZ sample within 120 minutes, respectively Q ≥ 70 % for a 500 mg MBZ sample within 60 minutes [105, 108]. One randomly chosen 100 mg tablet was placed into the apparatus containing 900 mL of 0.1 M HCl. A 10.0 mL sample was regularly withdrawn from the vessel (after 30, 60, 90 and 120 minutes) and replaced by dissolution medium. Diluting it equally (1:1), this sample was passed through a cellulose acetate membrane. A 500 mg tablet was placed into the apparatus containing 900 mL of a 1.0 % solution of sodium dodecyl sulphate (SDS)

Table 1: Different pharmacopoeial conditions for the dissolution analyses of ABZ, MBZ and PZQ samples. Resources: [104, 105, 115, 116]

	ABZ	**MBZ**			**PZQ**
Method	Ph. Int.	Ph. Int.	Ph. Int.	USP	USP
API content [mg]	200 400	100	500	100	600
Dissolution medium	0.1 M HCl	0.1 M HCl	0.01 M HCl + 1 % SDS	0.1 M HCl + 1 % SDS	0.1 M HCl + 2 mg/mL SDS
Rotation speed [rpm]	75	75	75	75	50
Sampling time [min]	10, 20, 30	30, 60, 90, 120	15, 30, 45, 60	30, 60, 90, 120	15, 30, 45, 60
Dilution	none 1:1	1:1	1:10	1:1	3:10
Q [%]	80	60	70	75	75

in 0.01 M HCl. A 10.0 mL sample was regularly withdrawn from the vessel (after 15, 30, 45 and 60 minutes) and replaced by dissolution medium. 1.0 mL of it was diluted with 9.0 mL before passing it through a cellulose acetate membrane. Unanimously, the content was determined by HPLC-UV (refer to chapter 3.6.2.2).

In accordance with USP-NF 41 on 100 mg gives, at least 75 % of the API are to be released within 120 minutes. One randomly chosen tablet was placed into the apparatus containing 900 mL of a 1.0 % solution of SDS in 0.1 M HCl. A 10.0 mL sample was regularly withdrawn from the vessel (after 30, 60, 90 and 120 minutes) and replaced by dissolution medium. The sample was diluted equally (1:1) before passing it through a cellulose acetate membrane [115]. Analysis of content was conducted by HPLC-UV in accordance to the respective specification of Ph. Int. 7 (refer to chapter 3.6.2.2)

3.6.1.3 Dissolution profiles of Praziquantel

Dissolution tests of PZQ referred to the criteria of USP-NF 41 to release at least 75 % of a 600 mg give of the API within 60 minutes [116]. A paddle apparatus was used at a spindle rotation speed of 50 rpm, the dissolution medium was equilibrated to 37 ± 0.5 °C. One randomly chosen tablet was placed into the apparatus containing 900 mL of 0.1 M HCl and 2.0 mg SDS per mL. A 10.0 mL sample was regularly withdrawn from the vessel (after 15, 30, 45 and 60 minutes) and replaced by dissolution medium. After filtering it through a cellulose acetate membrane, the content was detected by HPLC-UV in reference to Ph. Eur. 9 (refer to chapter 3.6.2.3).

3.6.2 High-performance liquid chromatography – ultraviolet spectroscopy

Aptitude of the different HPLC-UV methods described in Ph. Eur. 9 and Ph. Int. 7 was confirmed beforehand. In anticipation of SF drugs, system suitability tests were calculated by a five-point calibration to cover ranges from 10 % l.c. to 130 % l.c. In order to guarantee a high quality of results, each API was tested separately to define the most appropriate approach. Unanimously, specification limits (SLs) are set between 90 % and 110 % l.c. Concentration of API was assigned by applying UV light of a wavelength of 254 nm, taking the average of three measurements per sample. Screening for impurities came along with the analyses, referring to an established interpretation of HPLC chromatograms [20, 46, 104, 105]. Whenever suitable, assays on an anthelmintic batch were

triplicated. Owing to unsatisfactory manageability of especially *Albendafarm* samples, vetABZ brands were not tested.

3.6.2.1 HPLC-UV on Albendazole samples

The concentration of API in an ABZ sample was analysed – with minor adaptations – in accordance to Ph. Int. 7 [104, 106]. The stock solution was prepared by dissolving 25.0 mg of ABZ reference substance accurately in 5.0 mL of methanol / sulphuric acid (99/1 % v/v) and 15.0 mL of methanol. This was further dissolved to 25.0 mL with methanol. Defined volumes of 1.0 mL, 1.5 mL, 2.0 mL, 2.5 mL and 3.0 mL of the stock solution were diluted to 10.0 mL with methanol, respectively. The sample solutions were prepared depending on mass or volume: a tablet of 200 mg was dissolved in 5.0 mL of methanol / sulphuric acid (99/1 % v/v) and 15.0 mL of methanol, sonicated for 15 minutes and then diluted to 50.0 mL with methanol. Afterwards, 2.5 mL of this solution were diluted by another 50.0 mL of methanol, obtaining a concentration of 0.2 mg/mL. When analysing a tablet of 400 mg of API, the same steps were performed up to this point, only utilising 1.25 mL instead of 2.5 mL after the first dilution step. A volume of 5.0 mL of a suspension was equally dissolved (utilising either 2.5 mL of *Benpham* or 5.0 mL of both of the other suspensions after the first dilution step) and diluted by 50.0 mL of methanol to the concentration mentioned above. The resulting solution was filtered through a PTFE membrane (diameter 13 mm, pore size 0.2 µm; VWR International GmbH, Darmstadt, Germany) and transferred to a vial. Out of that vial, 20 µL were injected into a Hypersil™ ODS (C18) column (dimensions: 250 mm x 4.6 mm, particle size 5 µm, pore size 120 Å; Thermo Fisher Scientific™, Dreieich, Germany). The column was maintained at room temperature and operated with a flow rate of 0.7 mL per minute over 20 minutes, applying a gradient elution of 30 % of monobasic ammonium phosphate (solution of 1.67 g/L) / 70 % of methanol.

3.6.2.2 HPLC-UV on Mebendazole samples

The concentration of API in a MBZ sample was determined by slightly adapting Ph. Int. 7 [105, 106]. The stock solution was prepared by dissolving 100.0 mg of MBZ reference substance accurately in 30 mL of anhydrous formic acid, sonicating it for 20 minutes and then diluting it by 100 mL of ultrapure water / methanol (40/60 % v/v). Defined volumes of 2.0 mL, 3.0 mL, 5.0 mL, 7.0 mL and 8.0 mL of the stock solution were

diluted to 100 mL with ultrapure water / methanol (40/60 % v/v), respectively. The sample solutions were prepared depending on mass: a tablet of 100 mg was dissolved in 30 mL of anhydrous formic acid, sonicated for 20 minutes and then diluted by 100 mL of ultrapure water / methanol (40/60 % v/v). Afterwards, 5 mL of this solution were diluted by another 100 mL of ultrapure water / methanol (40/60 % v/v). When analysing a sample of 500 mg of API, the same steps were performed up to this point, only utilising 1mL instead of 5 mL after the first dilution. A volume of 5.0 mL (corresponding to 100 mg) of suspensions was prepared in compliance with 100 mg gives. Now equally concentrated to 0.05 mg/mL, this solution was then filtered through a PTFE membrane and transferred to a vial. Out of that vial, 10 µL were injected into a C18 YMC Pack Pro column (dimensions: 150 mm x 4.0 mm, particle size 3 µm, pore size 120 Å; YMC, Dinslaken, Germany). The column was maintained at room temperature and operated with a flow rate of 0.9 mL per minute over 60 minutes (to not exceed the specified pressure limit of the column used, the flow rate was – permissibly – reduced from a required 1.2 mL per minute), applying a gradient elution of 75 % of ammonium acetate (solution of 7.5 g/L) / 25% of acetonitrile.

3.6.2.3 HPLC-UV on Praziquantel samples

The concentration of API in a PZQ sample was assayed referring to the Ph. Eur. 9 [20]. The stock solution was prepared by dissolving 15.0 mg of PZQ reference substance accurately in 5.0 mL of ultrapure water / acetonitrile (55/45 % v/v), sonicating it for five minutes and then diluting it to 10.0 mL by ultrapure water / acetonitrile (55/45 % v/v). Defined volumes of 0.125 mL, 0.250 mL, 0.375 mL, 0.500 mL and 0.625 mL of the stock solution were diluted to 10.0 mL with ultrapure water / acetonitrile (55/45 % v/v), respectively. Concerning the sample solutions, a tablet of 600 mg was crushed and weighed for 150 mg of PZQ. This proportion was dissolved in 70 mL of ultrapure water / acetonitrile (55/45 % v/v), sonicated for 20 minutes and then diluted by ultrapure water / acetonitrile (55/45 % v/v). Afterwards, 3.0 mL of this solution were diluted to 100.0 mL with ultrapure water / acetonitrile (55/45 % v/v). This solution was then filtered through a PTFE membrane and transferred to a vial. Out of that vial, 20 µL were injected into a Hypersil™ ODS (C18) column (dimensions: 250 mm x 4.6 mm, particle size 5 µm, pore size 120 Å; Thermo Fisher Scientific™, Dreieich, Germany). The column was maintained

at room temperature and operated with a flow rate of 1.15 mL per minute over 30 minutes, applying a gradient elution of 55 % of ultrapure water / 45 % of acetonitrile.

3.7 Statistical analysis

Regarding the results of Minilab™-based tests, dissolution profiles and HPLC-UV findings, statistical analysis was done using SPSS® by IBM Analytics and Microsoft Excel. A descriptive assay on the different tablets and their characteristics (variables) was done in order to get an overview. A *p*-value of $p < 0.05$ was considered to be statistically significant, and standard deviations (SDs), relative standard deviations (RSDs) and 95 % confidence intervals (95 % CIs) were calculated whenever applicable. The Pearson correlation coefficient (*r*) allowed the illustration of the relation of numeric variables.

4 Results

The MBZ brand *Minazol* by Pokupharma Ltd. / Ghana was only discovered once (a single tablet could be bought) and hence evaluated for just availability, price and appearance. As not all remaining 88 disparate batches (resulting in 64 products) could be subjected to all tests performed, a completely equal comparison of products was not achieved. Analyses were carried out in any sample obtained, disregarding the fact that by the time of their purchase, at least ten products were not licensed for sale (only to be determined in Ghana and Tanzania). According to the indicated brand names, seven products were originator brand drugs (ABZ: *Zentel* from France, India and South Africa; MBZ: *Vermox* from Portugal and South Africa; PZQ: *Biltricide* from Germany and *Cesol* from Mexico). A majority of 48 brands was represented by branded generics: 19 seemed to be registered trademark brands, one appeared to be a non-registered trademark brand and 28 did not show any trademark labelling. Nine products were sold as generic drugs under their international non-proprietary names (INNs).

Always commencing with Minilab™ methods, the initial step was to identify the indicated and expected API, which all batches passed. This was performed by visual inspection of both packaging and tablet (in suspensions merely packaging), TLC and HPLC-UV for confirmation. Then, accompanying identification, a screening for impurities by TLC (screening) and HPLC-UV (confirming, and for possibly detecting more delicate impurities) took place – no product had to be classified as contaminated. Then, the samples underwent further analysis for mass uniformity, content and galenic characteristics. Concerning content, results of HPLC-UV surpassed TLC ones for their quantifiability and higher precision. In terms of galenic features, dissolution profiles were regarded as more critical than disintegration times. Hence, a failure in dissolution was considered more severe than a failure in disintegration, and consequently was the decisive condition besides a failure in HPLC-UV when labelling a sample insufficient in galenic and content aspects. A peculiarity in dissolution profiles of MBZ 100 mg gives had to be considered: pharmacopoeial analyses by both Ph. Int. 7 and USP-NF 41 pointed out on a higher suitability and comparability of USP-NF 41 (this shall be discussed later). When not having performed both tests, the criterion ‘dissolution’ did not contribute to its classification (applicable in B. No. 254 and 257 of *Astazole*, *Carben*, *Mebrone-100*, B. No. 71356 of *Natoa* and B. No. DOR 1701 of *Oziben*).

Merely 22.7 % (20 / 88) of the batches met the respective criteria in all assays, complying with visual examination of both packaging and tablets, mass uniformity, disintegration times, TLC, dissolution profiles and HPLC-UV. Suspensions, naturally, could only be tested for appearance of the packaging and HPLC-UV (TLC was conducted in some, although Minilab™ manuals do not specifically include them). Taking these sparse assays for suspensions into consideration and conceding to the fact that not all tests could be performed on each and every batch of tablets, a separate category had to be introduced for them, which contributed another 15.9 % (14 / 88) – they were approved to deliver satisfying results as well but had to be regarded with reservations. 56.8 % (50 / 88) failed in at least one of the following categories: Minilab™ tests of mass uniformity and / or

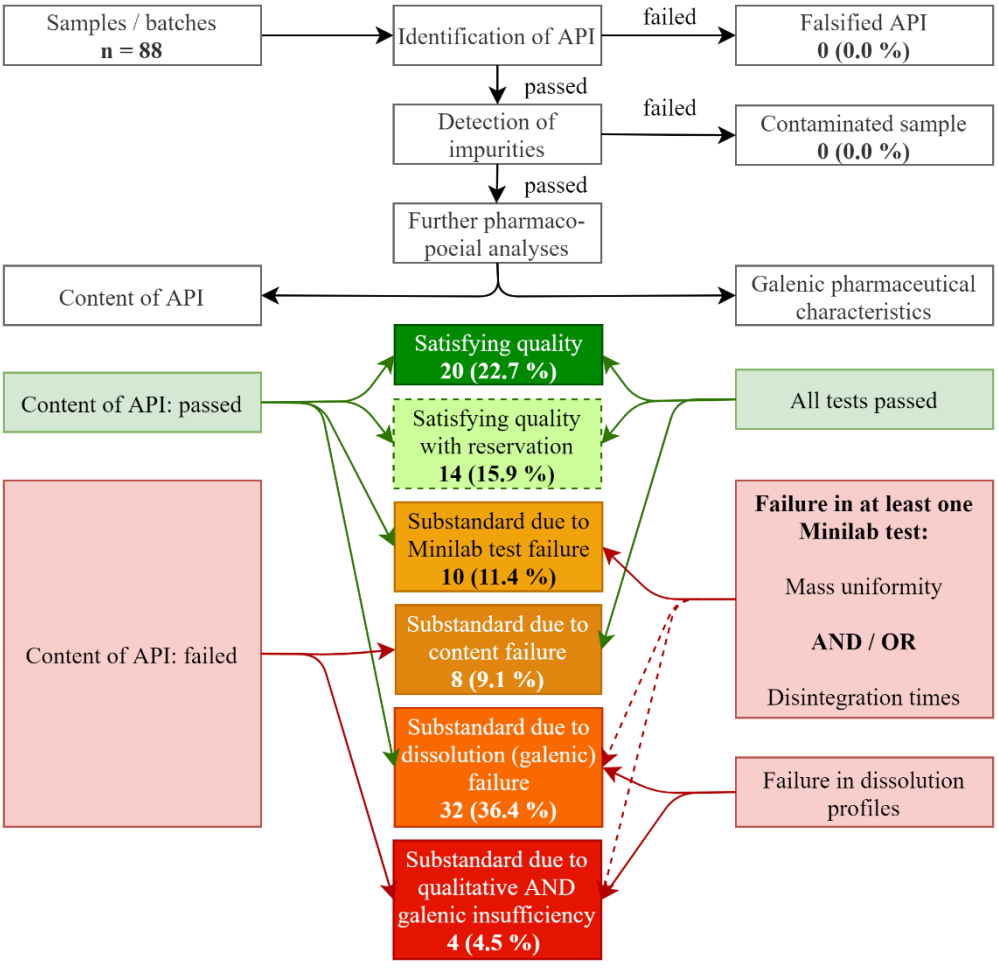


Figure 17: Flow chart of categorisation of the African samples obtained.
Due to its likelihood in the results, galenic insufficiency was evaluated to be more important than failure of content. Dissolution profiles were regarded as more expressive than Minilab results; failure of dissolution and disintegration regularly coincided. *Minazol* was excluded.
Satisfying quality with reservations: not all tests could be performed; the ones performed resulted in acceptable quality

disintegration times (11.4 %), content of API (9.1 %) and dissolution profiles (36.4 %). Accordingly, the last category appeared to have the greatest impact on the overall categorisation – an additional failure in the Minilab™ tests did not deteriorate but just contributed to this evaluation. 4.5 % (4 / 88) of the products finally revealed an insufficiency in both content and galenic features (all ABZ). While listed as an overview of performance in Table 2, detailed results of all analyses are illustrated in the following, divided into the counties of origin – Ghana, Burkina Faso / Côte d'Ivoire (most samples obtained were encountered in both countries) and Tanzania.

Table 2: Performance of all 88 batches of collected anthelmintics in accordance with the flow chart of categorisation.
(*): Dissolution profiles were not assessed by both Ph. Int. 7 and USP-NF 41 – this criterion did not contribute to the classification.

		Ghana	Burkina Faso / Côte d'Ivoire	Tanzania
Satisfying quality	ABZ	*Nesben*, *Wormplex 400* (both), *Zentel*	*Albendazole TM*, *Verzol* (TE-6677, TE-6716)	*Albendazole 400 mg*, *Albi*, *Anthel* (BV7004), *Azentel* (360766, 370425)
	MBZ	*Vermox*	*Mebendazole* (F0164), *Mebendazole* (MZ-1811), *Oziben* (DOR 1702), *Wormin 500* (R70E8001)	*Wormnil*
	PZQ			*Cesol*, *Distocide*
Satisfying quality with reservations	ABZ	*Albendazole oral susp.*		*Azentel* (350579), *Benpham susp.*, *Zentel*, *Zentel susp.*
	MBZ		*Oziben* (DOR 1701)*, *Wormin 500* (R70E8003)	*Natoa susp.*, *Vermox*, *Wormol susp.*
	PZQ		*Biltricide*	*Praziquantel-600* (160004)
	vetABZ			*Albendafarm 1500 + 2500*
Substandard due to Minilab test failure	ABZ	*Trazole-500*	*Carben**	*Alben* (170023)
	MBZ			*Astazole** (all three), *Mebrone-100**, *Natoa* (71356)*
	PZQ			*Prazikant* (both)
Substandard due to content failure	ABZ	*Tanzol*, *Wormzap*	*Verzol* (TE-6717)	*Alzental* (both)
	MBZ			*Mebendazole BP 500mg*
	vetABZ			*Ashialben 300 + 600*
Substandard due to dissolution (galenic) failure	ABZ	*Abee-400*, *Eskaben*, *Sequizol* (both), *Wormron 400* (both)	*Bendex-400*, *Elband 400*, *Lyben*, *Sanozol*, *Tanizol*, *Verex* (both)	*Alben* (180018, 180012), *Anthel* (BV6006), *Elyzole* (all three), *Womiban* (both)
	MBZ	*De Wome 500*, *Mentel*	*Mébendazole* (G07002), *Nebenda*, *T-Medazol*	*Natoa* (69900)
	PZQ	*Praziquantel 600*		*Bermoxel* (both), *Praziquantel-600* (140007, 170003)
Substandard due to qualitative AND galenic insufficiency		*Albenaz*, *Tacizol*, *Wormbat-400*	*ABZ*	

4.1 Evaluation of anthelmintic drugs collected in Ghana

4.1.1 Variable availability and prices of different brands

The accessibility to most anthelmintic drugs in the south-western parts of Ghana is simple, as especially ABZ and MBZ are regularly sold in both official pharmacies (alongside wholesalers and distributors) and small 'over the counter' (OTC) vending places. Owing to the sheer abundance of different brands of ABZ (approximately 30 registered products), it was difficult to determine whether all products obtained were available in each town. Generally speaking, the larger the city (Cape Coast, SK-TK), the wider the range. As to Figure 18, about one third of the samples was acquired in the village of Eikwe (8 / 25), where a decent range of different brands of predominantly ABZ could be encountered. In the other smaller towns (Axim, Elubo and Essiama) there were usually just one or two proper pharmacies, and some OTC shops. Here, merely some samples were obtained (two batches in each town) even though the variability was higher. In Cape Coast (n = 6) and SK-TK (n = 5) it was attempted to look for brands not detected so far and to fathom the range of ABZ and MBZ products disposable in the region. PZQ was overall sparsely available: only *Praziquantel 600* was occasionally sold because of being out of stock for several months.

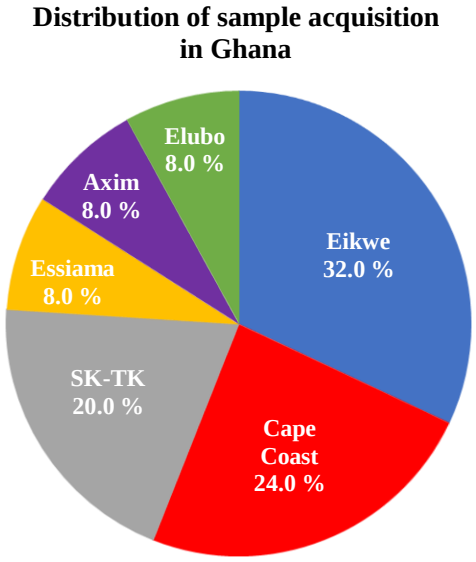


Figure 18: Ratio of samples collected per town in Ghana.

Prices ranged between 1.00 Ghanaian Cedi (GHC) and 8.00 GHC per therapeutic dose (TD) of 400 mg of ABZ, 500 mg of MBZ or 600 mg of PZQ (as reference quantity), which equalled a range between 0.17 € and 1.40 € (refer to Figure 19) [19]. A larger variation comparing cities (Cape Coast, SK-TK) to more rural towns and villages could not be detected. The most expensive drugs (8.00 GHC each) were the two originator brands *Vermox* (MBZ) by Lusomedicamenta - Sociedade Técnica Farmacêutica / Portugal (for Janssen-Cilag AG / Switzerland) and *Zentel* (ABZ) by Medreich Limited / India (for GSK). In general, patients had to pay between 1.00 GHC and 8.00 GHC per TD of ABZ (2.94 GHC ± 1.85 GHC; 3.00 GHC) (mean ± SD; median). A TD of MBZ would

also cost between 1.00 GHC (merely one product, *Trazole-500*, which was available in Eikwe) and 8.00 GHC (3.25 GHC ± 2.52 GHC; 2.25 GHC). The only brand of PZQ that was found was sold for 2.00 GHC per tablet, containing 600 mg of API.

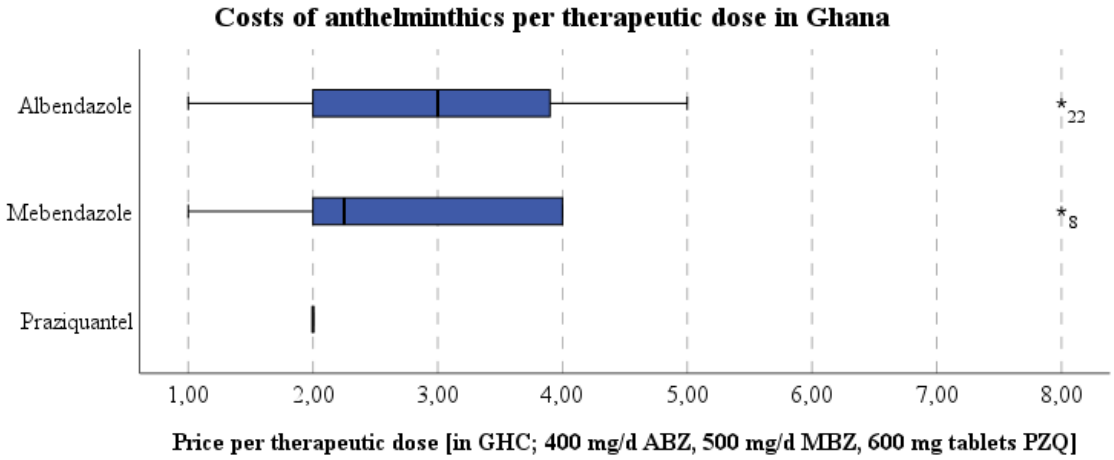


Figure 19: Costs of anthelmintics per TD in south-western Ghana.

4.1.2 Appearance and packaging

19 disparate brands of anthelmintics were collected in Ghana. According to the data available from FDA Ghana in March 2019, six products were not registered as therapeutic agents: four ABZ brands, the MBZ brand *Minazol* and the PZQ brand *Praziquantel 600*. Out of these four ABZ brands (30.8 % of all ABZ products gathered), two (*Abee-400* by Impulse Pharma Pvt. Ltd. / India and *Albendazole Oral Suspension* by Osaka Pharmaceuticals Pvt. Ltd. / India) were not registered at all; the registration of the other two brands (*Wormron 400* and *Wormzap* by G R Industries Limited / Ghana) had expired by 31st of December 2018. Both *Minazol* and *Praziquantel 600* were not licensed for sale either.

Apart from *Vermox* being manufactured in Portugal, the Ghanaian market of deworming agents seems to be dominated by both Ghanaian and Indian products: 52.6 % of them (n = 10) were manufactured in Ghana, 42.1 % (n = 8) in India (refer to Figure 20).

DoE of all 21 different samples were indicated on the packages, varying between 13 months (*Minazol*) and 45 months (*Zentel*) by the time of purchase.

Leaving *Minazol* aside, visual examination of the packages came up with only two discrepancies from the WHO tool. The DoM was missing on the packaging of *Praziquantel-600*, and a leaflet was not included in the ABZ brand *Eskaben* by Eskay Therapeutics

Ltd. / Ghana. The examination of the tablets resulted in more deficiencies: the texture of three products – ABZ brands *Abee-400*, *Wormzap* and the MBZ brand *Trazole-500* – varied significantly within a batch; two products showed minor breaks, cracks and splits (*Abee-400* and *Trazole-500*). Embedded surface spots or contaminations were detected in another two products (*Tacizol* by Imperia Life Sciences Pvt. Ltd. / India and *Trazole-500*). Despite, in summary, *Abee-400* and *Trazole-500* showing multiple irregularities, no product was suspected to be SF medicine as none appeared with critical aspects of 'incorrect labels, missing information about the strength, dosage, or expiration date' [135].

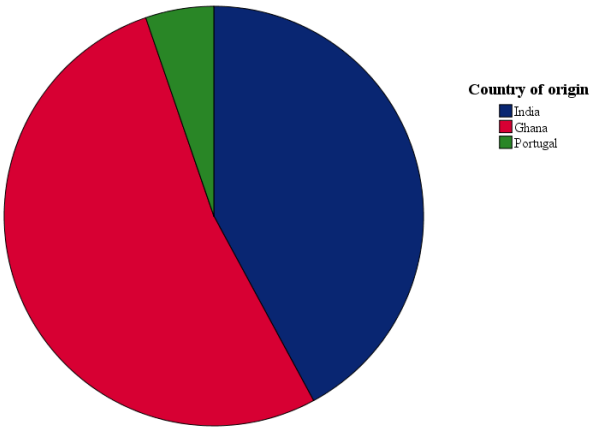


Figure 20: Different countries of origin of anthelmintic medicines available in Ghana.

4.1.3 Mass uniformity of samples obtained in Ghana

Determining a regular distribution of masses of various samples per product, 17 different anthelmintic drugs were taken into account: twelve ABZ brands, four MBZ brands and one PZQ brand. Owing to the large number of different ABZ and MBZ products and the goal of rather gathering different brands, in ten cases only ten samples per brand (alongside 15 tablets of *Trazole-500*) had been acquired and were consequently analysed for mass uniformity. As to be seen in Figure 21, all but the MBZ product *Trazole-500* (only 33.3 % of the samples tested deviated by no more than 5 % from the mean mass of 0.586 g) passed pharmacopoeial criteria.

4.1.4 Disintegration times of Ghanaian products

Excluding *Minazol*, all 17 brands acquired in Ghana could be tested for their disintegration profiles. As, in several cases, merely ten samples were obtained per batch, the minimum number of tablets to be assayed was reduced to four samples. Depicted in Figure 22, twelve brands (70.6 %) fully disintegrated within the SL of 30 minutes. Four products though (23.5 %) – *Albenaz*, *Eskaben 400*, *Tacizol* and *Mentel* – did not alter their composition at all after even 45 minutes of resting in 37 °C warm water – which was set to be the maximum time to be taken (unless a sample seemed to be very close to full

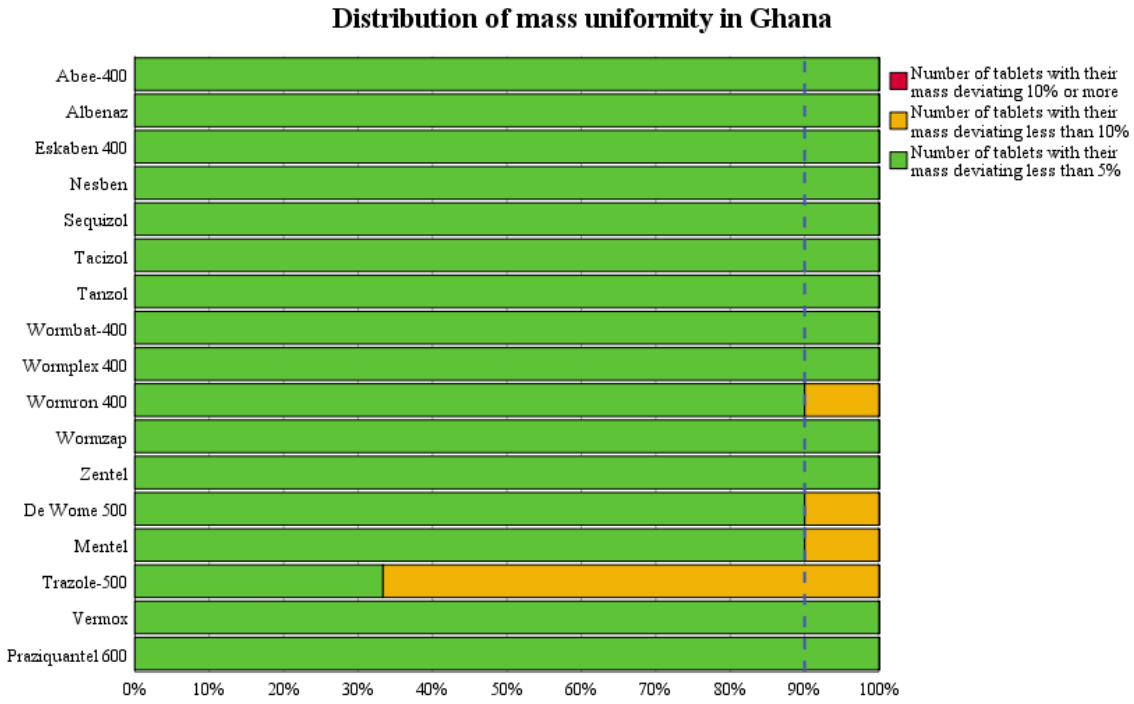


Figure 21: Distribution of mass uniformity in Ghana.
Percentages were indicated as not always a minimum of 20 tablets per product could be analysed. The blue dotted line indicates the 90 % limit (18 / 20 whenever possible), beyond which a product passed this test.

disintegration). One ABZ product, *Wormron 400*, had to be assessed more differentiated. Two disparate batches, B. No. WA1806 and WA1801, had been obtained in Eikwe, differing in colour of the tablets and taste (Image 5). When screening them, the green tablets (B. No. WA1806) revealed a clearly delayed disintegration profile between 38.25 and 46.75 minutes, retarded by approximately 14 minutes on average (41.3 minutes versus 27.7 minutes). B. No. WA1801 nevertheless, applied in St. Martin de Porres Hospital, could not really be offered as a preferable alternative either since two out of four samples tested failed to disintegrate within the required limits. Consequently, less than three out of four brands fully passed the criteria for disintegration times and thus presented with acceptable galenic features.

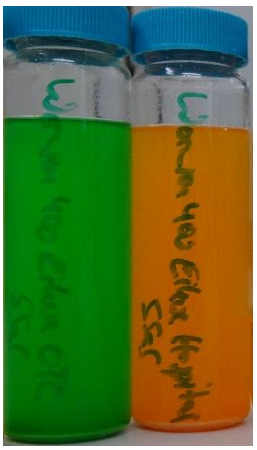


Image 5: B. No. WA1806 (left) and WA1801 (right) of *Wormron 400* during TLC preparation.

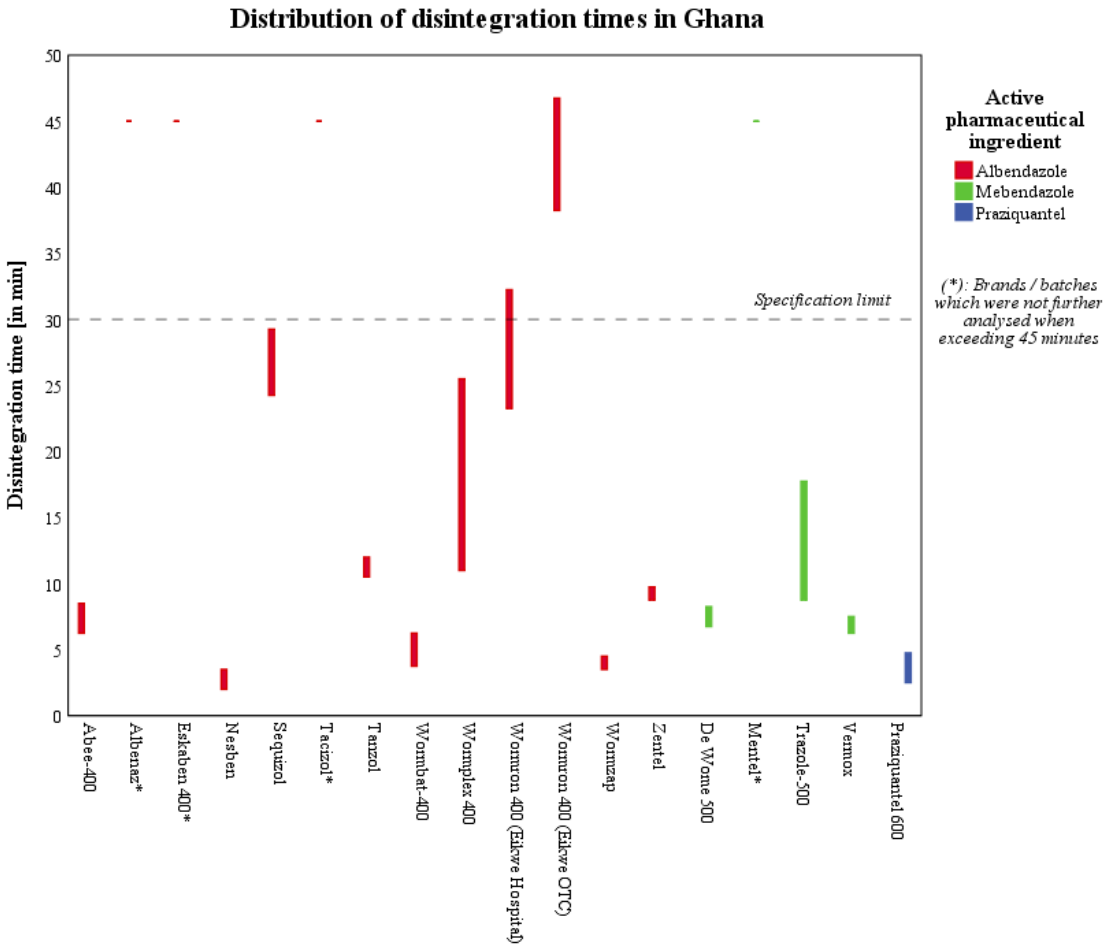


Figure 22: Disintegration times of Ghanaian products.

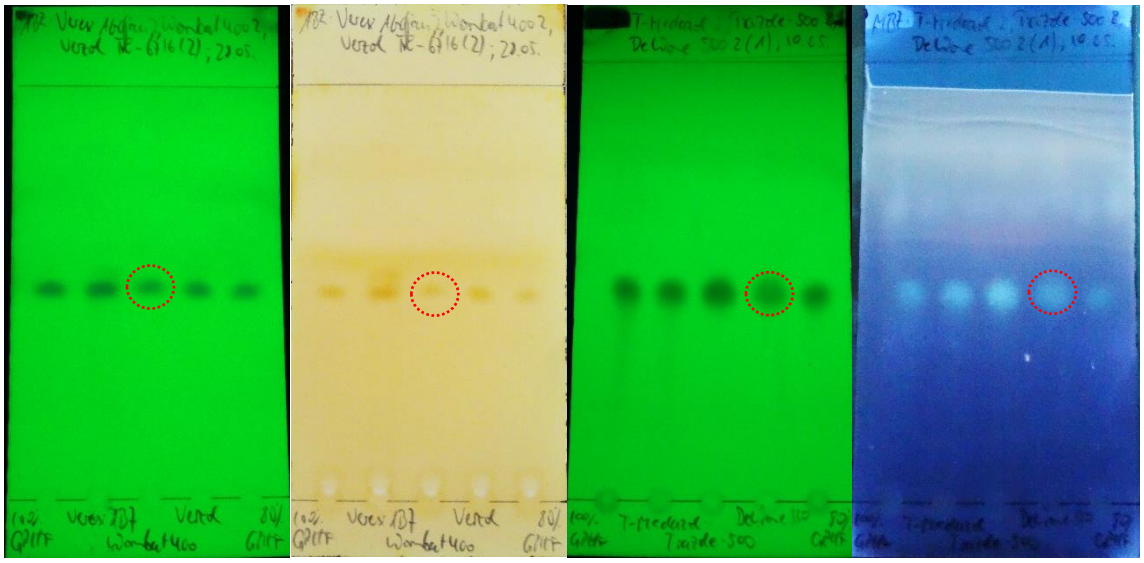
4.1.5 Thin-layer chromatography of samples from Ghana

20 different batches of tablets were analysed for TLC (refer to Table 3). Of these, not a single product was detected to be counterfeit or falsified. Two batches – one out of two samples of the Ghanaian products *Wormbat-400* (ABZ) and *De Wome 500* (MBZ), illustrated by Images 6 to 9 – seemed to (at least intermittently) undercut the LSL of 80 %

Table 3: Ghanaian TLC results.
Spots similarly strong as the 80 % LSL were assessed to be 'in range'.

Ghanaian TLC results	**ABZ** (n = 15)	**MBZ** (n = 4)	**PZQ** (n = 1)	**Total** (n = 20)
In range (API between 80 % and 100 % l.c.)	93.3 % (14)	0.0 % (0)	100.0 % (1)	75.0 % (15)
API exceeding 100 % l.c.	0.0 % (0)	75.0 % (3)	0.0 % (0)	15.0 % (3)
API undercutting 80 % l.c.	6.7 % (1)	25.0 % (1)	0.0 % (0)	10.0 % (2)
Falsified / counterfeit API	0.0 % (0)	0.0 % (0)	0.0 % (0)	0.0 % (0)

l.c. (10.0 %). In MBZ brands however, it rather occurred that samples exceeded the USL of 100 % l.c. (so-called 'overage'). Such an augmented amount of API (approximately 10 %) is a reasonable characteristic of medicines meant for sale in countries located in climate zone A according to the Köppen-Geiger Climate Classification [61] to guarantee sufficient API in tablets showing poor stability after some years. 75.0 % of the MBZ samples could be characterised in such way after having performed regular TLC and exposing the chromatoplates to methanolic sulfuric acid. ABZ batches (93.3 %) and *Praziquantel-600* were almost completely in range within the specification limits set by the Minilab™, even though 33.3 % of the ABZ batches (*Abee-400*, *Albenaz*, *Tacizol*, *Tanzol* and *Wormzap*) were assayed to be very close to the LSL.



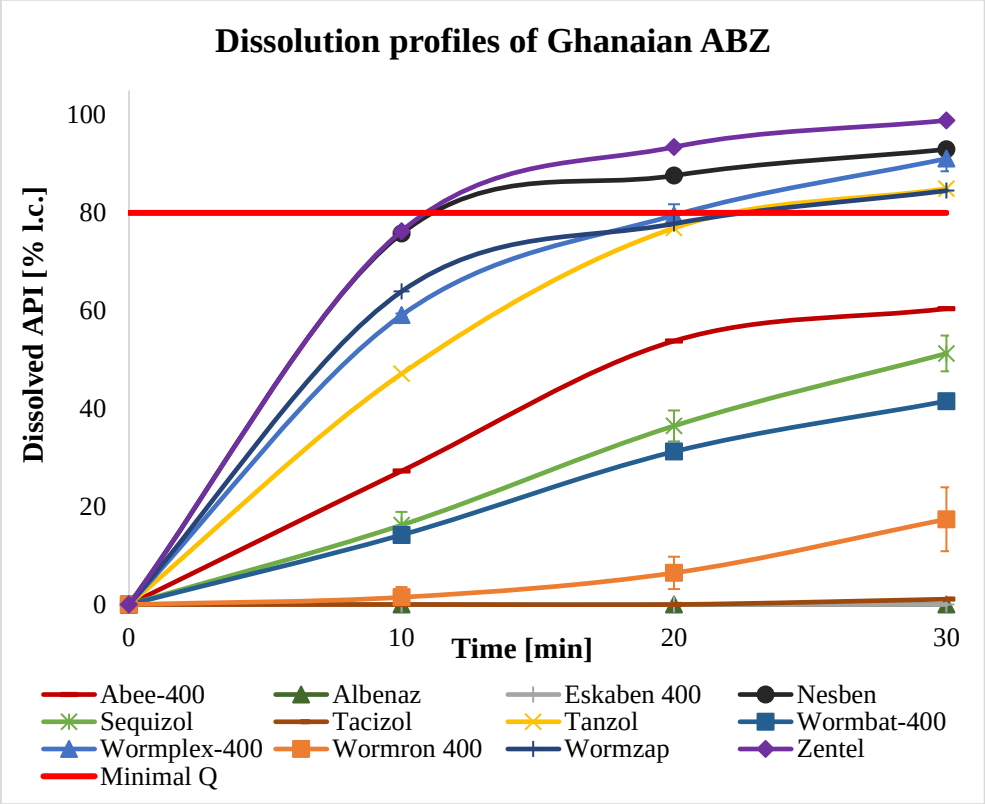
Images 6 – 9: TLC chromatoplates with *Wormbat 400* (red circle on the two images on the left) and *De Wome 500* (red circles on the two images on the right) appearing to undercut the 80 % LSL.

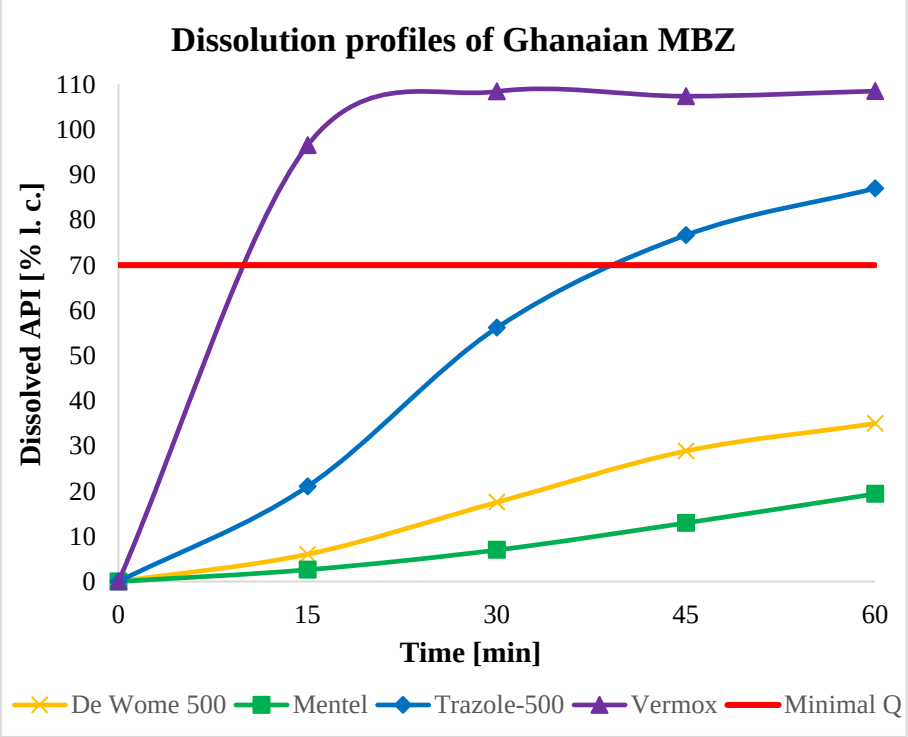
4.1.6 Dissolution profiles of Ghanaian products

20 different batches of deworming agents were taken into account: 15 ABZ (resulting in twelve different brands), four MBZ and one PZQ batch.

ABZ dissolution profiles (Figure 23) resulted in a heterogenous distribution: six out of 15 batches (40.0 %) passed pharmacopoeial criteria of Q ≥ 80 % l.c., ranging between 84.5 % l.c. (*Wormzap*) and 98.9 % l.c. (*Zentel*) after 30 minutes of analysis. Five batches (33.3 %) did not even dissolve to 25 % l.c.: *Albenaz* and *Eskaben 400* showed no

dissolution at all, *Tacizol* came up with minimal dissolution to 1.1 % l.c., and both batches of *Wormron 400* (WA1806: 12.8 % l.c., WA1801: 22.0 % l.c.) undercut this limit as well.





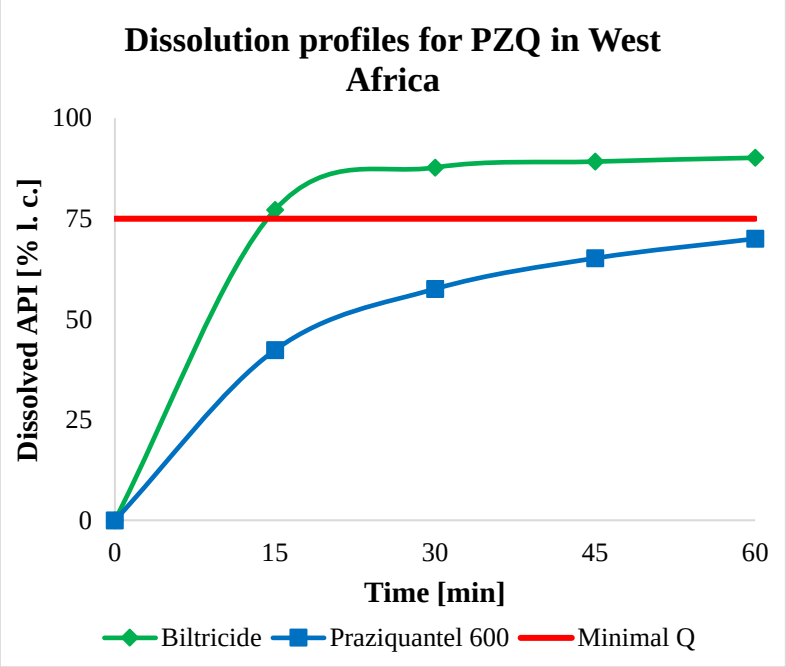


Figure 23 – 25: Distribution of dissolution profiles of Ghanaian products.
The red horizontal line indicates the specific minimal Q of each API. Whenever more batches of a brand were assessed, average (coloured spots) and SD (whiskers) were indicated.
Biltricide from Côte d'Ivoire is included in Figure 25 for better comprehensibility.

MBZ brands (Figure 24) resulted in two products passing the threshold of Q ≥ 70 % (*Trazole-500* with 87.0 % and *Vermox* with 108.5 %) while two brands failed to do so (*Mentel* with 19.4 % and *De Wome 500* with 35.0 %).

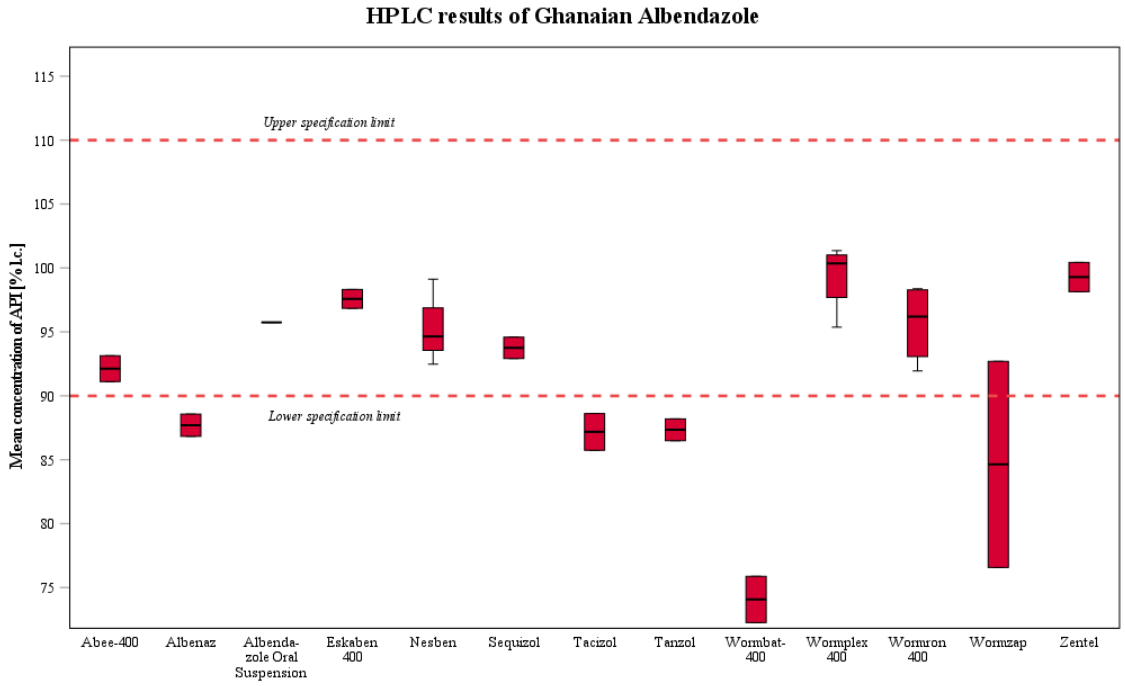
Praziquantel 600 dissolved after 60 minutes to merely 70.0 % l.c. and consequently narrowly missed the specific minimal Q set at 75 % l.c. (the data of *Biltricide* are included in Figure 25, too).

Overall, 40.0 % (8 / 20) of all anthelmintics collected in Ghana could be considered acceptable, the majority of 60.0 % (12 / 20) failed dissolution criteria.

4.1.7 HPLC-UV on samples from Ghana

All different batches of tablets collected in Ghana that had been assessed by the Minilab™ were analysed, as well as *Albendazole* oral suspension. Besides the latter one (only one portion), two to three tablets were assayed. In products of which more than one batch was collected, larger deviations from the average concentration of API were not encountered in the different batches – thus only the different brands shall be illustrated. 13 ABZ, four MBZ and one PZQ product(s) were tested.

In ABZ brands, API concentration varied between 74.1 % l.c. ± 3.5 % RSD (*Wormbat-400*) and 99.4 % l.c. ± 2.7 % RSD (*Wormplex 400*). Altogether, five products (*Albenaz*, *Tacizol*, *Tanzol*, *Wormbat-400* and *Wormzap*) just did not pass Ph. Int. 7 criteria. The remaining eight products ranged between 90 % l.c. and 100 % l.c. The large RSD of 13.5 % calculated in *Wormzap* based on only two tablets assayed – nonetheless, these two differed by more than 16 % l.c. (Figure 26).



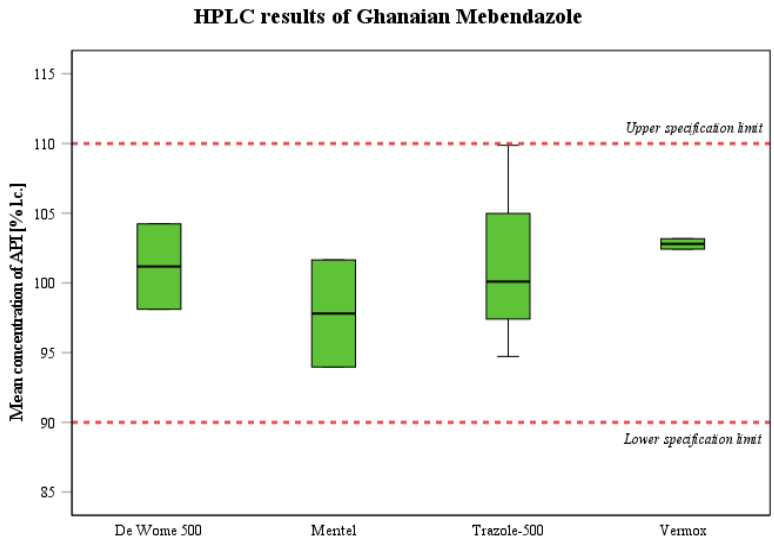


Figure 26 + 27: HPLC-UV results of Ghanaian ABZ and MBZ.
Ghanaian PZQ are illustrated in Chapter 4.3.7 (Figure 47) as a pan-African figure of PZQ HPLC-UV results)

MBZ brands presented with concentrations from 97.8 % l.c. ± 5.6 % RSD (*Mentel*) to 102.8 % l.c. ± 0.5 % RSD (*Vermox*). Apart from *Mentel*, the other three brands exceeded 100 % l.c. *Mentel* and *Trazole-500* (101.6 % l.c. ± 7.6 % RSD) both came up with a certain variability within the batch (Figure 27).

Praziquantel 600 was analysed with an average concentration of 101.5 % l.c. ± 0.9 % RSD (summarised in Figure 48).

On average, 72.2 % (13 / 18) of the products collected in Ghana were assessed to be within SL. The other five brands had to be rated as substandard.

4.2 Evaluation of anthelmintic drugs collected in Burkina Faso and Côte d'Ivoire

4.2.1 Variable availability and prices of different brands

As in neighbouring Ghana, the variety of different ABZ and MBZ brands is abundant. Thanks to a shared currency (the West African Franc CFA / FCFA), an intermingled economic community (and Burkina Faso depending, amongst others, on international trade via the port of Abidjan, which is connected by railroad to Banfora, Bobo Dioulasso and Ouagadougou), the range of medicines is similar in both nations. Large numbers of different ABZ and MBZ brands could be detected – the bigger the city, the more extended the range grew. The only PZQ brand that was available (beheld in only a few selected pharmacies) was *Biltricide*. The disparate choice of drug-selling agents (strictly licensed vendors in Côte d'Ivoire versus licensed pharmacies and street vendors in Burkina Faso) that were approached, however, revealed further products in Burkina Faso that were not seen in the southern neighbour (e.g. generics). Overall, 62.1 % of the 29 different samples obtained in these countries were obtained in Côte d'Ivoire (n = 18), 37.9 % (n = 11) in Burkina Faso (subdivided in Figure 28).

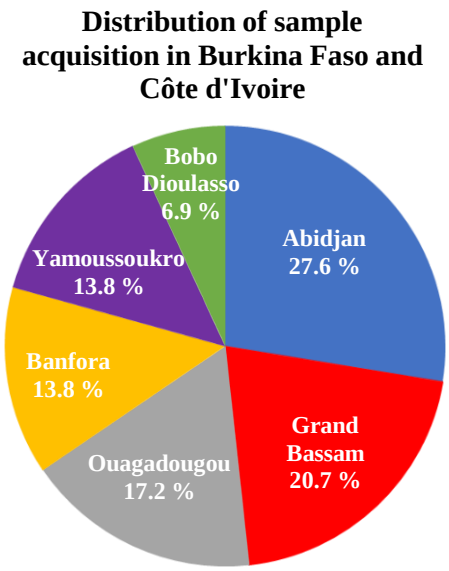


Figure 28: Ratio of samples collected per city in Burkina Faso and Côte d'Ivoire.

The average costs of ABZ brands were found to be equal in both countries. Products in Côte d'Ivoire were collected ranging between 381.67 FCFA and 1,000 FCFA per TD (677 FCFA ± 254 FCFA; 645 FCFA), where two brands (*Verex* by Cipharm / Côte d'Ivoire and *Verzol* by Gracure Pharmaceuticals Ltd. / India) were about twice as expensive as half of the others. In Burkina Faso, costs were distributed more heterogeneously – between 50 FCFA for a branded generic ABZ drug named *Elband 400* (by Kilitch Drugs Ltd. / India) and 1,100 FCFA for *Verex* (600 FCFA ± 357 FCFA; 745 FCFA). Relevant differences however became obvious in the average expenses on a TD of MBZ: in Côte d'Ivoire, products ranging between 350 FCFA and 1075 FCFA per TD were obtained (701 FCFA ± 303 FCFA; 772.50 FCFA); in Burkina Faso, no brand purchased was listed as trademark – consequently the average costs were significantly lower (240 FCFA ± 181 FCFA; 187.50 FCFA). *Biltricide* was sold in both nations in a small jar containing four tablets of 600 mg of API and cost 9,810 FCFA per jar (about 15 €) in each country (refer to Figure 29).

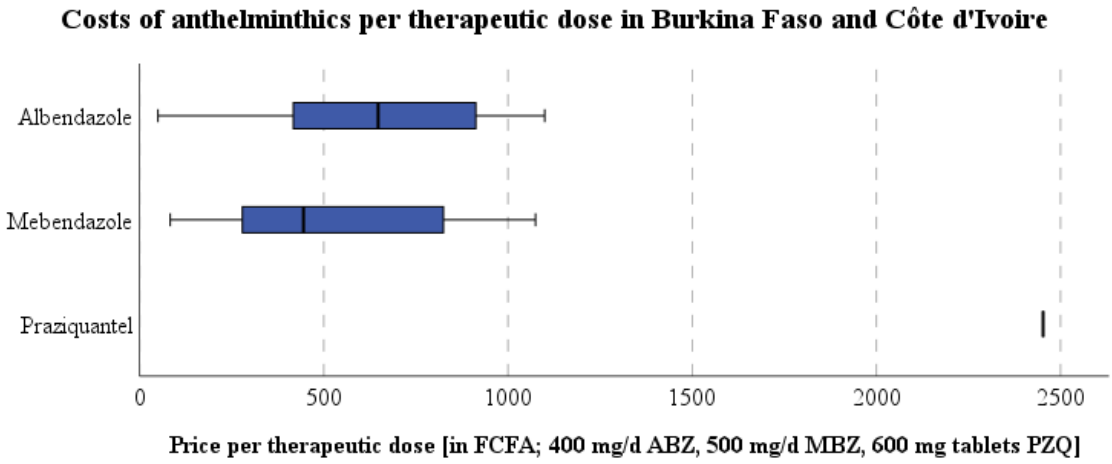


Figure 29: Costs of anthelmintics per TD in Burkina Faso and south-eastern Côte d'Ivoire. The price range of ABZ and MBZ products lay between 50 FCFA and 1,100 FCFA per TD, equalling 0.08 € and 1.68 € [19].

4.2.2 Appearance and packaging

In Burkina Faso and Côte d'Ivoire, 18 different products were purchased. Lacking official information about licensed drugs in both countries, the screening for trademark registration revealed that just six brands were officially registered. Four products (one ABZ, three MBZ) were sold under their INNs.

As in Figure 30, the vast majority of the 18 products gathered in both countries was manufactured in India (77.8 %, n = 14). The other four brands came from China, Côte d'Ivoire, Germany and Togo (5.6 % each).

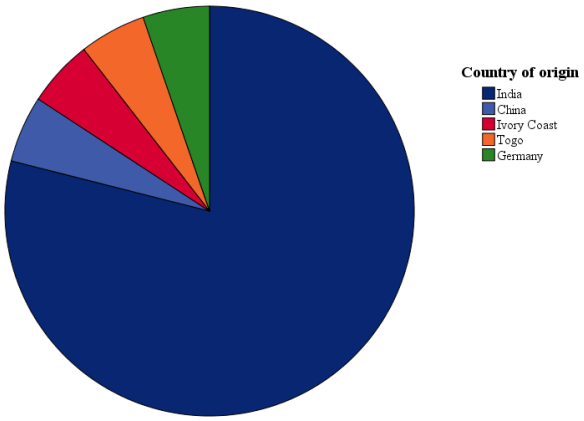


Figure 30: Different countries of origin of anthelmintic medicines available in Burkina Faso and Côte d'Ivoire.

DoE of all 23 different samples were indicated on the packages, varying between eight months (*Bendex-400*) and 33 months (B. No. R70E8001 of *Wormin 500* by Cadila Pharmaceuticals Limited / India). *Bendex-400* was the only product to expire within twelve months after sale.

Visual examination of the packages came up with a few discrepancies from the WHO tool. Three products from Burkina Faso (the ABZ drug *Elband 400*, *Mebendazole* tablets by Fourrts Laboratories Pvt. Ltd. / India and *Mébendazole*) were sold as plain blisters without any packaging – consequently, this aspect could not be assayed. The manufacturer's address was incompletely provided in the ABZ brand *Tanizol* by Donas Drugs & Pharmaceuticals (P) Ltd. / India. DoM were missing in two cases (*Mébendazole* and *Oziben*) and a leaflet was not included in the MBZ brand *Nebenda* by Syncom Formulations (I) Ltd. / India. The examination of the tablets also resulted in some deficiencies: the texture of two products – the ABZ brands *Albendazole TM* and *Sanozol* by Osaka

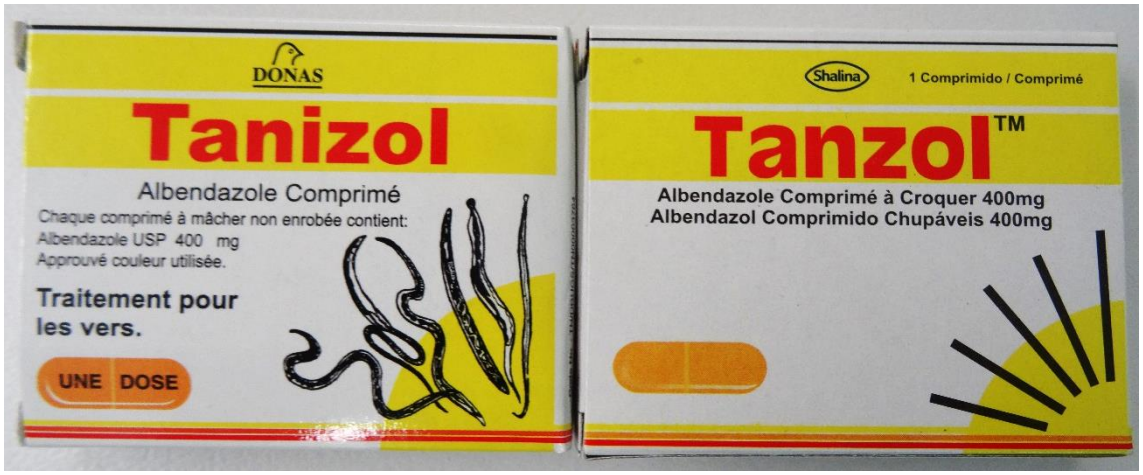


Image 10: Similar packages of *Tanizol* and *Tanzol*.

Pharmaceuticals Pvt. Ltd. / India – varied significantly within a batch; two products showed minor breaks, cracks and splits (*Elband 400* with six out of 20 samples split in half, and *Sanozol*). Even though *Sanozol* also exhibited embedded surface spots or contamination, again no product was suspected to be SF medicine. Striking however was the comparison of two ABZ products, *Tanzol* bought in Ghana and *Tanizol* bought in Burkina Faso. The similarity of both packages was so close that special focus was laid on these two brands in the further analytical steps to see whether one of these drugs was SF medicine (Image 10).

4.2.3 Mass uniformity of samples obtained in Burkina Faso and Côte d'Ivoire

In the western and northern neighbours of Ghana, overall 17 brands – eight ABZ products, eight MBZ products and one PZQ product – were assayed (see Figure 31). The ABZ brand *Lyben* had to be left aside, as obviously two differently sized batches were bought. Here again, the abundance of various ABZ and MBZ brands made it difficult to regularly purchase the adequate number of 20 or more tablets per brand / batch. This had proven to be an elaborate challenge when a certain product had only been available three-fold or four-fold in the vending place of choice (to be seen in eight samples of *ABZ*, ten samples of *T-Medazol* or twelve samples of *Tanizol* by Donas Drugs & Pharmaceuticals (P) Ltd., India). Five brands were analysed with 15 tablets, and another two brands with

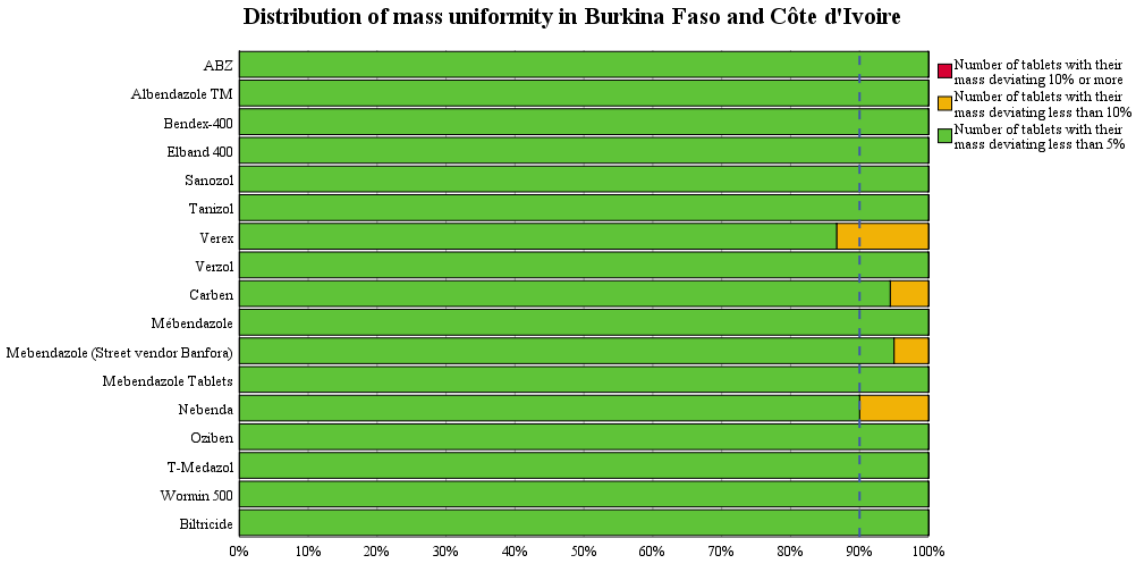


Figure 31: Distribution of mass uniformity in Burkina Faso and Côte d'Ivoire.
Percentages were indicated as not always a minimum of 20 tablets per product could be analysed. The blue dotted line indicates the 90 % limit (18 / 20 whenever possible), beyond which a product passed this test.

18 tablets per product. Nonetheless, this distribution resulted in merely one product, the ABZ drug *Verex* (86.7 % of the samples assay deviated by no more than 5 %), not passing the required standards – as in Ghana, the remaining 94.1 % of the products passed.

4.2.4 Disintegration times of Burkinabé and Ivorian products

Even under the concessions made to Ghanaian products, a minimum of four tablets per brand analysed could not always be guaranteed in Burkina Faso and Côte d'Ivoire. As a result, the disintegration profiles of *ABZ* (three samples assayed), *Lyben* (two samples assayed) and *Biltricide* (one sample assayed) only indicated a tendency of whether they passed the Minilab™ criteria. Nonetheless, all 18 brands were taken into account, resulting in two large groups: those completely passing and those not disintegrating at all after 45 minutes. 13 products (72.2 %) fulfilled the requirements, ranging between 0.25 (a sample of *T-Medazol*) and 24.25 minutes (a sample of *Tanizol*). The remaining five

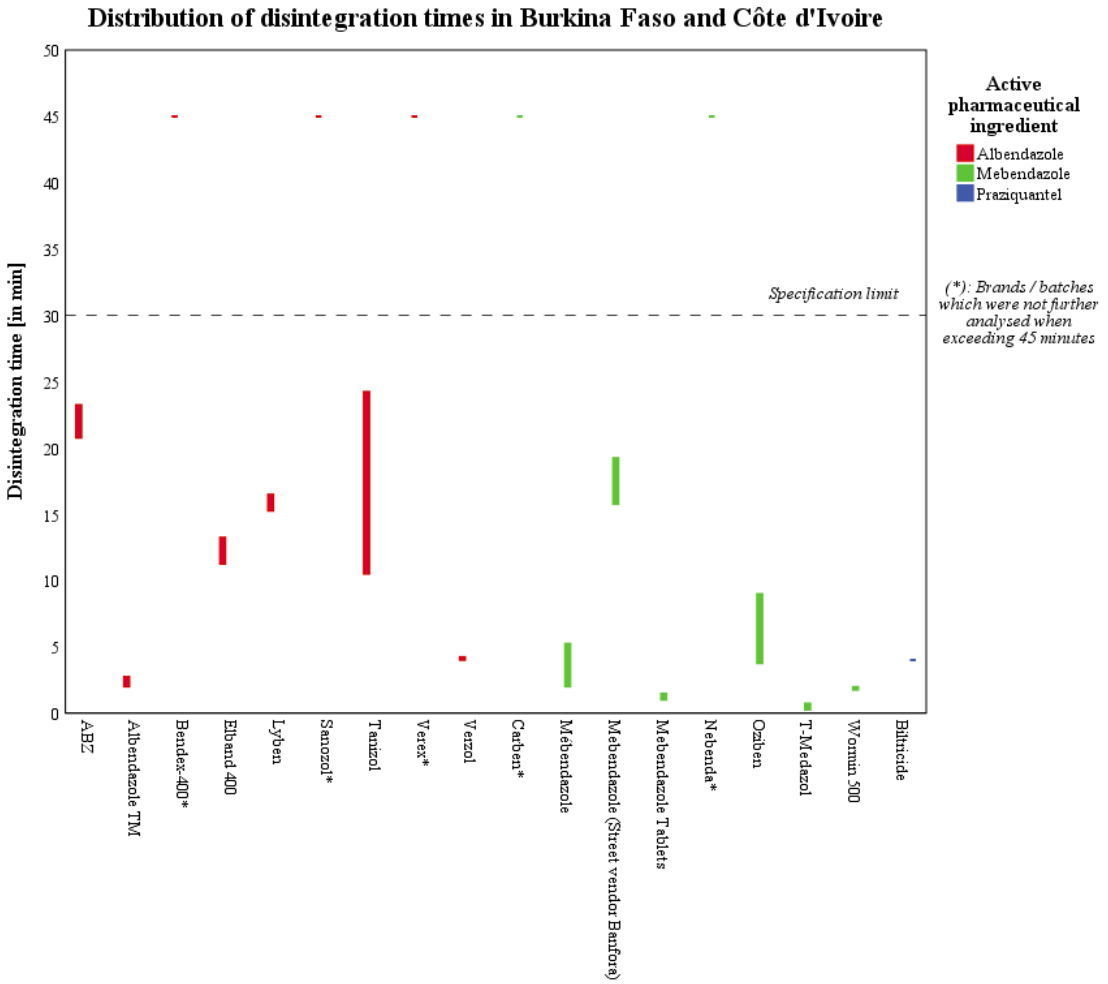


Figure 32: Distribution of disintegration times in Burkina Faso and Côte d'Ivoire.

products (*Bendex-400, Sanozol, Verex, Carben* and *Nebenda*) did not respond to the influence of water of body temperature at all. Overall again, less than three out of four brands fully passed the criteria for disintegration times and thus presented with acceptable galenic features (refer to Figure 32).

4.2.5 Thin-layer chromatography of samples from Burkina Faso and Côte d'Ivoire

23 different batches of tablets from both countries were analysed for TLC (Table 4). Like in Ghana, not a single product was detected to be counterfeit or falsified. It rather occurred, again, that samples exceeded the USL of 100 % l.c. Such excess was predominantly seen with MBZ batches (60.0 % of them appeared correspondingly after exposure to methanolic sulfuric acid) but also in B. No. 186 of *Verex*. ABZ batches (91.7 %) were almost completely in range within the SLs, even though 33.3 % of the ABZ batches (*Bendex-400, Elband 400, Sanozol* and *Tanizol*) were assayed to be very close to the LSL. Two MBZ brands (chewable *Mebendazole* purchased from a street vendor in Banfora and *Mébendazole*) and surprisingly *Biltricide* had to be characterised similarly.

Table 4: Burkinabé and Ivorian TLC results.
Spots similarly strong as the 80 % LSL were assessed to be 'in range'

Burkinabé and Ivorian TLC results	**ABZ** (n = 12)	**MBZ** (n = 10)	**PZQ** (n = 1)	**Total** (n = 23)
In range (API between 80 % and 100 % l.c.)	91.7 % (11)	40.0 % (4)	100.0 % (1)	69.6 % (16)
API exceeding 100 % l.c.	8.3 % (1)	60.0 % (6)	0.0 % (0)	30.4 % (7)
API undercutting 80 % l.c.	0.0 % (0)	0.0 % (0)	0.0 % (0)	0.0 % (0)
Falsified / counterfeit API	0.0 % (0)	0.0 % (0)	0.0 % (0)	0.0 % (0)

4.2.6 Dissolution profiles of Burkinabé and Ivorian products

22 different batches of anthelmintics were evaluated: twelve ABZ (resulting in nine different brands), nine MBZ (resulting in eight different brands) and one PZQ batch. B. No. R70E8003 of *Wormin 500* could not be evaluated.

ABZ dissolution profiles can be seen as tripartite: four of the twelve batches passed the criteria of Ph. Int. 7, ranging between 92.0 % l.c. (*Albendazole TM*) and 99.1 % l.c. (B. No. TE-6677 of *Verzol*). Four batches failed moderately, with *ABZ* just missing the respective threshold of $Q \geq 80$ % by dissolving to 77.5 % l.c. Four brands however

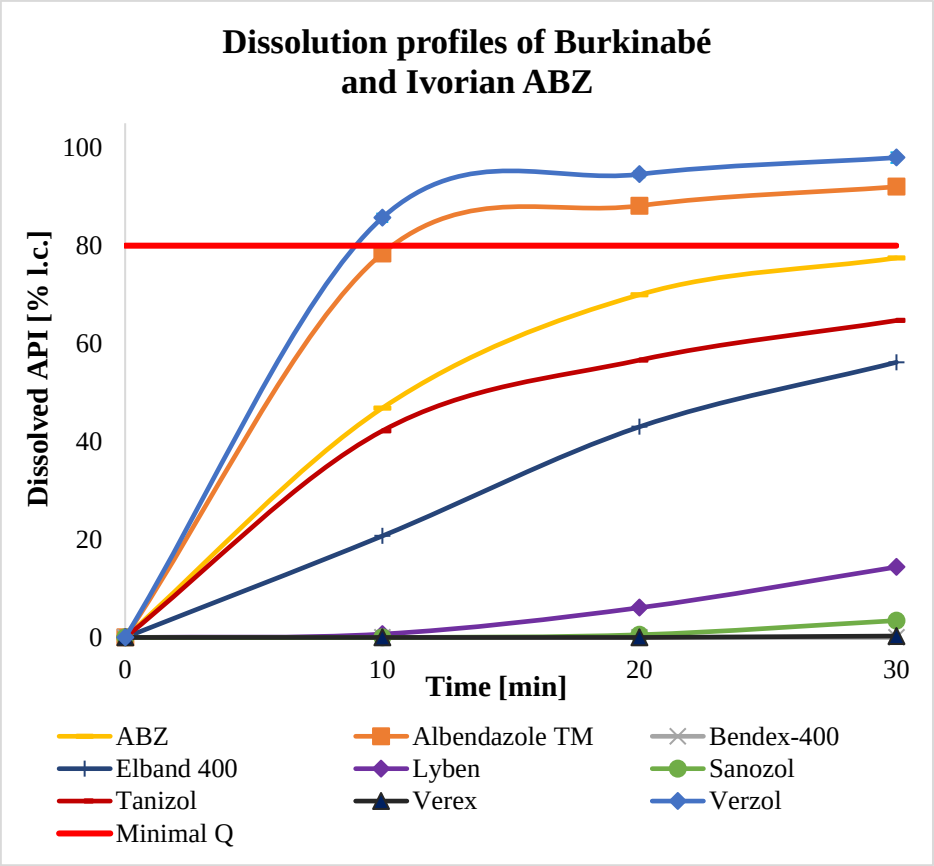
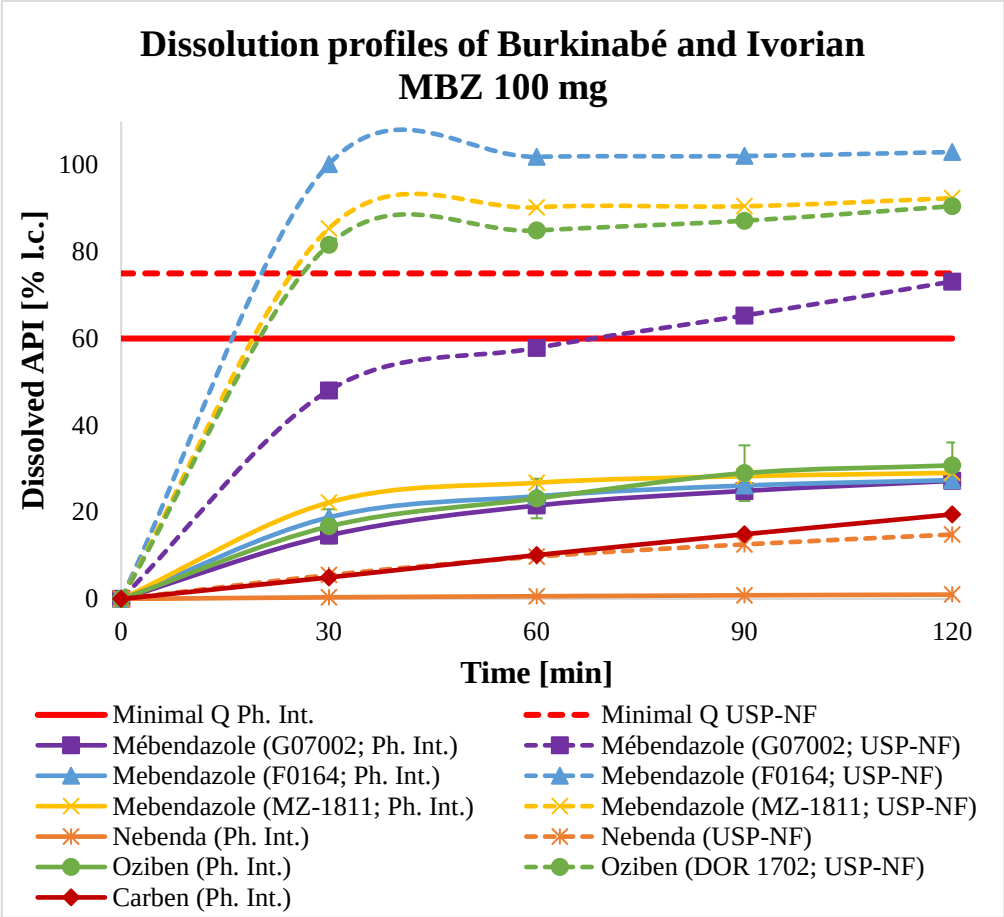


Figure 33: Distribution of dissolution profiles of Burkinabé and Ivorian ABZ brands. The red horizontal line indicates the specific minimal Q of each API. Whenever more batches of a brand were assessed, average (coloured spots) and SD (whiskers) were indicated.

did not even dissolve to 5.0 % l.c.: *Bendex-400* did not dissolve at all, and the other three brands (both *Verex* batches to less than 0.5 % l.c. and *Sanozol* to 3.4 % l.c.) merely showed minimal dissolution (refer to Figure 33).

Demonstrated in Figure 34 and 35, MBZ batches from these two countries had to be assessed depending on the formulation and the pharmacopoeia applied: when testing 100 mg batches (7 / 9) according to Ph. Int. 7, not a single batch passed the indicated Q ≥ 60 % – dissolution ranged between 1.0 % l.c. (*Nebenda*) and 34.5 % l.c. (*Carben*). However, when subjecting 100 mg samples to USP-NF 41 criteria (applicable to only five of the batches), the respective threshold of Q ≥ 75 % was reached by three batches, ranging from 14.9 % l.c. (*Nebenda*) to 103.0 % l.c. (*Mebendazole* tablets, B. No. F0164). 500 mg gives (2 / 9) were analysed in reference to Ph. Int. 7 and varied between 69.1 % l.c. (*T-Medazol*) and 88.9 % l.c. (B. No. R70E8001 of *Wormin 500*).



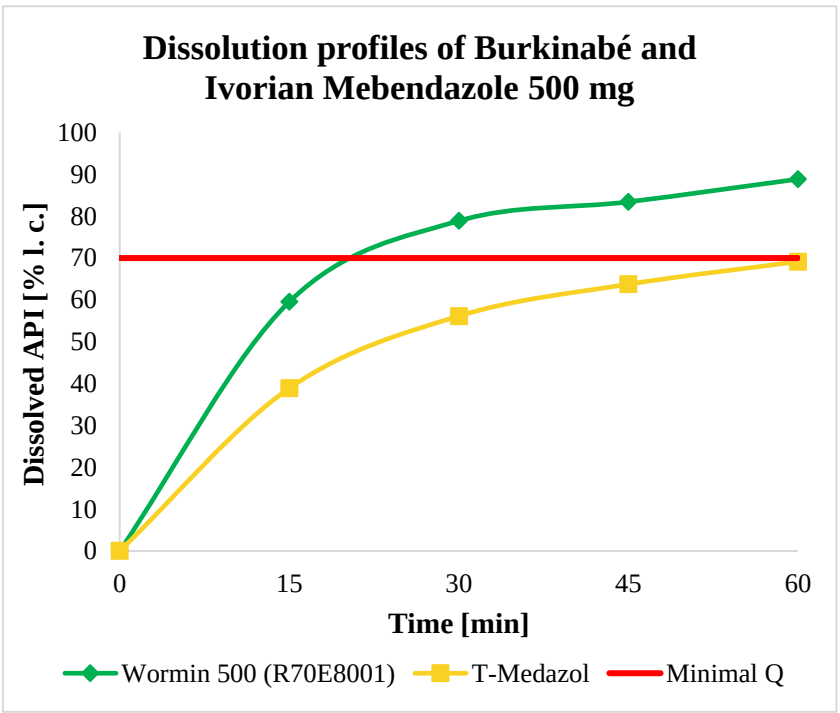


Figure 34 + 35: Distribution of dissolution profiles of Burkinabé and Ivorian MBZ brands. The red horizontal line indicates the specific minimal Q of each API. Whenever more batches of a brand were assessed, average (coloured spots) and SD (whiskers) were indicated. Dotted lines: USP-NF 41 criteria for MBZ products.

Biltricide, the only PZQ product encountered in these countries, dissolved to 90.2 % l.c. and therefore passed the USP-NF 41 target of $Q \geq 75$ % (the illustration is to be found in Chapter 4.1.6 alongside the results of Ghanaian *Praziquantel 600*).

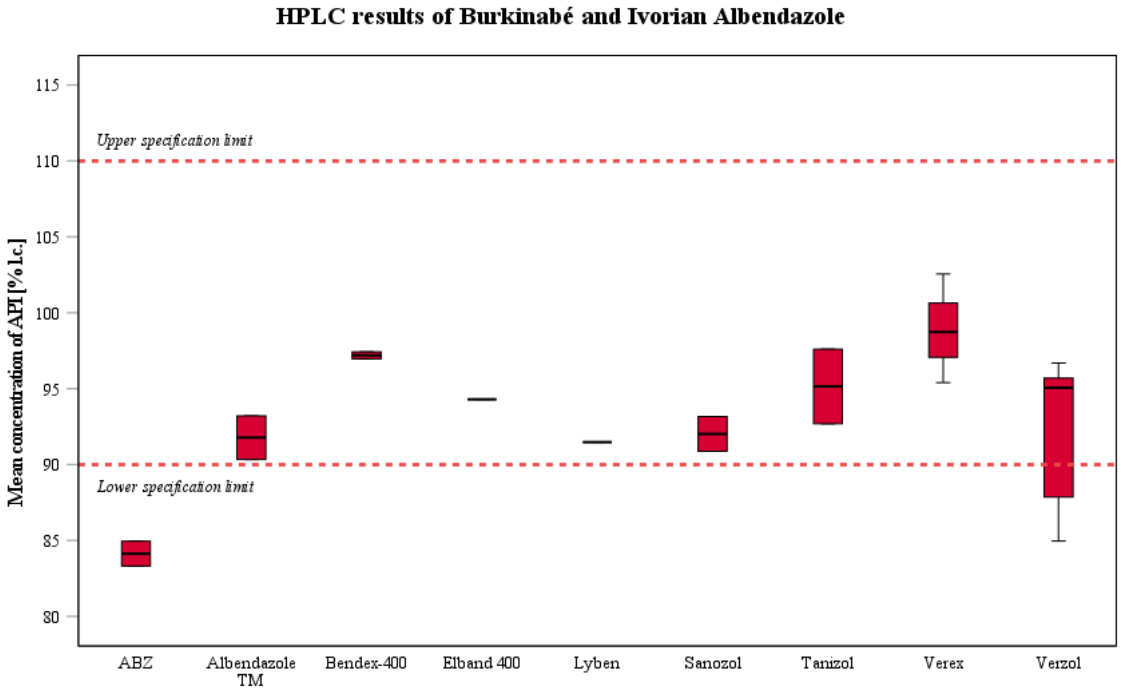
In summary, merely 27.3 % (6 / 22) of all Burkinabé and Ivorian batches collected and evaluated passed Ph. Int. 7 criteria; again, the majority of 72.7 % (16 / 22) did not do so (USP-NF 41 resulted in a more balanced ratio of 44.4 % passing and 55.6 % failing).

4.2.7 HPLC-UV on samples from Burkina Faso and Côte d'Ivoire

Every batch purchased between Grand Bassam and Ouagadougou was analysed, varying between one and three tablets. As in Ghana, larger deviations from the average concentration of API were not detected when having bought more than one batch of a product. This led to nine ABZ, eight MBZ and one PZQ brand(s) being tested.

In ABZ brands, API concentration varied from 84.1 % l.c. ± 1.4 % RSD (*ABZ*) to 98.9 % l.c. ± 3.6 % RSD (*Verex*). *ABZ* was the only brand to not pass Ph. Int. 7 criteria. All other products ranged between 90 % l.c. and 100 % l.c. (refer to Figure 36).

MBZ brands presented with concentrations from 90.0 % l.c. ± 2.3 % RSD (*Mebendazole* tablets, B. No. MZ-1811) to 106.4 % l.c. ± 0.6 % RSD (*Carben*). Besides this indicated generic MBZ brand just passing, one product passed between 90 % l.c. and 100 % l.c. while the other six were set between 100 % l.c. and 110 % l.c. (refer to Figure 37).



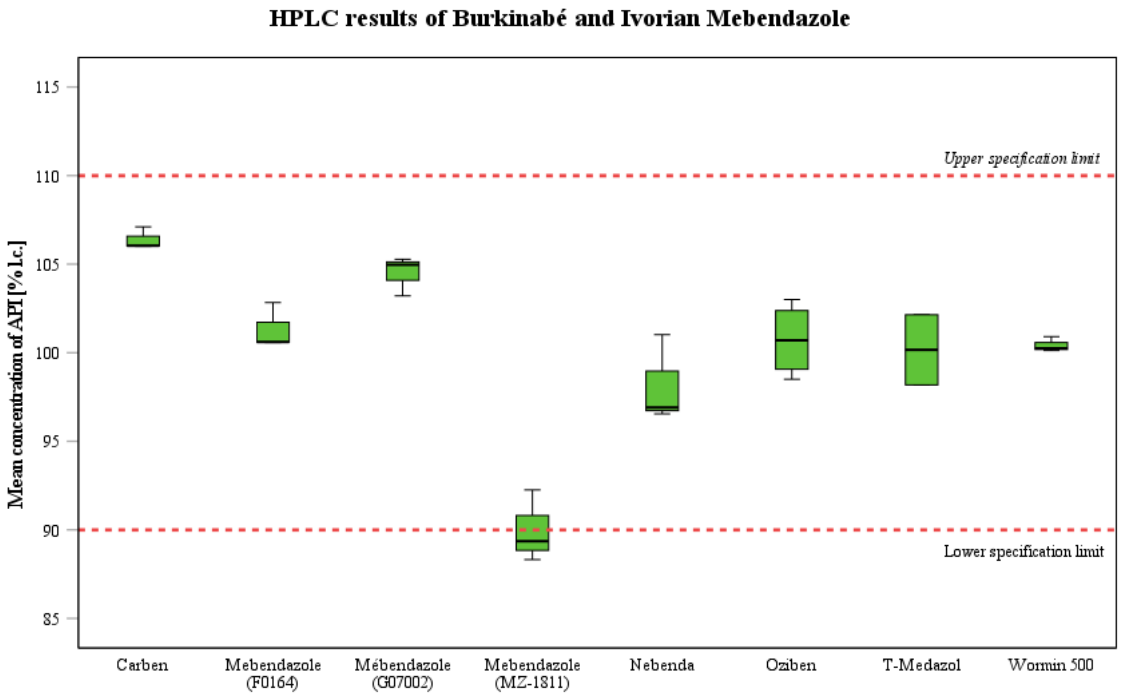


Figure 36 + 37: HPLC-UV results of Burkinabé and Ivorian ABZ and MBZ.
Biltricide is included in Figure 48 into a pan-African figure of PZQ HPLC results.

Biltricide (illustrated in Chapter 4.3.7) was analysed with a concentration of 106.5 % l.c. (only one tablet assayed, hence no RSD).

On average, 94.4 % (17 / 18) of the products collected in Burkina Faso and Côte d'Ivoire were assessed to be within SL. One of these products, B. No MZ-1811 of a generic MBZ brand, resulted in a marginal quality.

4.3 Evaluation of anthelmintic drugs collected in Tanzania

4.3.1 Variable availability and prices of different brands

Across the different towns and regions in northern Tanzania, a variable choice of different ABZ, MBZ and PZQ products could be encountered. In reference to Figure 38, virtually all the products seen in the survey area could be bought in Mwanza itself – 24 of the 47 samples acquired were obtained there. As Bukoba (n = 7), Musoma (n = 5) and Nansio (n = 2) are directly supplied by distributors and wholesalers from Mwanza, no unexpected products were discovered (except for *Albendazole 400mg* by GSK, only in Nansio) – variation was understandably less abundant in the smaller towns. Local emphasis was put on the ABZ brands *Alben* and *Zentel* (tablets and suspensions), the MBZ

brands *Astazole* and *Wormol* (as suspension, by Elys Chemical Industries Ltd. / Kenya) and the PZQ brand *Praziquantel-600* by Shelys. Kasulu (n = 5) and Kigoma (n = 4) are partly supplied via Mwanza and partly via Dar Es Salaam directly. Thus, products like *Mebrone-100* by Strides Shasun Limited / India and *Mebendazole 500mg BP* by Remedica Ltd. / Cyprus could particularly be found there.

4.3.1.1 Price range in Mwanza and the surrounding Lake Zone region

For one TD of ABZ, patients in and around Mwanza would have to pay between 233 TZS and 5000 TZS (1681 TZS ± 1478 TZS; 1250 TZS). A single dose of *Anthel* (by Lincoln Pharmaceutical Ltd. / India) was found to be about fourfold more expensive (1000 TZS instead of 233 TZS) outside Mwanza than in the city itself. One TD of MBZ cost between 100 TZS and 15,000 TZS (median 500 TZS), with *Vermox* being significantly more expensive than any other MBZ product available in Mwanza. Different samples of *Astazole* comparatively showed the greatest variability between 200 TZS per TD

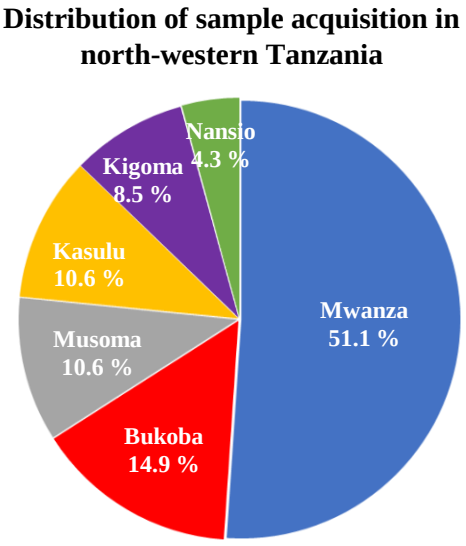


Figure 38: Ratio of samples collected per town in north-western Tanzania.

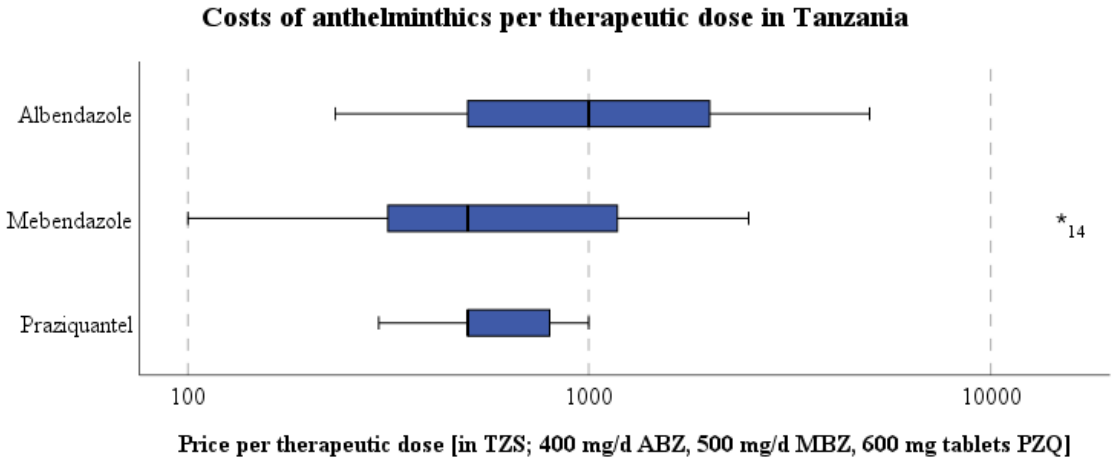


Figure 39: Costs of (human) anthelmintics per TD in north-western Tanzania.
A logarithmic illustration was chosen to encompass *Vermox* (*14), which cost 15,000 TZS / 5.67 €. Except for *Vermox*, the price range was between 100 TZS and 5000 TZS per TD, equalling 0.04 € and 1.89 € [19].

and 500 TZS per TD. PZQ products ranged between 300 TZS and 1000 TZS (700 TZS ± 271 TZS; 800 TZS), the prices per 600 mg formulation being slightly more expensive outside Mwanza (refer to Figure 39). VetABZ samples (n = 4) were bought in varying quantities of API per TD without having the exact prices of each product at avail, which left the costs difficult to compare.

4.3.1.2 Price range in Kigoma region

Anthelmintics in western Tanzania were sold at more homogenous prices than in the Lake Zone area. *Azentel* (a TD cost just one sixth less than in Mwanza) and *Natoa* (833 TZS instead of 100 TZS because it was sold in a package per six tablets of 100 mg, rather than in a tin of 1,000 tablets) were slightly beyond average, but apart from that, expenses on ABZ (833 TZS ± 561 TZS; 583 TZS) and MBZ (517 TZS ± 280 TZS; 417 TZS) samples acquired were settled between 300 TZS and 667 TZS per TD. PZQ brands again were a little more difficult to get hold on, costing however just 500 TZS per 600 mg give in any case.

4.3.2 Appearance and packaging

27 different products of anthelmintic medicines were acquired in north-western Tanzania (*Cesol* was provided by CUHAS and consequently not bought nor found to be available for sale). Four of them (14.8 %) were not registered by September 2018 (according to TFDA Mwanza, even by the first round of collecting samples from Mwanza in June 2018, these brands were not registered). *Albendazole 400mg* by Medreich Limited / India (9.1 % of all ABZ products collected) and *Wormnil* by Aurochem Pharmaceuticals Pvt. Ltd. / India, *Mebrone-100* and *Mebendazole BP 500mg* (37.5 % of all MBZ products collected) were not licensed as treatment for sale.

As to be seen in Figure 40, most of the 28 products gathered were manufactured in Asia (57.1 %, n = 16). 39.3 % (n = 11) of them came from India, 10.7 % (n = 3) from South Korea and just 7.1 % (n = 2) from China. However, a significant amount of products (28.6 %, n = 8) was manufactured on the African continent as well, with 14.3 % (n = 4) coming from Kenya, 7.1 % (n = 2) coming from Tanzania itself and another 7.1 % (n = 2) from South Africa. The other products were manufactured in Cyprus (7.1 %, n = 2), in France (3.6 %, n = 1) and in Mexico (3.6 %, n = 1).

DoE of four out of 47 different samples could not be evaluated since they were bought in small sachets. DoE of the other batches varied between less than two months (*Praziquantel-600* in Bukoba) and 45 months (*Alben* batches from 2018). Four batches (8.5 %) were to expire within less than twelve months from the date of sale.

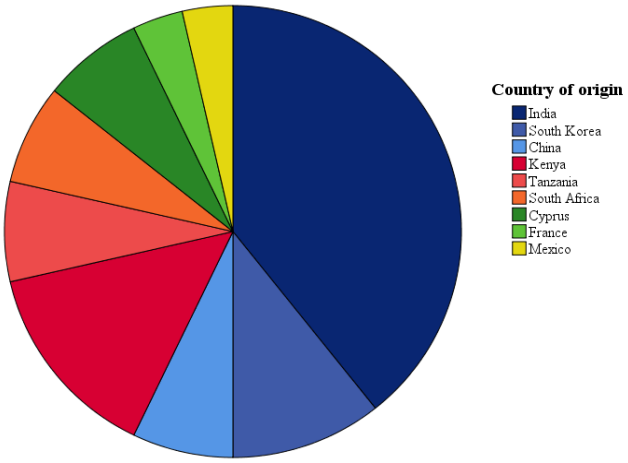


Figure 40: Different countries of origin of anthelmintic medicines available in Tanzania.

Visual examination of the packages itself did not reveal any SF products; all but *Vermox* and *Cesol* (not indicating DoM) passed the criteria without constraint. The appearance of the tablets resulted in some deficiencies: the texture of two products – *Ashialben 600* and *Praziquantel-600* – varied significantly within a batch; four products showed minor breaks, cracks and splits (*Ashialben 300*, *Bermoxel*, *Prazikant* and *Wormnil*). Overall and analogous to the evaluation of the West African products, in spite of some irregularities, no Tanzanian brand was suspected to be SF medicine.

4.3.3 Mass uniformity of samples obtained in Tanzania

Determining a regular distribution of masses of various samples per product, 24 different anthelmintic drugs were taken into account: nine ABZ, six MBZ, five PZQ and also four vetABZ brands (refer to Figure 41). However, besides the expensive originator brands *Zentel* and *Vermox*, four out of the 20 non-veterinarian products could not be assayed to full extent as the minimum required number of 20 samples per product could not be collected (only six tablets of *Albi* by Korea Arlico Pharm. Co., Ltd. / South Korea, ten tablets of *Womiban* by Blue Cross Laboratories PVT LTD / India, 14 samples of *Mebrone-100* and 15 samples of *Prazikant* by S Kant HEALTHCARE Ltd. India). The four veterinarian ABZ drugs though weighed a lot more than the 'regular' ABZ ones (between 3.93 g and 10.43 g instead of a maximum of 1.06 g for *Azentel* samples). Because of these higher masses and consequently larger SDs, just ten samples per product

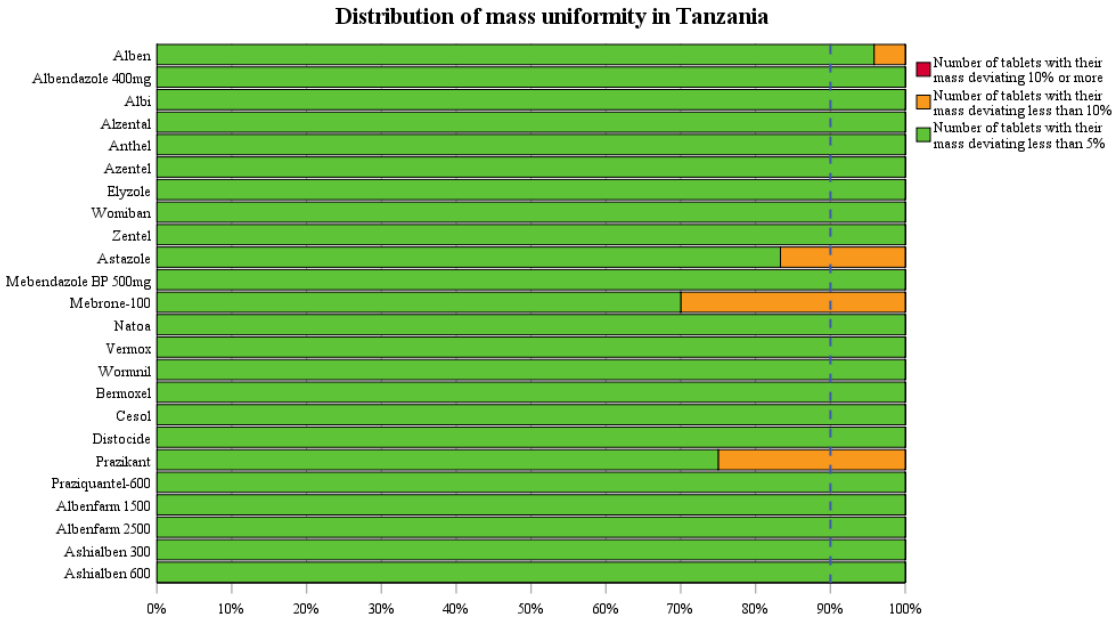


Figure 41: Distribution of mass uniformity in Tanzania.
Percentages were indicated as not always a minimum of 20 tablets per product could be analysed. The blue dotted line indicates the 90 % limit (18 / 20 whenever possible), beyond which a product passed this test.

were accepted (still, only three tablets of *Ashialben 600* had been obtained). Nevertheless, results show that only three medicines – the two MBZ brands *Astazole* (83.3 % not deviating more than 5 %) and *Mebrone-100* (70.0 % not deviating more than 5 %) as well as the PZQ brand *Prazikant* (75.0 % not deviating more than 5 %) – did not pass mass uniformity test (12.5 %); the remaining 21 medicines (87.5 %) were within acceptable limits.

4.3.4 Disintegration times of Tanzanian products

Owing to merely a few tablets purchased, *Zentel*, *Vermox* and *Ashialben 600* were not tested at all, and only three tablets of *Albi* could be tested, thus not being fully representative in accordance to the guidelines. Notwithstanding, out of these 21 remaining brands (*Albi* included), 16 (76.2 %) disintegrated within the SL of 30 minutes regardless of any specific batch. Two brands, *Alzental* and *Praziquantel-600*, showed differences within the batches though. *Alzental* B. No. S001 was fully in range (only two samples

Image 11: Pinkish *Natoa* samples after 30 minutes of (non-)disintegration.

could be tested), whereas B. No. S002 (four samples tested) failed completely with two tablets exceeding even 45 minutes. *Praziquantel-600* B. No. 140007 and 160004 also met the requirements, disintegrating between 5.5 and 16 minutes. Contrary to this, samples of B. No. 170003 disintegrated significantly more slowly, between 24.75 and 35.5 minutes (meaning that 50 % of this very batch exceeded SLs). *Alben* disintegrated to full extent but too slowly (between 35.75 and 49.75 minutes). *Elyzole* conversely did not completely disintegrate within the extended 45 minutes – merely thin flakes were breaking off the tablets (Image 12). *Natoa* samples did not alter their composition whatsoever (Image 11). Consequently, almost one out of four anthelmintic

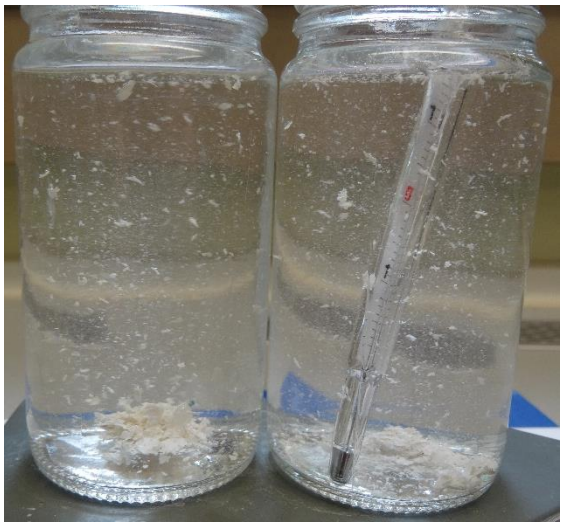


Image 12: *Elyzole* samples disintegrating too slowly and in thin flakes.

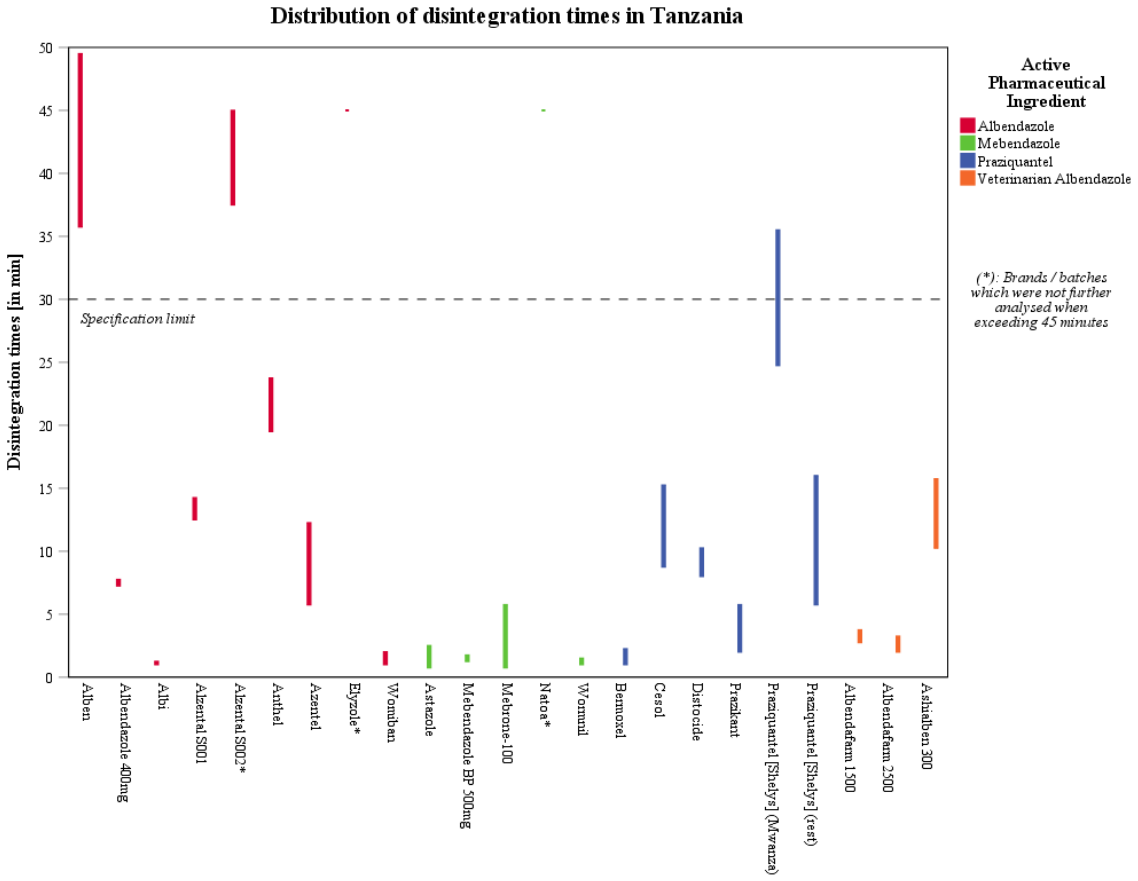
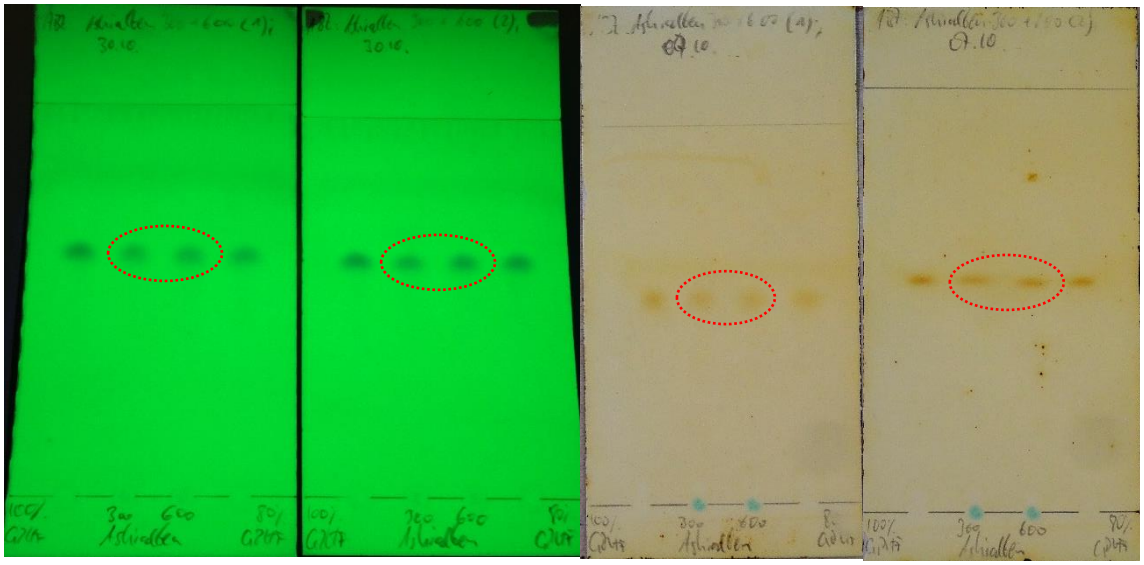


Figure 42: Distribution of disintegration times in Tanzania.

medicines revealed deficiencies in terms of their disintegration profile and hence in their galenic characteristics as well (refer to Figure 42).

4.3.5 Thin-layer chromatography of samples from Tanzania

40 different batches of tablets were analysed for TLC. Of these, not a single product was detected to be counterfeit or falsified. Two batches – the vetABZ products *Ashialben 300* and *Ashialben 600* (Images 13 – 16) – seemed to (at least intermittently) undercut the LSL of 80 % l.c. (10.0 %). An excess beyond the USL was predominantly seen with MBZ batches (88.9 % of them could be characterised accordingly after exposure to methanolic sulfuric acid). ABZ and PZQ batches were appeared to be completely in range within the SLs set by the Minilab™ (refer to Figure 5).



Images 13 – 16: TLC chromatoplates with *Ashialben 300* (always the left sports within the red circles) and *Ashialben 600* (always the right sports within the red circles) appearing to undercut the 80 % LSL.

Table 5: Tanzanian TLC results.
Spots similarly strong as the 80 % limit were assessed to be 'in range'.

Tanzanian TLC results	ABZ (n = 18)	MBZ (n = 9)	PZQ (n = 9)	Vet. ABZ (n = 4)	Total (n = 40)
In range (API between 80 % and 100 % l.c.)	100.0 % (18)	11.1 % (1)	100.0 % (9)	50.0 % (2)	75.0 % (30)
API exceeding 100 % l.c.	0.0 % (0)	88.9 % (8)	0.0 % (0)	0.0 % (0)	20.0 % (8)
API undercutting 80 % l.c.	0.0 % (0)	0.0 % (0)	0.0 % (0)	50.0 % (2)	5.0 % (2)
Falsified / counterfeit API	0.0 % (0)	0.0 % (0)	0.0 % (0)	0.0 % (0)	0.0 % (0)

4.3.6 Dissolution profiles of Tanzanian products

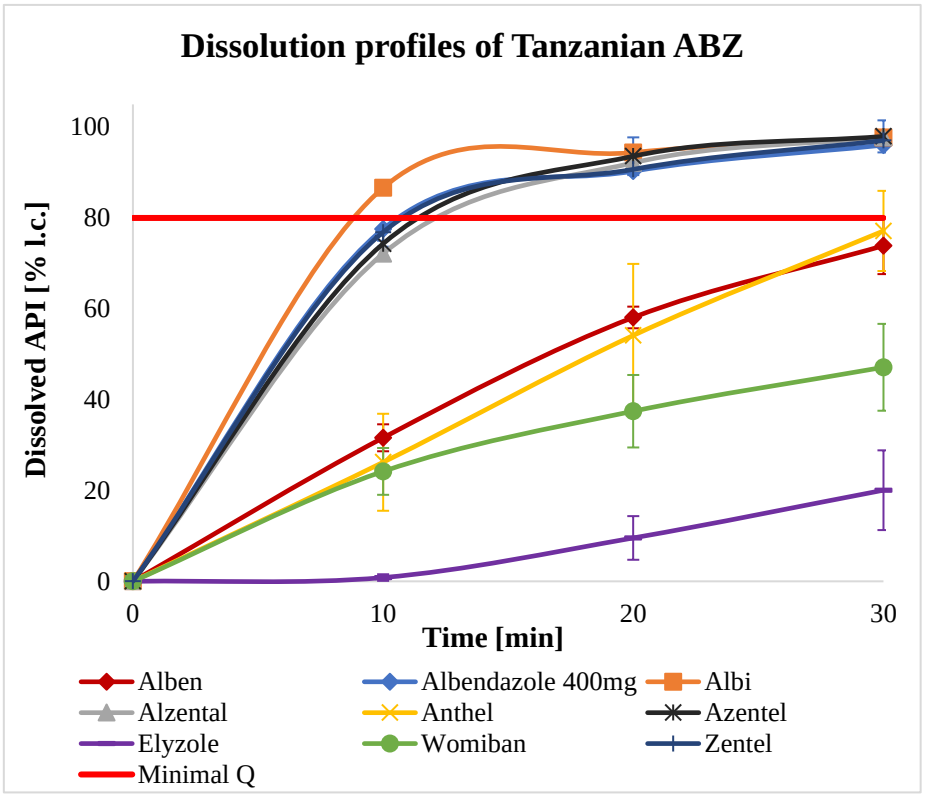
27 disparate batches of anthelmintic medicines were tested (31 batches when counting MBZ Ph. Int. 7 assays): 16 ABZ resulting in nine different products, three (USP-NF 41) / seven (Ph. Int. 7) MBZ (resulting in three / four different products) and eight PZQ batches (resulting in five different products). B. No. ALZET S001 of *Alzental*, B. No. 350579 of *Azentel*, *Mebendazole 500mg BP*, *Vermox* and B. No. 160004 of *Praziquantel-600* were not taken into consideration as there were not enough tablets available.

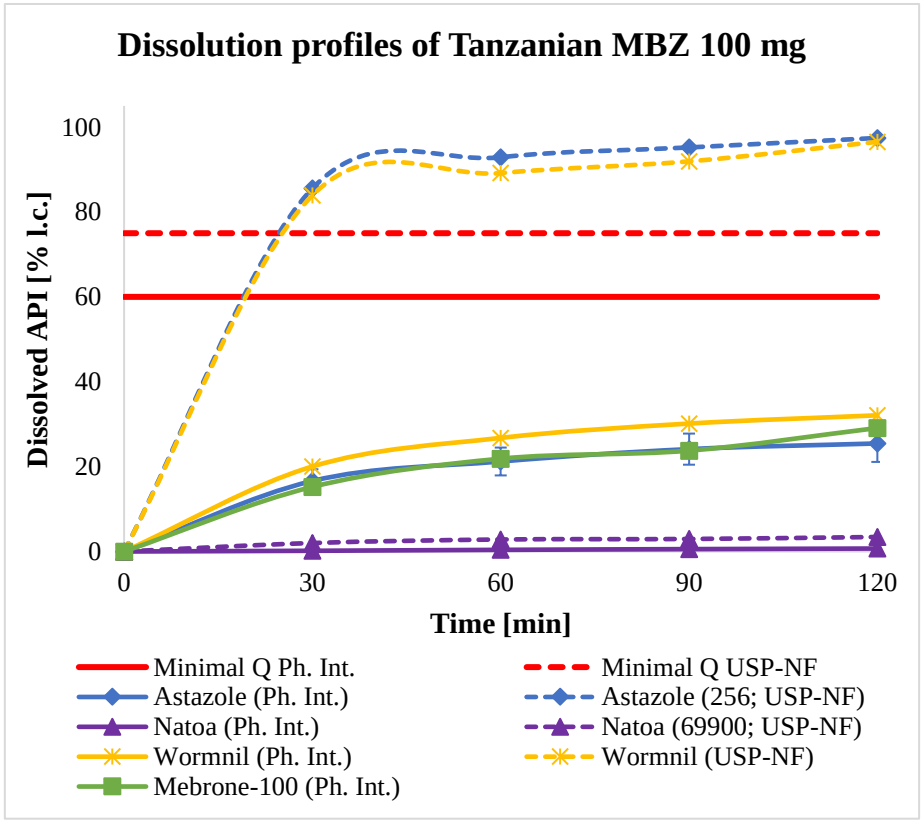
Unlike in West Africa, half of the ABZ batches passed Ph. Int. 7 criteria: eight out of 16 batches (50.0 %) dissolved to more than 80 % l.c. These samples ranged between 81.0 % l.c. (B. No. 170023 of *Alben*) and 100.5 % l.c. (B. No. 360766 of *Azentel*). In both *Alben* and *Anthel*, samples just passing the respective Q were met by some failing this specification limit by around 10 % l.c. One product, *Elyzole*, performed worse than the others, dissolving to not more than 25 % l.c. (refer to Figure 43).

Similar to the West African products, no MBZ batch containing 100 mg passed Ph. Int. 7 criteria to dissolve to $Q \geq 60$ % (see Figure 44). They ranged between non-dissolution (B. No. 69900 of *Natoa*) and 32.1 % l.c. (*Wormnil*). Applying though USP-NF 41 criteria, which was possible in *Astazole*, *Natoa* and *Wormnil*, these products performed significantly better: *Astazole* (97.4 % l.c.) and *Wormnil* (96.5 % l.c.) passed convincingly, *Natoa* dissolved at least minimally (3.4 % l.c.). Despite not having analysed *Vermox*, reference data from Ghanaian *Vermox* pointed out on satisfactory results.

As illustrated in Figure 45, PZQ batches (purely 600 mg tablets) were overall performing more balanced, ensuing in four out of eight batches (50.0 %) being acceptable according to USP-NF 41. Three brands – *Cesol*, *Distocide* and *Prazikant* – passed these criteria, dissolving between 75.6 % l.c. (*Prazikant* from Mwanza) and 90.1 % l.c. (*Distocide*). Two brands (*Bermoxel* and *Praziquantel-600*) failed to meet with pharmacopoeial requirements, being determined at 47.3 % l.c. (B. No. 170003 by *Praziquantel-600*) and, really close to SL, at 73.7 % l.c. (B. No. 140007 of *Praziquantel-600*).

Under revised conditions, 51.9 % (14 / 27) of the assayed Tanzanian batches surpassed the respective SL. Referring to MBZ Ph. Int. 7, only 38.7 % (12 / 31) of the tested batches did so.


Dissolution profiles of Tanzanian ABZ
Dissolved API [% l.c.]
100
80
60
40
20
0
0
10
20
30
Time [min]
Alben
Albendazole 400mg
Albi
Alzental
Anthel
Azentel
Elyzole
Womiban
Zentel
Minimal Q


Dissolution profiles of Tanzanian MBZ 100 mg
Dissolved API [% l.c.]
100
80
60
40
20
0
0
30
60
90
120
Time [min]
Minimal Q Ph. Int.
Minimal Q USP-NF
Astazole (Ph. Int.)
Astazole (256; USP-NF)
Natoa (Ph. Int.)
Natoa (69900; USP-NF)
Wormnil (Ph. Int.)
Wormnil (USP-NF)
Mebrone-100 (Ph. Int.)

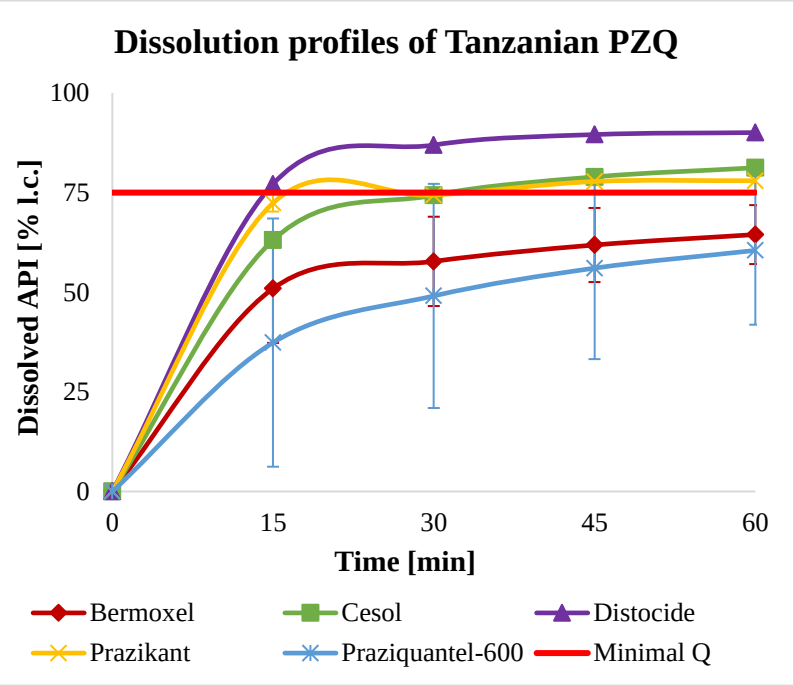


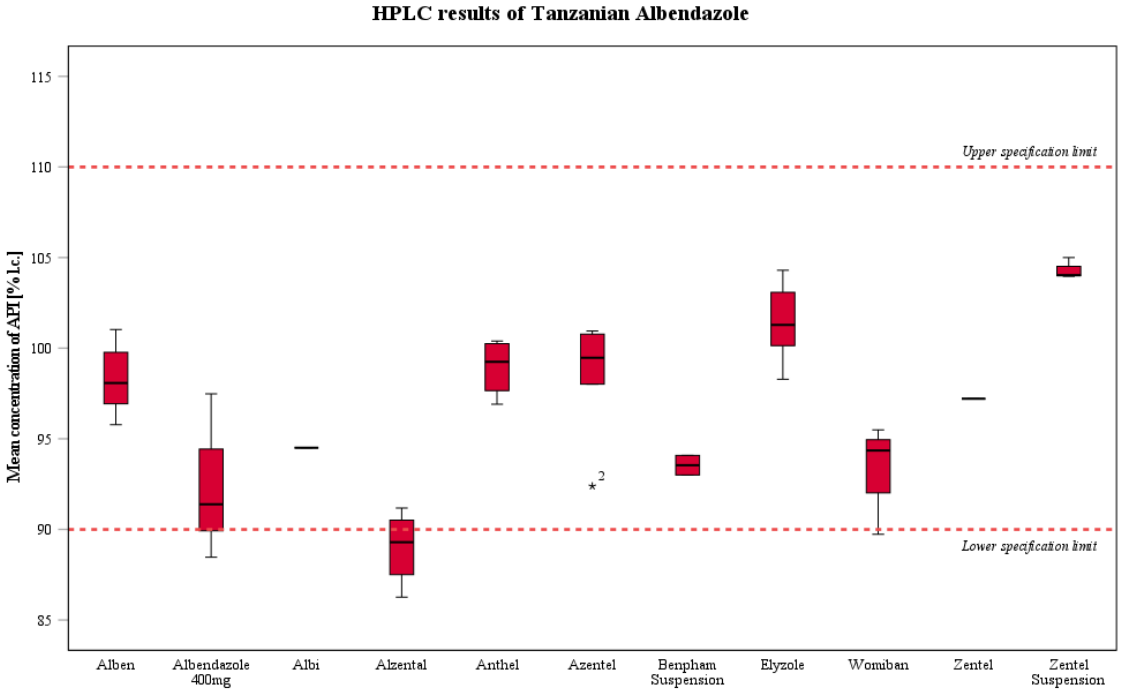
Figure 43 – 45: Distribution of dissolution profiles of Tanzanian products.
The red horizontal line indicates the specific minimal Q of each API. Whenever more batches of a brand were assessed, average (coloured spots) and SD (whiskers) were indicated. Dotted lines: USP-NF 41 criteria for MBZ products.

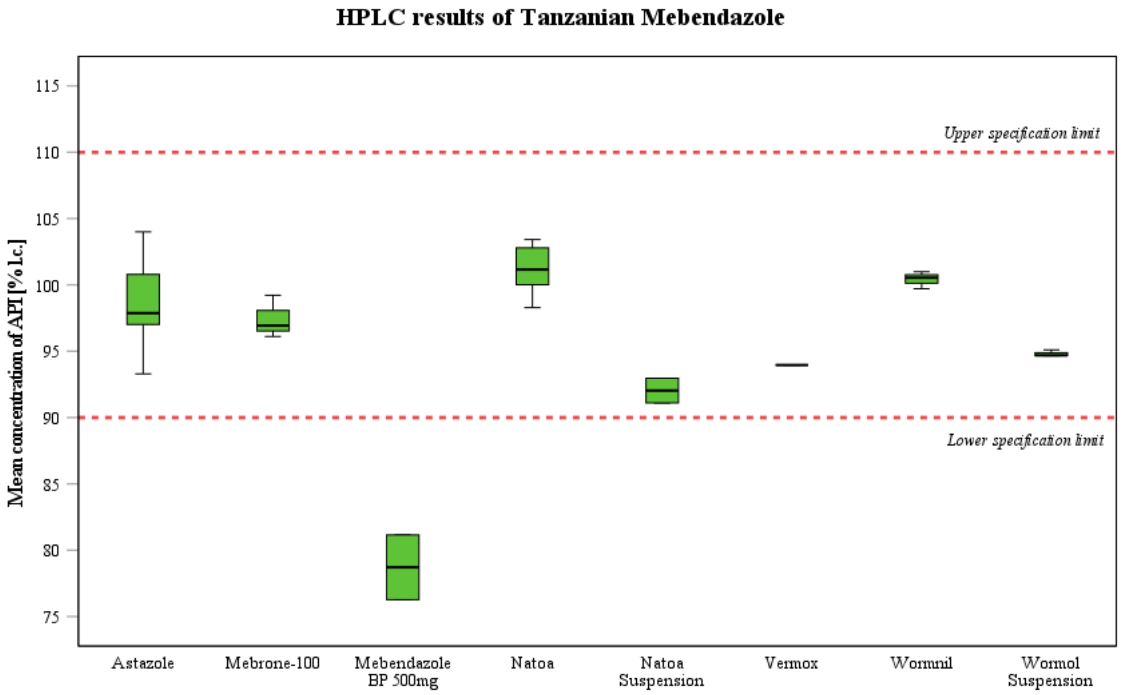
4.3.7 HPLC-UV on samples from Tanzania

Except B. No. 160004 of *Praziquantel-600*, all batches obtained in Tanzania were taken into consideration (including suspensions) and were analysed, varying between once (*Zentel* tablets and *Vermox*) and tenfold (B. No. 256 of *Astazole*). In products of which more than one batch was collected, larger deviations from the average concentration of API were not encountered in the different batches – thus only the different brands shall be illustrated. Eleven ABZ, eight MBZ and five PZQ products from north-western Tanzania were analysed.

In ABZ brands (refer to Figure 46), API concentration varied from 89.9 % l.c. ± 1.4 % RSD (*Alzental*) to 104.3 % l.c. ± 0.6 % RSD (*Zentel* suspension). Only one product, *Alzental*, just did not pass Ph. Int. 7 criteria. Eight products ranged between 90 % l.c. and 100 % l.c., the remaining two products ranged between 100 % l.c. and 110 % l.c. *Albendazole 400 mg* however, despite passing the LSL, showed variable concentrations throughout the samples tested (92.4 % l.c. ± 5.0 % RSD).

Depicted in Figure 47, MBZ brands presented with concentrations from 78.7 % l.c. ± 4.4 % RSD (*Mebendazole BP 500 mg*) to 101.1 % l.c. ± 1.9 % RSD (*Natoa*). Again, one product – *Mebendazole BP 500 mg* – missed international standards. Five out of the eight brands passed between 90 % l.c. and 100 % l.c., and two brands were found between 100 % l.c. and 110 % l.c.





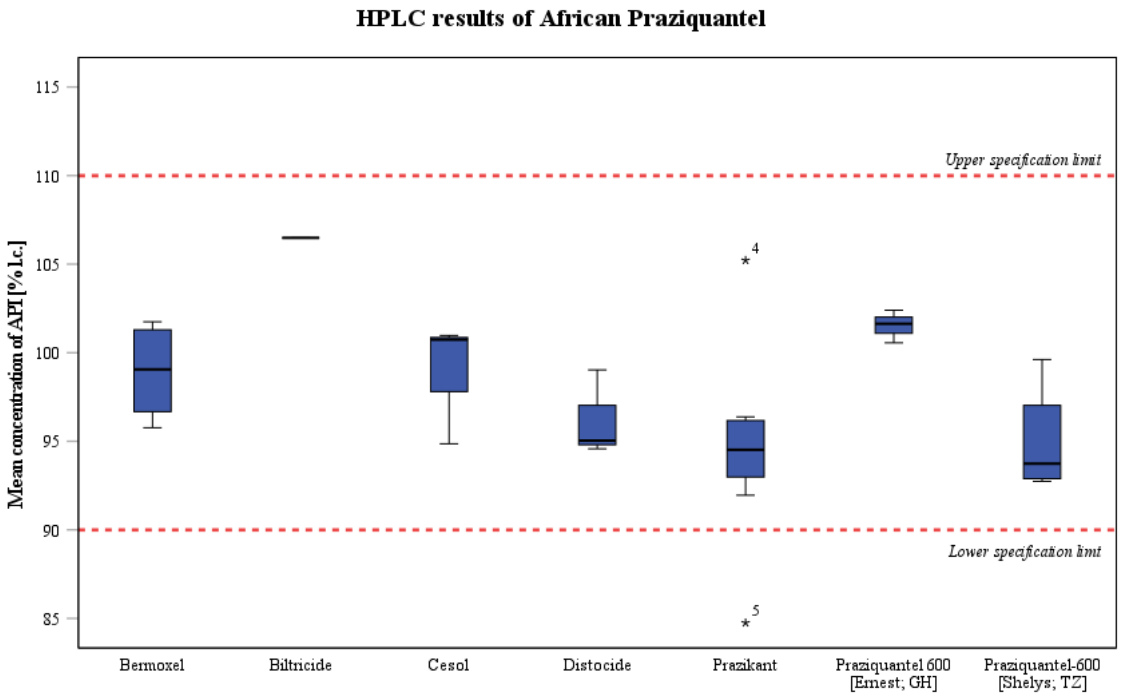


Figure 46 – 48: HPLC-UV results of Tanzanian anthelmintics.
Illustrating the comparatively small number of disparate African PZQ products, Figure 47 includes both brands collected in West Africa.

PZQ products were analysed with concentrations from 94.7 % l.c. ± 5.9 % RSD (*Prazikant*) to 98.9 % l.c. (*Bermoxel:* 2.6 % RSD / *Cesol:* 3.5 % RSD). Consequently, all five brands passed pharmacopoeial criteria between 90 % l.c. and 100 % l.c. (shown in Figure 48).

On average, 91.7 % (22 / 24) of the products collected in Tanzania were assessed to be within SL. One product, *Albendazole 400 mg*, resulted in a marginal quality, and two brands (*Alzental* and *Mebendazole BP 500 mg*) had to be rated as substandard.

5 Discussion

Continuing to successfully combat NTDs and hence warranting reliable and dependable access to safe therapeutics, a thorough QA of the respective agents must not be neglected in LMICs. By this study, the African map of reproducibly analysed Albendazole, Mebendazole and Praziquantel was expanded by products obtainable in Burkina Faso, Côte d'Ivoire, Ghana and Tanzania. Some of these medicines are not exclusively available in the countries of collection: products purchased in Tanzania tend to be officially licensed throughout the East African Union (Kenya, Uganda, Rwanda and Burundi) and neighbouring anglophone nations; Ghanaian anthelmintic may be sold all the way to Nigeria as well; and the drugs collected from Burkina Faso and Côte d'Ivoire are likely to be distributed in surrounding francophone neighbours. Despite having expected similarly, the positive results of overall sufficient content of API were substantially marred by the large share of more than 50 % of products failing in galenic testing.

5.1 Drug sampling and visual examination: taking local availabilities and conditions into account

Throughout the four countries, the focus of research and collection of samples lay on gaining an overview of the different brands of ABZ, MBZ and PZQ available in the respective regions. Registered / licensed products and those not registered likewise were consequently encompassed into this cross-sectional study, with distinctive interest in the latter ones (as far as this could be determined in Ghana and Tanzania). In contrast to other studies analysing the quality of API and galenic properties, a standardised number of samples purchased could not regularly be established. While other researchers had set a minimum number of 50 or 100 tablets per batch [97, 101], this study contented itself with at least ten tablets per batch and 20 tablets per brand – which was not always possible, especially with drugs sold as a single tablet (400 mg gives of ABZ, 500 mg gives of MBZ). In products acquired at smaller numbers, a prioritisation was made: even though not being the most economic approach in LMICs, HPLC-UV and dissolution profiles were regarded as more expressive than Minilab™ assays, so that especially mass uniformity and disintegration times could only indicate a tendency under such circumstances. Mass uniformity would deliver a relative distribution instead of an absolute number (at a minimum number

of 20 tablets tested), and disintegration times would delimit a less precise range (turning out difficult when samples varied strongly within a batch, but being acceptable when they oscillated around a certain value).

Some authors recommend an overt approach to wholesales, pharmacies and unofficial stalls but sending a 'mystery' shopper who would explain to the vendor why he or she needed the anthelmintics asked for [84]. A setting which focusses on large quantities of samples to be bought may be predestined for such strategy. Vendors suspicious of non-local customers or wary of random quality controls may be appeased by justifications like

- one member of a larger family / group travelling by had been sent due to medical advice or familiar symptoms in other members of this group [101];
- one person had to purchase medicines on behalf of a whole village [60, 84].

This research did not opt for such approach, as the number of samples acquired was never large enough to arouse distrust. Neither vendors in any of the four countries appeared to be cautious because of a foreigner addressing them and asking for a few deworming drugs. Blinding the colleagues assisting in sample collection to the real purpose of their task [4, 101] was discarded as well – they were aware of the research and had participated in the decision to screen for the variability of the local market.

All samples collected were shipped back to Germany and tested in Würzburg. Even though most Tanzanian drugs were assayed at BMC Mwanza as well, virtually each specimen acquired outside Mwanza (and in West Africa) was locally obtained and transported under simple conditions across the respective region. It could always be guaranteed to not expose them to direct sunlight and to keep them shaded, but transporting them in ambient moisture and temperature was not constantly achievable in local means of transport. Furthermore, especially samples purchased from street vendors in Burkina Faso had naturally been exposed to tough conditions for an indefinite period of time. These aspects resulted, when analysing the medicines, in answers to the study questions on quality and composition of the anthelmintics, excluding however a discrimination between GMP and GDP. While deficiencies in GMP would rather tend to manifest in different batches of one product that could be detected at various occasions and places, lacking diligence in GDP could become obvious in variable peculiarities of substandard quality within one batch, of which different samples had been collected at disparate places. Divergent conditions in transportation and storage of the drugs may have affected anomalies

in GDP. Whenever samples of the same batch were obtained in different towns (in Ghana: *Tanzol* / ABZ, *Trazole-500* / MBZ and *Praziquantel 600*; in Burkina Faso and Côte d'Ivoire: *ABZ* and *Albendazole TM* / both ABZ), Minilab™ assays specially focussed on alterations between them. As hints of the influence of distribution in adverse conditions could not be found, this assumption was extrapolated to the other specimen – even if it was not intended to deduce a general statement about GDP [17, 18, 129, 134].

Visual examination is the simplest approach to determining the trustworthiness of a drug. Apparent spelling mistakes, discrepancies in DoM or DoE printed on the packaging and the wrapping / blister of a medicine or inconsistent colouring / inscriptions / texture of a tablet can already be observed by ordinary customers, who often seem to be aware of the problem of SF medicines circulating in the local market [9]. Unfortunately, illiteracy is still widespread among especially poorer communities in LMICs. Here, people do rely on the information given to them by vendors, and they are left to trust them – with a mere suspicion of being treated with SF products [9, 47]. In such environment, solely screening pharmaceutical products for their outward characteristics appears to still unveil SF drugs [110]. Yet, packages of SF drugs can nowadays be printed so accurately that a simple inspection of a container does not suffice. Re-printing a DoE, realistic imitations of a manufacturer hologram: without a genuine reference product, unobtrusive deviations are easily missed [149] – especially in drugs, which are administered as a single dose regimes. In this study, the main difficulty appeared to be the verifiability of the products obtained. The overall question whether a brand was sold as discovered by the indicated pharmaceutical company often could not satisfyingly be answered. Exemplary in the two West African brands *Tanizol* and *Tanzol*, only the latter one could be confirmed to be available as purchased. Nevertheless, just taking the appearance into account, no East or West African drug collected was suspected to be counterfeit or falsified. More realistically though, ill quality could have been assumed (when taking more than one sample) in tablets with irregular coating, as to be seen in *Abee-400*, *Sanozol* and *Trazole-500*. Since none of them failed in HPLC-UV tests, and only *Sanozol* failed in both disintegration and dissolution, a general evaluation and significance of the feature 'irregular coating' could not be extrapolated from this presumption.

Working with the WHO 'Be Aware' tool, visual inspection of both tablets and their containers could be performed diligently. Even though some aspects like the smell

of a tablet or the presence of a trademark sign have limited practical significance in LMICs, a screening for products of questionable quality according to this checklist covers all relevant aspects of especially the packaging. Herein, incorrect labelling and a lack (or incoherence) of information about strength, dosage or DoE are specifically mentioned to be reported to the WHO (or national NMRA) owing to a strong suspicion of an SF product. A few limitations of the tool, however, were noticed throughout its application.

- Suspensions could not properly be evaluated as this checklist does not specifically target them. A thorough and standardised visual inspection of both container and formulation would contribute to an elevated awareness at a screening stage of QA, particularly since suspensions are regularly taken by children who are regularly part of the population at risk.
- Even some originator brands do not feature all the required characteristics: packages of *Vermox* manufactured in South Africa, for example, are not provided with a DoM nor with a specific logo.
- The official registration of a certain drug is – predominantly in LMICs with basic NMRA – sometimes difficult to comprehend and prove. As it was experienced in Burkina Faso and Côte d'Ivoire, a lack of continuously updated lists of registered products can result in complete unawareness of the size of a local (legal) drug market. Usually, certain reasons can be determined why distinctive brands are not listed (any more): low quality, pending approval, expired registration, lacking licence for sale (like in the anthelmintics governmentally distributed for regular PC), … A profound expertise of a national legal drug market would be required to perform visual inspection appropriately but can often not be expected.

In this research, these limitations did not have a significant impact on the evaluation of a certain brand – all samples obtained were systematically analysed. In a setting of simple screening though, such uncertainties have potential consequences: valuable and (sometimes) scarce resources may be spent excessively, suspicious formulations other than tablets may be missed. Moreover, the WHO checklist does not offer any obvious decision support in products failing in one or more categories other than incorrect labelling or missing indications about strength, dosage or DoE. Having identified a need for improvement as well, Schiavetti et al. [96] just recently designed an advanced version of the WHO

tool, which focusses on LMICs and the availability of merely limited resources. Herein, the authors emphasise the importance of corresponding finding of an external container and its internal packaging, and give instructions for different formulations: tablets, syrups, suspensions, powders and liquids. Moreover, each aspect is categorised into one of the following groups: '[r]easonably safe for dispensing', '[d]ispense with explanation' and '[q]uarantine and make a risk-benefit evaluation before dispensing' – accompanied by an explanation how to apply the checklist. Especially when informing customers about the most obvious aspects of a medicine, frontline health workers may consider this checklist helpful and more feasible than the WHO tool to contribute to a more attentive use of drugs (even though a child-resistant safety cap on anthelmintic suspensions, as proposed by the authors, was never encountered during collection for this study).

5.2 Justification of the Minilab™ as a simple screening method in low- and middle-income countries

In order to perform effective QA in LMICs, confirmatory test systems are paramount to keep track of local drug markets, which are regularly found to be scantily monitored. Most international researchers on the quality of deworming drugs applied pharmacopoeial standards that are well established. The concentration of API was routinely determined by HPLC [5, 6, 47, 59, 66, 97, 101]; whenever galenic aspects were intended to be analysed, dissolution profiles were evaluated [5, 6, 101]. In a setting of research, with financial support from non-LMICs, this approach may be considered appropriate. Precise and quantifiable results reliably depict the quality of drugs on local markets. When performing routine QA in their own country though, NMRAs have to deploy their budgets and resources wisely. Gold standard methods like HPLC or ^{1}H nuclear magnetic resonance spectroscopy, which are usually accessible only in few selected NMRA centres (usually capitals or large centres), may be applied in products strongly suspected of being SF medicine. For screening the market, more simple and cost-effective methods are implemented, such as the Minilab™, colorimetric reactions, spectrometric devices (Raman spectroscopy, near infrared spectroscopy, …) and others. Relevant aspects in the decision for one of these options include portability, fast operation speed, simplicity of the tool, reproducibility and functionality without electricity, initial drug preparation and supplementary chemicals / reagents. Whichever method is applied in screening for SF medicines:

in case of an exceptional finding a confirmation test is required, especially in methods strongly depending on the skills of the researcher [49, 63]. This results in a hierarchic system well known in LMICs: multiple assays with simple screening methods on a rural level, initial confirmation tests of suspicious drugs by advanced systems in urban centres and affirmative QA at NMRAs [49].

The results drawn from the Minilab™ assays reflected the expectations concerning the quality and the composition of the anthelmintic drugs ABZ, MBZ and PZQ: sufficient content of API (similar findings were described by Petersen et al., too [90]) but variable disintegration times. In Tanzania, it can be assumed that more than 90 % of all drug controls are limited to the first, rural stage, and only a small minority of tests are being performed according to internationally acknowledged standards of QA [49] – highlighting the significance of simple screening methods. Despite ambivalent evaluation of the accuracy and reliability of the Minilab™ [49, 63, 87, 90, 93, 124], it was chosen as screening method because of the availability in both Mwanza and Würzburg as well as the scientific expertise at MMI Würzburg where this tool had been implemented right from its beginnings. Additionally, the principal field of application of the Minilab™ are anti-infective medicines (78 out of 103 APIs), yielding on-site analyses for predominantly antibiotics and antimalarial drugs [4, 51, 60, 90, 93]. In this context, the use of this tool was extended to the three anthelmintic drugs listed in the manual.

In contrast to comparable studies conducted in the past, the 2020 Minilab™ manual does not contain colorimetric assays any more. As the previous editions had no specific method for PZQ at avail, this method of API testing was discarded right from the beginning. Despite their direct visualisation, colorimetric assays may be limited in their validity by, for instance, coloured coating of tablets influencing the colour reaction or ingredients that are similarly structured as the desired API [49]. Further concessions had to be made to two features of the respective chapters of the manual. Firstly, and unlike all other chemicals needed (specifically purchased for this research), acetic acid 96 % solution could not be found in Mwanza, nor in Dar Es Salaam or Nairobi. Consequently, glacial acetic acid had to be diluted (available in Mwanza and donated by TMDA Mwanza as well) with distilled water to a 96 % solution. Secondly, owing to the structural similarity of the two benzimidazoles ABZ and MBZ, the manual lists two disparate methods to distinguish both APIs from each other. Herein, chromatoplates bearing MBZ samples were exposed

to methanolic sulphuric acid after regular analysis. Concerning this chemical, difficulties were encountered in effectively equalising the acidity of this solution and hence properly disposing of it. Lacking any other reasonable options but spending larger quantities of alkaline agents, the decision was reached to not perform this very test on-site in Mwanza but to catch up on it back in Würzburg. In general, disposing of hazardous reagents like toluene is a tremendous problem in LMICs like Tanzania: there are no adequate facilities to recycle such chemicals. If they are not safely stored until a solution is presented, they may simply be drained into the sewer. These limitations culminated in repeating TLC testing of most samples acquired in the Lake Zone area and analysed in Mwanza in Germany, in confirming the testing prerequisites in Tanzania and in fulfilling the MBZ verification methods.

In the supplementary method verifying MBZ against ABZ, most products tended to emit a more intense fluorescence than GPHF reference standards and thence exceeded the USL (Image 17 demonstrating examples of this finding). 73.9 % (17 / 23) of all MBZ batches collected could be characterised accordingly. HPLC-UV assays confirmed a certain surplus: 61.1 % (11 / 18) of the tablet brands analysed ranged beyond 100 % l.c. TLC findings however appeared to be prone to distinctively exceed (not really quantifiable, as reference standards were never concentrated to more than the USL of 100 % l.c.), while mean overage concentration of the respective MBZ HPLC-UV data was calculated at just 101.9 % l.c. (95 % CI: 100.7 % l.c. – 103.1 % l.c.). In conclusion, an analysis by this method unveiled a potential risk of overestimating the likelihood of both an overage and the concentration of API in MBZ products. Combined with the logistical obstacles mentioned above, a substantial benefit could not be recognised.

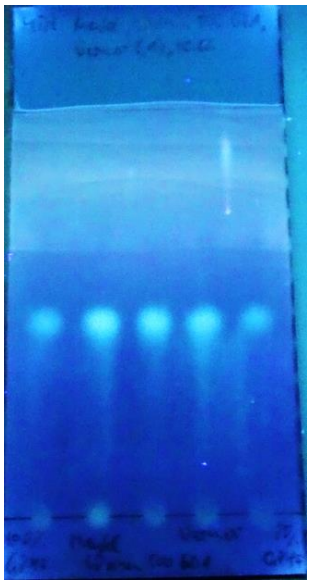


Image 17:
West African *Mentel, Wormin 500* and *Vermox* (second to fourth spot) tested against GPHF reference standards, all distinctively exceeding the USL.

- to the very left: 100 % l.c.
- to the very right: 80 % l.c.

HPLC-UV results came up with

- *Mentel*: 97.8 % l.c. ± 5.6 % RSD
- *Wormin 500*: 100.6 % l.c. ± 0.5 % RSD
- *Vermox*: 102.8 % l.c. ± 0.5 % RSD

5.3 Active pharmaceutical ingredient as most critical feature of African anthelmintics?

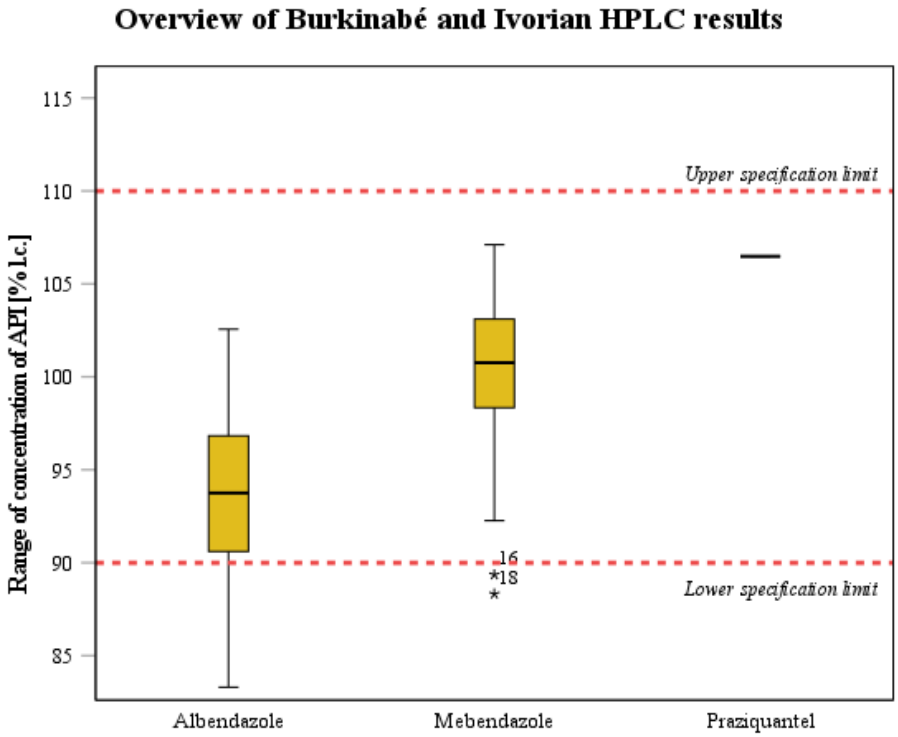
In previous studies on QA of anthelmintic drugs, the question of falsification of samples locally available was regularly determined to be the principal goal of research. According to the WHO, falsified drugs are defined as 'medical products that deliberately / fraudulently misrepresent their identity, composition or source' [144]. When performing QA of local drug markets, particularly anti-infective medicines seem to be prone to alterations: within seven years from 2013 to 2020, WHO drug alerts on 31 antimalarial batches (Chloroquine, Quinine, Sulfadoxine/Pyrimethamine and Artemether/Lumefantrine) as well as on eight batches of antibiotics (Amoxicillin mostly in combination with Clavulanic Acid, Penicillin V and Cefixime) were issued, of which a majority was detected in Africa [138]. As listed in Chapter 2.3, TMDA (by that time still TFDA) recorded that anti-infectives contributed by 83.3 % to the local SF drugs detected from 1999 to 2015 [49]. Such SF medicines are known to induce growing antimicrobial resistances, which nowadays regularly occur in regions of extensive use of antibiotics – as assessed in both African centres of this research, Eikwe / Ghana [52] and Mwanza / Tanzania [79], but also in various other parts of the world [13, 57]. Increasingly as well, the generous global use of antimalarials pushed *Plasmodium* spp. into developing resistances against long-standing therapeutics like Chloroquine and Mefloquine, but also against the relatively innovative Artemisinin derivates [11, 98]. Contributing to and aggravating this issue, commonly applied anti-infectives are repeatedly administered in patients presenting with unspecific symptoms, in which an infectious disease is suspected [55, 109]. However, those who suffer from schistosomiasis or STH may not present with clinically striking and pathognomonic symptoms. Usually, both NTDs are initially experienced in (pre-)school childhood when, for instance, playing together near contaminated waters bodies – they are addressed by regular MDA. The more often they undergo a certain helminthiasis, the less likely and prominent they develop all the clinical signs of an initial manifestation. Moreover, heavy infestations leading to acute local and systemic hypersensitivity reactions (Katayama fever, Löffler's syndrome) and, later on, to dramatic clinical symptoms like an ileus are limited to a comparatively small number of patients [53]. A majority of patients rather presents with fatigue, anaemia, malnutrition or growth retardation at a medical facility, a therapeutic approach with ABZ, MBZ or PZQ is – at

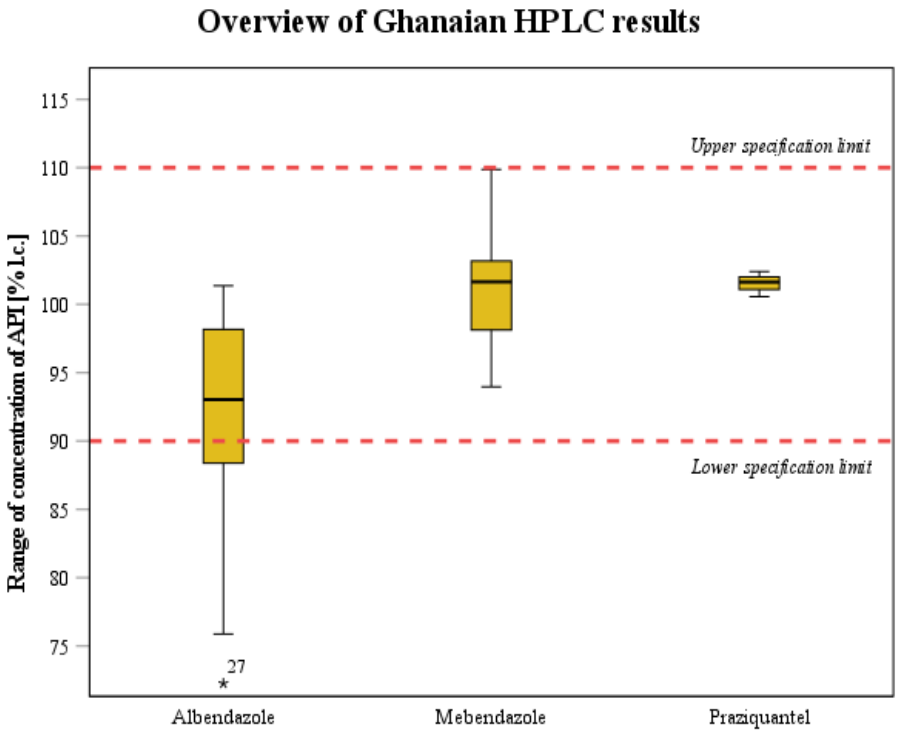
most – just occasionally the foremost treatment option. Instead, patients may tend to rather ask for medicines, which are more realistically expected to be of help: anti-infective drugs like antibiotics and antimalarials, analgesics or vitamins [55]. This tendency sustains a certain neglect of QA in deworming drugs.

Although complete absence of stated API in anthelmintic medicines has virtually never been reported [5, 6, 47, 66, 90, 97, 101], nor were any WHO drug alerts issued lately [138], incentives for a possible falsification are obvious: about 612 million African people were infected with at least one NTD in 2018. They were approached by both therapy and MDA of internationally donated PC – the latter one reaching 54 % (for STH) respectively 63 % (for schistosomiasis) of the target group [137]. Consequently, a significant proportion of patients had to rely on products locally available. Whether a prescription for an anthelmintic medicine was actually required or not: while gathering samples on the local markets for this research, in all but one drug-selling facilities the requested medicine was handed out without further enquiries (an exception was experienced in SK-TK / Ghana owing to a shortage of PZQ in the whole region). Explanations on how to take the respective anthelmintic were scarcely offered – especially when applying PZQ though, the TD per kg body weight needs to be calculated to sufficiently target the patient's underlying helminthiasis. Failing to do so – just as in antibiotic, antifungal or antimalarial therapy – allows and forces parasites to gradually develop mechanisms to protect themselves from these harmful agents, particularly after repetitive rounds of MDA of PC or treatment. Despite not having to fear them on a large scale yet, resistant parasites have indeed been described [1].

To emphasise the necessity of quality-assured anthelmintics, this research aimed at evaluating their content in the four selected countries, despite being aware of earlier unobtrusive findings. As to be expected, the sheer presence of API in Burkinabé, Ghanaian, Ivorian and Tanzanian anthelmintics did not seem to be the most vulnerable aspect of QA – not in a single drug a complete lack of or a wrong API was discovered. An exchange of ABZ and MBZ, which the 2020 Minilab™ manuals dedicate paragraphs to, was not reported either. The content was assessed by two sequential approaches: the Minilab™ as screening method, with the advantages and disadvantages illustrated above. A confirming method, the HPLC-UV, was then applied in almost all samples collected to quantify the amount of API. This gold standard method was able to confirm the

applicability of the screening tool in terms of categorising the amount of API in anthelmintic medicines. The combined results showed only minor deviations from the ranges of acceptance: screening deworming drugs, predominantly MBZ products appeared to exceed SLs; confirming them, ten batches missed these limits, ranging from averages of





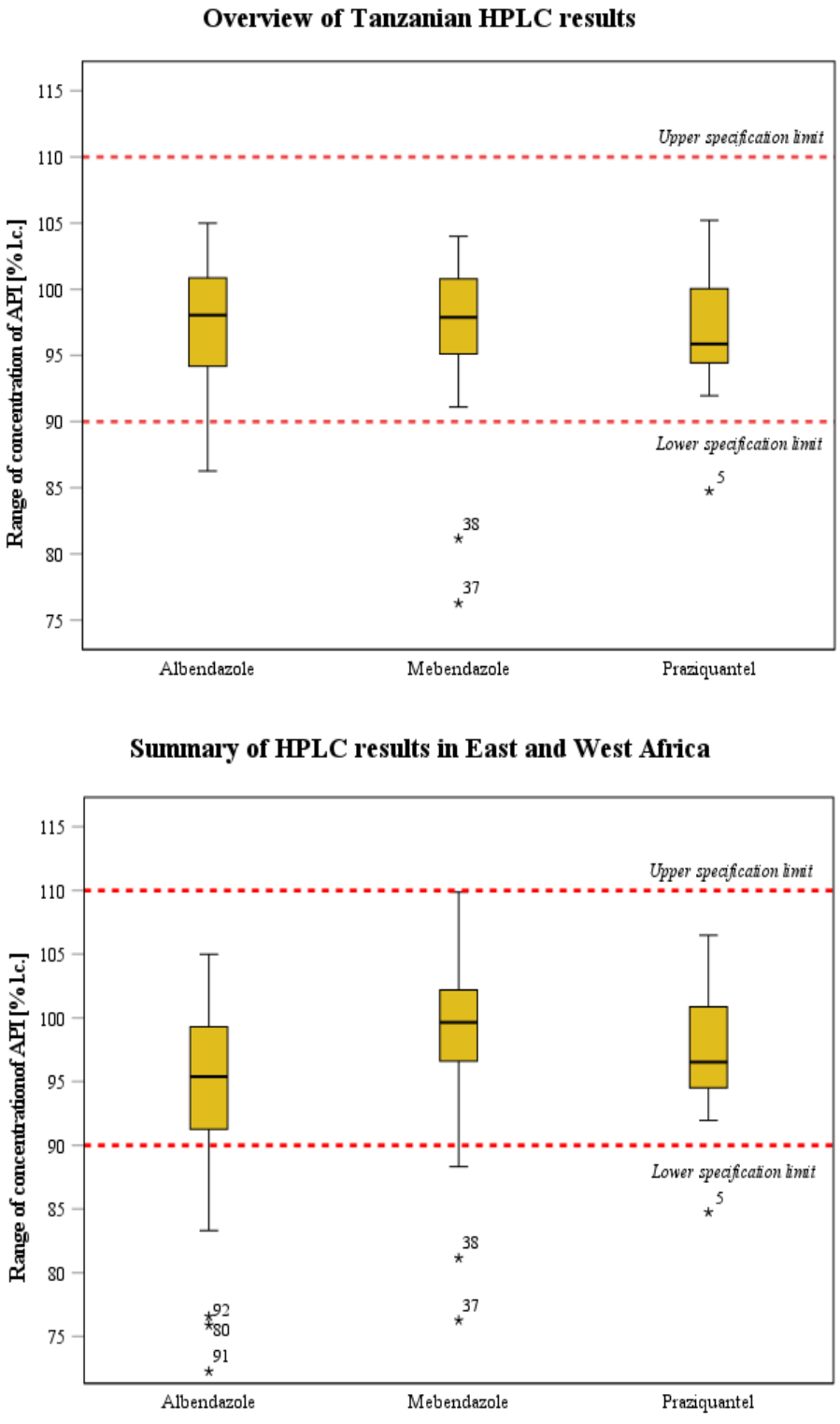


Figure 49 – 52: Summary of Burkinabé and Ivorian, Ghanaian, Tanzanian and overall African HPLC-UV results.

74.1 % to 89.9 %. Owing to the scarcity of Minilab™ studies on anthelmintic quality, comparison to respective TLC results is not extensive – nonetheless, grossly substandard

drugs were not detected [90]. As visualised in Figures 49 – 52, HPLC-UV findings from this analysis accorded with comparable outcomes on ABZ (occasionally undercutting the 90% LSL by no more than 10% but overall well in range) and PZQ (decent quality) [5, 6, 47, 66, 97, 101], even though MBZ brands were analysed to be concentrated more irregularly (more often failing SLs, more likely to present with an overage of up to 10 % l.c.) [6, 101].

Since TLC and HPLC-UV set ranges of acceptance that differ by 10 % l.c. (TLC: 80 % – 100 % l.c.; HPLC-UV: 90 % – 110 % l.c.), the results drawn from this research must be evaluated at a broader view. In TLC, samples closely veering around SL can hardly be assessed as 'passing' or 'failing'; it is a subjective evaluation based on nuances that cannot deliver a reliable classification. On the other hand, products that are tested by HPLC-UV and that just undercut the 90 % limit would not be identified as such by the Minilab™. Nevertheless, an overall concordance can definitely be acknowledged – despite the debatable benefit from applying methanolic sulphuric acid to duly prepared MBZ samples. In all but two batches, the subjective assessment of ABZ, MBZ and PZQ by TLC (taking the uncertainties around specification limits into account) was confirmed by HPLC-UV. Conflicting outcomes were only seen in *De Wome 500* and *Mebendazole BP 500 mg*. According to TLC results, *De Wome 500* tended to contain less than 80 % l.c. whereas HPLC-UV analyses came up with an amount of 101.2 % l.c. ± 4.3 % RSD. With *Mebendazole BP 500 mg*, it was the other way around: TLC results showed a content of beyond 100 % l.c. while the amount determined by HPLC-UV was set at an average of 78.8 % l.c. ± 4.4 % RSD. These differing findings may be explained by the small number of samples analysed. Not enough tablets were purchased to increase the power of the results drawn or to constitute a possible heterogeneity within these two batches. Moreover, a difference of 5 – 10 % l.c. may not be obviously distinguishable when subjectively evaluating fluorescence.

5.4 Fluctuating results in testing for galenic properties

Even though researchers had been used to define the content of API as the most relevant aspect in QA, duly performed assays on deworming agents identified significant uncertainties in the release of an API from its pharmaceutical formulation [5, 6, 90, 101]. These results were confirmed and complemented by findings of this study: just more than

one fourth (26.8 %) of the brands of oral solid forms included at least one batch failing to disintegrate within 30 minutes; failure in dissolution analyses occurred in more than half (or almost two third, depending on the pharmacopoeia) of the brands tested. These two galenic characteristics showed a significantly strong negative correlation – an extended disintegration time with a decreasing dissolution and vice versa – in ABZ (r = -0.71, $p < 0.001$) and in MBZ 100 mg batches (r = -0.69, p = 0.006 – dissolution profiles in reference to Ph. Int. 7) whereas in MBZ 500 mg (r = -0.67, p = 0.15) and in PZQ batches (r = -0.55, p = 0.13), the correlation was strong but not significant.

By the two methods adopted, both the solidness of the tablets analysed and the aqueous solubility into the bloodstream could be determined. These characteristics are of particular interest as, according to the Biopharmaceutics Classification System, ABZ is listed in class IV, PZQ in class II and MBZ in both – which means that the solubility of all three anthelmintics must be regarded as 'low'. Additionally, class IV medicines like ABZ are poorly absorbed in the small intestine (whilst MBZ and especially PZQ penetrate more easily the intestinal wall into the venous system) [143]. Consequently, for ABZ and MBZ products aiming at intestinal helminths it is important to fully disintegrate in order to successfully compete for the target protein, a β-subunit of the nematodal tubulin molecule [78]. To then reach both intraluminal and extraintestinal helminths, ABZ, MBZ and PZQ need to dissolve as thoroughly as possible to have enough API activated by (ABZ to systemically active ABZSO) or overcome (MBZ and PZQ) hepatic first pass metabolism. Whenever tablets do not disintegrate nor dissolve appropriately, there is a risk of insufficient therapy of systemic helminthiases inducing resistances – analogous to the aspects mentioned in the previous chapter: not enough API may reach and harm the helminths. It was shown that deficiencies of ABZ samples in dissolution profiles detected *in vitro* may correlate with diminished curing and egg reduction rates in patients suffering from ancylostomiasis [5] – the less effective drug *Bendex-400* referenced by Belew et al. was included in this research as well, confirming poor dissolution. These findings however were not detected in ascariasis (both tested brands performed well) nor in trichuriasis (both tested brands performed weakly). The authors concluded that not only pharmacological characteristics but also factors intrinsic to the parasite (metabolism, susceptibility or protective features) determine the efficacy of an anthelmintic therapy [5].

Disintegration had not been described as quality prone to deficiencies. Rarely assayed in deworming medicines so far, disintegration times seemed to routinely comply with respective criteria [6, 90, 101]. In contrast to those findings, ten out of 56 products (17.9 %) from the four countries of research were encountered to not disintegrate at all; another five (8.9 %) exceeded the SL of 30 minutes. Even though all of them were labelled as chewable tablets, this identification does not exclude them from pharmacopoeial criteria. Despite differentiating between ABZ / MBZ chewable and non-chewable formulations, Ph. Int. 7 does not provide disparate methods of analysing disintegration times. Both monographs moreover state that chewable tablets 'may be chewed, swallowed whole or crushed and mixed with food or liquid' – implying that galenic characteristics should not depend on sufficient fragmentation of the tablets prior to gastric passage [104, 105]. The place of manufacture seemed to play a certain role in the quality of disintegration: comparing products from Africa and Asia to each other (European and American ones did not fail disintegration), African brands were associated with a significantly elevated risk of failing this test (OR = 4.73, 95 % CI: 1.28 – 17.51).

Insufficient dissolution profiles were reported for all three APIs [5, 6, 90, 101]; some of the brands tested *in vitro* in this research were analysed to fail in previous studies as well: *Natoa* / MBZ from Kenya (Q = 7.9 % [90] compared to Q ≤ 1.4 %) dissolved just marginally. *Bendex* mentioned above (Q = 20.1 % [5] compared to non-dissolution) and *Bermoxel* / PZQ from Cyprus (Q = 63.4 % [6] compared to Q ≤ 69.7 %) were confirmed to fail, too. In contrast to the occasionally or moderately failing dissolution profiles described, outcomes of this study illustrated a larger and wider spectrum: 53.7 % (36 / 67) of all batches of solid formulations tested (applying the USP-NF 41 method for 100 mg MBZ formulations) did not meet the respective criteria – among these, eight samples (seven ABZ batches, one MBZ batch) did not even release 10.0 % of the API. Overall,

Table 6: Proportions of ABZ, MBZ and PZQ passing and failing the respective minimal Q.
* MBZ 100 mg tested in accordance with Ph. Int. 7
° MBZ 100 mg tested in accordance with USP-NF 41

	ABZ (n = 43)	**MBZ 100 mg** (n = 14*/8°)	**MBZ 500 mg** (n= 6)	**PZQ** (n = 10)	**Total** (n = 73*/67°)
Dissolution ≥ Q	41.9 % (18)	0.0 % (0)* 62.5 % (5)°	50.0 % (3)	50.0 % (5)	35.6 % (26)* 46.3 % (31)°
Dissolution < Q	58.1 % (25)	100.0 % (14)* 37.5 % (3)°	50.0 % (3)	50.0 % (5)	64.4 % (47)* 53.7 % (36)°

ABZ samples presented the most critical results: 25 (58.1 %) out of 43 samples did not reach the required minimal dissolution. As Ph. Int. drafted a revised proposal for chewable ABZ, which implemented an improved procedure of dissolution testing in 2020 [151], six of the collected brands (*Albendazole TM*, *Anthel*, *Bendex-400*, *Sanozol*, *Tanzol* and *Womiban*) were accordingly assessed post hoc. Doing so, none of these brands passed; nevertheless, each one showed an increased dissolution: the absolute increments ranged between 3 % and 36 % l.c. (refer to Figure 53 in the supplementary data). Slightly better off, 42.9 % (6 / 14) of the MBZ batches and 50.0 % (3 / 6) of the PZQ batches failed their SLs (refer to Table 6). Comparable to disintegration tests, the place (continent) of manufacture appeared to be associated with an – although not significant – risk of (not) passing dissolution assays: products from (sub-)tropical regions (i.e. African and Asian ones) were rather failing (OR = 3.13; 95 % CI: 0.30 – 32.31); within (sub-)tropical brands, African ones were associated with a non-significantly elevated risk of failure (OR = 3.05; 95 % CI: 0.85 – 10.90).

Remarkably, dissolution of 100 mg MBZ formulations was strongly influenced by the pharmacopoeia referred to: Ph. Int. 7 criteria came up with not a single batch passing the SL set at $Q \geq 60\%$ (0 / 14), whereas USP-NF 41 assessed 62.5 % (5 / 8) of the samples to meet the SL of $Q \geq 75$ %. This disparity between both methods may, most likely, be traced back to the composition of the dissolution medium. While Ph. Int. 7 just applies 0.1 M HCl, USP-NF 41 recommends a solution of 1 % SDS in 0.1 M HCl. Working with 0.1 M HCl, none of the tested tablets reached the required minimal Q – whereas dissolving 100 mg MBZ gives in 0.1 M HCl + 1 % SDS enables 5 out of 8 tablets to pass the SL. This observation has already been described by other authors as well [31, 103], who examined the dependence of the solubility of MBZ on the concentration of added SDS by comparing purely 0.1 M HCl to either 0.1 M HCl + 1 % SDS [103] or to gradually increasing concentrations of added SDS (up to 2 %) [31]. During the initial methodical evaluation, 100 mg samples of *Vermox* available in Germany were tested applying both dissolution methods, and both pharmacopoeiae led to satisfactory results. The oral formulation though contained surfactant SDS – which reaffirms the statement that, even in small quantities, SDS does increase the solubility of MBZ. Thence, the assumption may be drawn that 100 mg gives purchased in Tanzania and West Africa did not contain any surfactant SDS. As the exact ingredients of the evaluated samples were unknown though,

this observation is difficult to be confirmed. Taking into consideration that 500 mg gives of MBZ are unanimously analysed by applying 1 % of SDS, comparable dissolution tests of 100 mg gives without added SDS – despite setting lower SLs at $Q \geq 60$ % – appear to not be suitable when generating a comprehensive illustration of MBZ solubility.

Dissolution media as proposed by USP-NF 41 may deliver higher rates of passing MBZ products by incorporated SDS; a differentiation between the three polymorphs A, B and C however is hardly possible under these conditions. As elaborated before, form C is the pharmaceutically preferred and most efficacious one. The solubility of the disparate forms can be categorised as C > B > A (sometimes, B was described to exceed C) – in purely 0.1 M HCl. As soon as adding SDS, ranks cannot properly be discerned any more: A ≈ B ≈ C [7, 102, 103]. Thus, SDS-based dissolution methods do not hint at therapeutic quality and efficacy of a MBZ product assessed. Several factors were analysed to induce a conversion of the preferred polymorph C into the stable and hence least soluble polymorph A: increasing temperature and moisture, traces of form A in the original sample when having constant climatic conditions [7]. Sparse data indicate that the efficacy of MBZ products containing more than 30 % of polymorph A is not superior to a placebo [103]. Transferring such knowledge, one has to admit that the conditions of distribution and storage of the analysed products prior to their collection were unknown. As a special analysis for the disparate polymorphs had not been purposed, it was not possible to define the proportions of forms A, B and C. Hence, no statement could be reached as to whether GDP criteria were met, whether the products were exposed to extensive heat or humidity (conditions that especially in small OTCs or street vendors have to be suspected when located in a climatically challenging environment of sub-Saharan Africa [62]) or whether they had initially contained polymorph A. Testing then for dissolution profiles, SDS-based USP-NF 41 delivered valid but general results of sufficient solubility in 62.5 % (5 / 8) of the samples assayed appropriately whereas all eight samples failed by Ph. Int. 7 criteria. Swanepoel et al. [103] had determined the following proportion of solubility:

- in 0.1 M HCl: form A with 20 % < form B with 37 % < form C with 70 %;
- conversely in 0.1 M HCl + 1 % SDS: form B with 94 % < form A with 98 % < form C with 100 %.

Although not meaning to transfer their findings to the given outcomes, it would not be appropriate to conclude that all eight MBZ batches contained exclusively polymorph C.

Whether a potential ‘contamination’ with form A or a substantial degradation of form C to form A (leading to a dramatically reduced shelf life [7]) resulted in the diminished dissolution profiles: pharmacopoeial analyses according to Ph. Int. (7) revealed a potential source of misinterpretation and over-estimation of positive results when just relying on the standard set by USP-NF (41). The *in vitro* findings though could not be extrapolated to a corresponding response in affected patients due to extensive polymorph A, a prematurely expired shelf life or other reasons – the framework of this study was not intended to exceed its cross-sectional character to a randomised controlled trial evaluating the disparate findings of Ph. Int. 7 and USP-NF 41*in vivo* in patients.

5.5 The economic aspect in patients’ choice: low prices equal low quality?

Regarding PC of helminthiases, all three medicines are still allocated through the WHO and the donating pharmaceutical companies GSK (ABZ), Janssen-Cilag (a Johnson & Johnson company; MBZ) and Merck (PZQ) [137], and distributed through national NTD programs. While provision of ABZ (until elimination) and PZQ (unlimited) is secured over the next (most likely) decades, Johnson & Johnson agreed on a commitment for MBZ donation until 2025 [137]. When not being eligible for PC or when in need for swift cure though, patients need to seek for medicines from local markets. As observed during sample collection for this research, most pharmacies have heterogeneously priced deworming drugs at avail, offering a large variety of originator and generic brands (produced regionally and overseas) of particularly the broad-spectrum anthelmintics ABZ and MBZ. Consequently, patients’ choice of medicine depends to a lesser extent on the overall availability of an anthelmintic but rather on other (general) aspects [3, 32, 88]:

- knowledge of the available variety including generic medicines – several studies show that in tropical regions, consumers are not extensively informed about generic medicines (in some, just more than half of the study population knew about them);
- attitude towards generics and thus towards cheap(er) brands – worse performance, less rapid response and second-class-treatment are aspects patients worry about; however, information by professionals, advertisement, experience and appropriate costs of therapeutic need to be taken into consideration;

- physicians' / pharmacy professionals' habits – a distinctive reluctance to prescribe generics (reservations were similar to patient' ones) was identified to be a major issue, particularly when avoided by physicians (patients tend to esteem physicians' advice higher than pharmacy professionals'); improved advertisement and guidelines though are gladly accepted.

Even though the aspects of overall knowledge and physicians' / pharmacy professionals' habits were not addressed, this research was able to take a stance on two concerns patients expressed: impaired quality or performance of a medicine because of its generic origin and because of its lower prices. As illustrated, quality in terms of content was not the main concern – performance due to galenic deficits resulted in a disparate qualitative evaluation. Herein, originator brands performed obviously better: all seven products passed disintegration and / or dissolution sufficiently (as far as tested with merely small numbers of units acquired). Supporting the uttered worries by patients, deficiencies thus solely occurred in generic brands. Within these, one may distinguish between branded generics (n = 48) and generics (n = 9). Interestingly, branded generics were associated with a worse performance than INN generics: both disintegration (OR = 2.94; 95 % CI: 0.33 – 26.31) and dissolution (OR = 3.24; 95 % CI: 0.56 – 18.76) pointed out that a branded generic with its more appealing and memorable name does not necessarily perform better than a generic merely labelled with its INN. With their better marketability, there is a relevant risk of ineffective treatment in patients suffering from a helminthiasis.

Naturally, generics cost less than originator drugs: development, trials and FDA approval do not have to be financed. After patent protection for an originator brand expires, prices adjust to supply and demand and hence regularly fall. In Africa, ABZ, MBZ and PZQ (developed about 40 years ago) are extensively applied – a heterogenous distribution of costs of disparate products in local markets is the logical consequence. Having a look though at international supplier costs of especially ABZ and MBZ, production costs would not justify variable prices: according to the 2015 International Medical Products Price Guide [80], the median price for a chewable TD of 400 mg of ABZ was 2.19 US cent; a chewable TD of 500 mg of MBZ cost a median of 3.05 US cent. Local market prices are listed in Table 7, depicting median prices being at least seven (MBZ) or even twenty times (ABZ) more extensive than the international median. Even though disparate high-low ratios of costs were observed (ranging from 2.62 in Ivorian ABZ products to

150.00 in Tanzanian MBZ drugs), the respective API appears to be produced cheaply enough to be contained in each tested batch – and in the vast majority of samples appropriately concentrated. PZQ is usually sold as 600 mg give, and should be adapted according to body weight (or body size in PC of children), referring to the treatment doses list illustrated in chapter 2.1. This adds up to four or five tablets in an adult if administered as a 'single-dose' therapy. Median international supplier prices were set at 10.99 US cent – resulting in roughly 0.50 US$ per adult TD [80]. Median market prices were even higher in the four countries: from 0.22 US$ in Tanzania to 4.19 US$ in Burkina Faso / Côte d'Ivoire per 600 mg give, which resulted in 1.10 US$ and 20.97 US$ per weight-adjusted TD respectively – making PZQ an expensive therapy in LMICs. Under such circumstances, cheaper treatment prices become attractive. When not depending on the quality of content, galenic characteristics need to be regarded as relevant for pricing. Prolonged disintegration times however did – at best – weakly and not significantly correlate with decreasing prices (ABZ: r = -0.08, p = 0.62; MBZ 100 mg: r = 0.04, p = 0.90; MBZ 500 mg: r = -0.18, p = 0.67; PZQ: r = -0.20, p = 0.59). A relevant, strong (but non-significant) correlation was only seen in Tanzanian PZQ (r = -0.61, p = 0.11). The correlation between good performance and high(er) product prices in dissolution assays needs to be presented in a more differentiated manner. In ABZ, Tanzanian (r = 0.48, p = 0.07) and particularly Ghanaian medicines (r = 0.59, p = 0.02) came up with positive (and in drugs from Ghana significant) correlations whereas Burkinabé / Ivorian medicines did not reveal any solid correlation (r = 0.04, p = 0.89). MBZ 100 mg gives depicted no more than a weak correlation (r = 0.18, p = 0.53) – 500 mg gives conversely suggested a strong yet

Table 7: Median prices of Ghanaian, Burkinabé, Ivorian and Tanzanian anthelmintics compared to international supplier prices of ABZ, MBZ and PZQ.
Applicable exchange rates (against 1 US$): 2262.2022 TZS (06/2018) and 2263.46699 TZS (09/2018); 5.01989 GHC (03/2019); 584.73614 FCFA (04/2019; fixed against the Euro) [19].

	ABZ 400 mg	**MBZ 500 mg**	**PZQ 600 mg**
Median international supplier unit price	***0.0219 US$*** (for chewable tablets)	***0.0305 US$*** (for chewable tablets)	***0.1099 US$***
Median costs in Ghana	3,00 GHC ≈ ***0.5976 US$***	2,25 GHC ≈ ***0.4482 US$***	2,00 GHC ≈ ***0.3984 US$***
Median costs in Burkina Faso	745 FCFA ≈ ***1.2741 US$***	187.50 FCFA ≈ ***0.3207 US$***	N/A (equal to costs in Côte d'Ivoire)
Median costs in Côte d'Ivoire	645 FCFA ≈ ***1.1031 US$***	772.50 FCFA ≈ ***1.3211 US$***	2452.50 FCFA ≈ ***4.1942 US$***
Median costs in Tanzania	1000 TZS ≈ ***0.4418 US$***	500 TZS ≈ ***0.2209 US$***	500 TZS ≈ ***0.2209 US$***

non-significant correlation (r = 0.60, p = 0.21). Tanzanian PZQ (outweighing with 77.8 % of the obtained brands) illustrated no correlation (r = -0.02, p = 0.97) – nonetheless, unambiguous West African results suggested an overall clearer correlation in African PZQ. To put it in a nutshell, patients' concern of low prices being connected to impaired performance can partly be rebutted. In Ghanaian and Tanzanian ABZ as well as in MBZ 500 mg however, cheaper products may lead to a reduced clearance of parasites. Despite the results of PZQ products, a lack of choice in West Africa and a comparable performance of similarly priced Tanzanian brands do not have a practical consequence for local patients in the fight against trematode and cestode infections.

5.6 Limitations of this study

The approach to rather collect many disparate products and, by this, depict the variety of local African drug markets diminished the chance of always obtaining enough samples. As mentioned before, low numbers of units per batch resulted in a prioritisation in favour of pharmacopoeial assays (HPLC-UV and dissolution). Even the recommendations of five to ten units per batch – which is seen as a practical compromise since 30 units, suggested ideally, are not regularly available in rural tropical regions – could not always be gathered [84]. To pass the respective criteria, Minilab™ manuals demand 20 units for mass uniformity (a non-destructive method) and six for disintegration; three samples have to be tested by TLC before rejecting a batch. In addition, at least six units are required for dissolution profiles; for HPLC-UV analyses, pharmacopoeiae do not demand a certain number of units. This research tried to adapt the requirements and contained itself with 20 units for mass uniformity and four units for disintegration per brand when necessary. As far as achievable, TLC was performed twice per batch (together with internal repetition of the very unit), HPLC-UV twice to thrice. Whenever these minimal numbers of units were not reached, only tendencies could be illustrated. This had the most significant impact on dissolution profiles: in all brands but Tanzanian *Astazole*, no more than three units per product could be included (one unit per batch each) – *Astazole* was multiply assessed to validate the test system. Moreover, MBZ 100 mg gives were not unanimously assessed according to both Ph. Int. and USP-NF; the implications of a possibly substantial degradation of the favourable polymorphic form C and, as a result, a potentially reduced *in vivo* efficacy could consequently not be evaluated. For suspensions,

Minilab™ manuals do not state any specific procedures. Since pharmacopoeial instructions have neither been exhaustive so far (merely including mass uniformity and HPLC-UV), these formulations were just inconsistently incorporated.

Despite acknowledging these constraints by establishing a separate category in the overall comparison, a completely equal analysis of all 64 products could not be achieved. Within the process of selecting and collecting products, a certain selection bias became apparent: while referring to FDA Ghana and TMDA lists of licensed brands and purposefully incorporating non-registered ones (whenever encountered), such stratification could not be applied in Burkina Faso and Côte d'Ivoire as FDA data were not at avail. In some of the (non-licensed) brands, authenticity was difficult to be confirmed because of lacking information online about the very product or even the manufacturing company. Thus, a differentiation between licensed and non-licensed products was not conducted.

5.7 Conclusion and prospect of the future fight against Neglected Tropical Diseases

Anthelmintic medicines available in Burkina Faso, Côte d'Ivoire, Ghana and Tanzania were not encountered to be falsified nor contaminated. Despite non-licensed products reaching almost 20 % of the brands purchased in Ghana and Tanzania, appearance of packaging and tablets as well as mass uniformity delivered acceptable results. Most of the products contained enough API to comply with the ranges of international pharmacopoeiae: screening of the products by TLC as key feature of the GPHF Minilab™ – even though limited in its expressiveness – was sufficiently confirmed by HPLC-UV despite shifted SLs. Galenic characteristics of the assayed brands however were determined to be more uncertain and variable than expected. Disintegration times and, in particular, dissolution results raised suspicion of impaired bioavailability in more than 50 % of the tablets. As such troubling findings are not entirely meaningful when having incorporated suspensions, the WHO is adapting and revising dissolution chapters of Ph. Int., adding now the handling of suspensions [150]. By this, they are extending standardised analysis to these formulations, which are highly relevant in paediatric treatment.

With regard to perfectible therapeutic efficacy of current PC and treatment options of NTDs in LMICs as well as the existing threat of growing resistances against anthelmintic medicines, new drugs, formulations and combinations are gradually being developed and evaluated. Besides the already mentioned Moxidectin (a long-standing broad-

spectrum veterinarian drug, which is about to be approved as an alternative treatment to IVM in onchocerciasis [85]), Oxantel pamoate (another old veterinarian anthelmintic yet to be approved in human parasitoses) and Tribendimidine as effective combination partners against trichuriasis [12] as well as Fexinidazole against *Trypanosoma brucei gambiense*, the most important progress targets PC and therapy of schistosomiasis in children. The comparatively large and bitter-tasting PZQ pills of 600 mg cannot be called an appropriate medicine for young ones on whom regular MDA of PC focusses. Addressing this hindrance of a successful control strategy, the Pediatric Praziquantel Consortium was founded in 2012. Consisting of pharmaceutical and (non-)governmental partners from Brazil, Côte d'Ivoire, Germany, Japan, Kenya, the Netherlands, Switzerland and the United Kingdom, the Consortium developed a noticeably smaller and better-tasting orally dispersible tablet of 150 mg. A dose-finding phase II trial was conducted in rural Côte d'Ivoire (2016 – 2018), followed by a phase III trial in Côte d'Ivoire and Kenya (ongoing) proving safety and efficacy compared to originator brands. As of 2022, drug authority approval and the introduction into local markets are aspired [89].

Even though the global variety of effective anthelmintics is slowly increasing, the overall range of disparate medicines on drug markets is rapidly growing. Targeted therapeutics are more and more frequently approved – largely in high-income countries, but also – gradually – in LMICs. With such growing supply, the tremendous importance and scope of a decently and thoroughly monitored drug market, particularly when situated in a region endemic for NTDs, becomes apparent when temporary shortages – owing to supply bottlenecks or delayed distribution into rural areas during adverse weather conditions – occur. Even a basic provision of at least essential medicines appears to regularly be difficult to guarantee in the aftermath. In times of international crises or political instability, especially those drugs donated within international control or eradication programmes are prone to not being sufficiently available any more. Subsequently, having to suspend mitigating measures and expertise potentially implies a resurgence of the targeted diseases, as the history of African combat against HAT after gaining independence from former European colonial powers proved [100]. In the last weeks of 2019 though, a new global crisis emerged, which led to a virtually complete slump in international mobility and thus an interruption of most aid programmes in LMICs – including NTD control [8] (which will be noticeable in the 2020 PC coverage data). COVID-19, a formerly

unknown version of coronavirus disease, manifested itself in Wuhan / China and, spreading from there all over the world, turned into a global pandemic. Having expected disparately, COVID-19 itself affected the African population to a far lesser extent than European or American people. The consequences however have been dramatic for Africa: an abrupt stop of international cooperation has severely been jeopardising the progress of reaching any SDG on the continent. Concerning the combat against NTDs, every year lost in optimising and applying control strategies such as MDA of PC, WASH, IDM, IEC or adequate therapy means a certain regression. Depending on the life cycle of a pathogen and the progress a country has made so far, the implications may be relatively mild (for long-living *Brugia* or *Wuchereria* spp. causing LF, a significant resurgence is not expected) – conversely, a disruption of established MDA of PC against schistosomiasis in highly endemic areas like Tanzania can result in a setback by up to five years [8, 12, 70]. Measures have already – even before COVID-19, for countries that could not lower their prevalences despite effective NTD programmes – been proposed to accelerate and intensify a resumption: higher frequencies of MDA; a community-based approach to distribution of PC; a co-administration of PC to simultaneously address, for instance, LF and STH or schistosomiasis; improvements in vector control, WASH and IEC [8, 67, 70, 94, 125]. Between August and November 2020, some countries like Burkina Faso, Côte d'Ivoire, Guinea and Togo were comparatively swiftly able to resume NTD programmes as well as adequate distribution of PC and were hence not expecting major disruption of pre-existing structures – let alone the management of blinding trachoma owing to an increased risk of exposure to aerosols during examination of patients. Other West African nations like Ghana conversely were falling short [54]. With an ongoing COVID-19 pandemic and substantial additional costs to be expected in picking up national programmes (from 2,000 US$ to 36,000 US$, according to data from Benin, Côte d'Ivoire, Guinea and Togo [54]), local drug markets may continue to provide a large share of the respective medicines. Taking into consideration that a reduced *in vitro* performance of deworming drugs in galenic testing was shown to correlate with a diminished *in vivo* response in patients [5], effective, reliable and trustworthy medicines are even more paramount. Regular and (wherever required) intensified QA on locally available anthelmintic medicines is strongly advocated, yielding at both therapeutic and preventive security. Applying them in MDA, the distribution of either originator brands (which are otherwise donated under

the London Declaration of 2012) or quality-assured generic products (that, ideally, underwent pre-qualification by the WHO or NMRAs) is highly recommended. Contributing the data generated in this study, a comprehensive database of both quality and composition of anthelmintic medicines in LMICs can gradually be developed and extended. As deworming drugs are one of the crucial pillars in a successful combat against seven of the 20 NTDs, efforts to provide this security to people in affected regions does not only contribute to the SDGs 3.3 and 3.8 [146]. The WHO target to finally terminate both schistosomiasis and STH as public health burden [133, 137] – despite a not yet fully fathomable impact of COVID-19 – will become just more attainable.

6 Summary

Within the framework of a partner project between the MMI Würzburg and CUHAS Mwanza to control and contain the NTD schistosomiasis on Ijinga Island in Lake Victoria, Tanzania, this study covers the quality and composition of anthelmintics regularly used in the (sub)tropics. This includes ABZ and MBZ in the fight against widespread geohelminthiases such as ascariasis or ancylostomiasis, as well as PZQ against trematodes like human pathogenic *Schistosoma* spp. and cestodes. Due to a frequent neglect of pharmacovigilance on local drug markets as well as extensive international campaigns to control and contain these NTDs in affected regions, the efficacy, safety and reliability of these deworming drugs are of particular importance.

Samples of 88 different batches were obtained from randomly selected facilities and subjected to *in vitro* analysis. Sampling took place in north-western Tanzania, western Burkina Faso, south-eastern Côte d'Ivoire and south-western Ghana. Visual examination of both packaging and samples was performed according to the WHO 'Be Aware' tool. Products were then screened with the GPHF Minilab™, consisting of tests of mass uniformity, disintegration times and TLC (applied in Mwanza and Würzburg). Confirmatory tests accorded with international pharmacopoeiae, applying assays for dissolution profiles and HPLC-UV (both performed by colleagues of the Institute for Pharmacy and Food Chemistry of the University of Würzburg).

Despite minor irregularities, the appearance of the 64 disparate products did not hint at falsified medicines. However, 19.6 % of the brands collected in Ghana and Tanzania were not officially licensed for sale. Mass uniformity was confirmed in 53 out of 58 brands of tablets. 41 out of 56 products passed disintegration times; ten out of the 15 failing products did not disintegrate at all. Evaluating TLC results, only four out of 83 batches narrowly missed SLs, 18 batches slightly exceeded them. No more than 46.3 % (31 / 67) of the batches assayed passed the respective pharmacological criteria for dissolution (MBZ 100 mg tablets were assessed by two different pharmacopoeiae, leading to varying results). HPLC-UV findings confirmed TLC results despite SLs shifted by 10 % l.c.: ten out of 83 tested batches contained less than 90 %, none exceeded 110 %.

The results generated are consistent with the (sparse) literature: anthelmintics available in (sub-)tropical regions usually contained sufficient amount of API, whereas deficiencies of galenic properties occurred more regularly. Hence, inadequate galenic

qualities in anthelmintics may pose a greater risk in LMICs than over- or underdosing of API, which – in this research – presented less frequently and merely slightly. By the 'Be Aware' tool (that, for better applicability, has already been extended to suspensions) and the Minilab™, two cost-effective methods are at avail, which (in the present study) delivered valid results as screening tests and whose application could thus be regarded as appropriate in LMICs. Dissolution profiles of MBZ 100 mg tablets were of particular interest: while the method suggested by USP-NF did not distinguish between 100 mg and 500 mg doses and thus produced more comparable data, Ph. Int. differentiated between the two doses, allowing (if this had been intended beforehand) conclusions concerning the different polymorphic forms of MBZ and thus about a possibly impaired efficacy.

Local drug markets represent one of the most important sources of medicines in the combat against NTDs. A safe armament of anthelmintics in LMICs is paramount to successfully pursue a continuous realisation of the respective SDGs, especially in times of COVID-19.

6a Zusammenfassung (summary in German)

Dem Partnerprojekt zur Kontrolle und Eindämmung der vernachlässigten Tropenkrankheit (NTD) Schistosomiasis auf Ijinga Island im Lake Victoria, Tansania, zwischen dem Missionärztlichen Institut Würzburg und der Catholic University of Health and Allied Sciences Mwanza entlehnt, beschäftigt sich die vorliegende Arbeit mit der Qualität und der Zusammensetzung regelmäßig in den (Sub-)Tropen verwendeter Antihelminthika. Hierunter fallen sowohl Albendazol und Mebendazol im Kampf gegen weitverbreitete Geohelminthen wie *Askaris* oder *Ancylostoma* als auch Praziquantel gegen Trematoden wie humanpathogene Schistosomen und Cestoden. Aufgrund teils ungenügend kontrollierter lokaler Medikamentenmärkte sowie breit angelegter internationaler Kampagnen zur Kontrolle und Eindämmung dieser NTDs in betroffenen Regionen kommt der Wirksamkeit, Sicherheit und Verlässlichkeit der verwendeten Mittel eine besondere Bedeutung zu.

Hierfür wurden 88 unterschiedliche Antihelminthika-Chargen sowohl in Ostafrika (nordwestliches Tansania) als auch in Westafrika (westliches Burkina Faso, südöstliches Côte d'Ivoire und südwestliches Ghana) von zufällig ausgewählten Verkäufern erworben und einer *in vitro* Analyse zugeführt. Zur Suche nach qualitativ beeinträchtigten

Produkten kamen eine Begutachtung von Verpackung und Medikament gemäß der WHO Checkliste „Be Aware“ sowie das GPHF Minilab™ zum Einsatz, mit Tests auf Masseneinheitlichkeit (mass uniformity), Tablettenzerfall (disintegration) und Dünnschichtchromatographie (TLC; angewandt in Mwanza und in Würzburg). Die bestätigenden Methoden der Wirkstofffreisetzung (dissolution) und der Hochleistungsflüssigchromatographie (HPLC-UV; beide von den Kollegen des Instituts für Pharmazie und Lebensmittelchemie der Universität Würzburg durchgeführt) orientierten sich an internationalen Arzneimittelbüchern.

Trotz leichter Unregelmäßigkeiten ließen die äußerlichen Untersuchungen der 64 verschiedenen Produkte keine Rückschlüsse auf gefälschte Präparate zu; jedoch waren 19,4 % der in Ghana und Tansania verkauften Medikamenten nicht zum Verkauf zugelassen. 53 von 58 Produkte entsprachen den festgelegten Kriterien für Masseneinheitlichkeit. 41 von 56 Produkten wiesen normwertige Zerfallszeiten auf; von den 15 auffälligen Produkten zeigten zehn überhaupt keine Veränderungen. In den TLCs verfehlten lediglich vier von 83 getesteten Chargen knapp die geforderten Grenzwerte, 18 weitere übertrafen sie geringfügig. Die Wirkstofffreisetzung ergab, dass nicht mehr als 46,3 % (31 / 67) der getesteten Chargen die pharmakologischen Anforderungen bestanden (Mebendazol 100 mg Tabletten wurden nach zwei unterschiedlichen Arzneimittelbüchern analysiert, was zu unterschiedlichen Resultaten führte). Die HPLC-UV Daten bestätigten die TLC Bestimmungen, obschon sich die geforderten Grenzen der Methodik um 10 % unterscheiden: zehn der 83 untersuchten Chargen enthielten weniger als 90 % Wirkstoff, keine überschritt 110 %.

Die Ergebnisse stehen im Einklang zur (spärlichen) Literatur: auch andere Autoren stellten einen meist hinreichenden Wirkstoffgehalt von Antihelminthika in (sub-)tropischen Regionen fest, während galenische Eigenschaften der Medikamente bisweilen unzureichende Resultate lieferten. Daraus lässt sich ableiten, dass in Ländern mit niedrigem oder mittlerem Einkommen (LMICs) ein größeres Risiko von einer eingeschränkten Galenik bei Antihelminthika ausgeht als von einer, in dieser Studie seltener detektierten und nur geringen, Über- oder Unterdosierung. Mit der WHO Checkliste (welche zur besseren Anwendbarkeit mittlerweile auf Suspensionen erweitert worden ist) und dem Minilab™ stehen zwei kostengünstige Methoden zur Verfügung, welche (in der vorliegenden Arbeit) valide Ergebnisse als Suchtests lieferten und damit einen berechtigten Stellenwert

als solche in LMICs haben. Auffällig waren in den Analysen insbesondere die Wirkstofffreisetzungen von 100 mg Mebendazol Tabletten: während das amerikanische Arzneimittelbuch nicht zwischen 100 mg und 500 mg Dosierungen unterschied und damit vergleichbarere Daten hervorbrachte, ließ die Methode des WHO Arzneimittelbuchs durch eine Unterscheidung zwischen beiden Dosierungen (mögliche) Rückschlüsse auf die verschiedenen Formen des aktiven Wirkstoffs und damit auf eine zu erwartende Wirksamkeit zu.

Gerade in Zeiten von COVID-19 stellen lokale Medikamentenmärkte mit die wichtigste Quelle für Therapeutika im Kampf gegen vernachlässigte Tropenkrankheiten dar. Um ein sicheres Arsenal an Antihelminthika in LMICs garantieren zu können, sind regelmäßige Qualitätsanalysen unerlässlich. Nur so lassen sich die entsprechenden globalen Ziele für nachhaltige Entwicklung auch weiterhin zuverlässig verfolgen.

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Appendix

I Abbreviations

ABZ	Albendazole
ABZSO	Albendazole sulfoxide
API	active pharmaceutical ingredient
ARR	absolute risk reduction
ATP	adenosine triphosphate
BMC	Bugando Medical Centre [of Mwanza]
B. No.	batch number(s)
C18 / ODS	octadecylsilyl
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CUHAS	Catholic University of Health & Allied Sciences [of Mwanza]
DEC	Diethylcarbamazine
DoE	date(s) of expiry
DoM	date(s) of manufacture
DRC	Democratic Republic of the Congo
EDQM	European Directorate for the Quality of Medicines & HealthCare
ESPEN	Expanded Special Project for Elimination of Neglected Tropical Diseases
FCFA	[West African] Franc CFA
FDA	Food and Drug Authority
GAHI	Global Atlas of Helminth Infections
GDP	Good Distribution Practice
GHC	Ghanaian Cedi
GMP	Good Manufacturing Practice
GPHF	Global Pharma Health Fund e.V.

GSK	GlaxoSmithKline
GSMS	Global Surveillance and Monitoring System
HAT	human African trypanosomiasis
HCl	hydrochloric acid
HPLC	high-performance liquid chromatography
IDM	innovative and intensified disease management
IEC	information, education and communication
INN	international non-proprietary name
IVM	Ivermectin
JMP	Joint Monitoring Programme [for Water Supply and Sanitation]
JMU	Julius-Maximilians-University [of Würzburg]
l.c.	label claim
LF	lymphatic filariasis
LMICs	low- and middle-income countries
LSL	lower specification limit
MBZ	Mebendazole
MDA	mass drug administration
MDG	Millennium Development Goal
MMI	Medical Mission Institute [of Würzburg]
NMRA	National Medicine Regulatory Authority
no.	number(s)
NTD	Neglected Tropical Disease
OTC	over the counter
PC	preventive chemotherapy
PCT	preventive chemotherapy and transmission control
Ph. Eur.	European Pharmacopoeia
Ph. Int.	The International Pharmacopoeia
PTFE	Polytetrafluoroethylene

PZQ	Praziquantel
r	Pearson correlation coefficient
RF	retention factor
rpm	revolutions per minute
RSD	relative standard deviation
Q	[minimal] quantity [in dissolution testing]
QA	quality assessment
S.	Schistosoma [species]
SD	standard deviation
SDG	Sustainable Development Goal
SDS	sodium dodecyl sulphate
SF	substandard and falsified [medical products]
SK-TK	Sekondi-Takoradi
SL	specification limit
spp.	species
SSaS	stock sample solution
SSS	stock standard solution
STH	soil-transmitted helminthiases
TD	therapeutic dose
TFDA	Tanzania Food & Drugs Authority
TLC	thin-layer chromatography
TMDA	Tanzania Medicines & Medical Devices Authority
TZS	Tanzanian Shilling
UN	United Nations
UNICEF	United Nations Children’s Fund
USP-NF	United States Pharmacopeia and National Formulary
UV	ultraviolet [spectrophotometric detection of content]
USL	upper specification limit

v	volume
vetABZ	veterinarian Albendazole
WASH	water, sanitation and hygiene
WHO	World Health Organization
WSaS	working sample solution
WSS	working standard solution

II List of figures

III List of images, maps and tables

IIIa Images

IIIb Maps

IIIc Tables

IV Supplementary data

IVa Ethical clearance from CUHAS

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CUHAS/BMC RESEARCH & ETHICAL COMMITTEE (CREC)
ETHICAL CLEARANCE FORM

Date	11th September 2018
Research Clearance Certificate No	CREC/304/2018
Name of researchers/PI	Humphrey Mazigo (PhD) Moritz Seitzer
Purpose of the research	RES
Title of the Research	The Quality of the Composition of Albendazole, Mebendazole and Praziquantel Tablets available in Northern Tanzania
Budget and Sponsor (s)	Euro 1,000/= Medical Mission Institute
Research period	September 2018 to August 2019

Ethical clearance is hereby granted.

A progress report shall be submitted to the relevant Directorate every 6 months.

CREC Chairperson

CREC Secretary

Director RESEARCH AND PUBLICATION CATHOLIC UNIVERSITY OF HEALTH AND ALLIED SCIENCES - BUGANDO P. O. BOX 1464 MWANZA, TANZANIA

IVb Abbreviated 'Be Aware' tool: data form on the categorisation of the tablets' appearance and their packaging

#	Brand/Generics	Packaging												Physical characteristics of the tablet (visual)							
		Container and Closure (yes/no)	*Label (yes/no)*																		
			Trade/Brand name	Name of active ingredient	Manufacturer's name and logo	Manufacturer's full address	Medicine strength (mg/unit)	Dosage form	Number of units per container	Dosage statement	Batch/lot number	Date of manufacture and expiry	Storage information	Leaflet or package insert	Uniformity of shape	Uniformity of size	Uniformity of colour	Uniformity of texture	Markings	Breaks, cracks and splits	Embedded surface spots or contamination	Smell

IVc ABZ 400 mg gives according to Ph. Int. 7 and revision of Ph. Int. 9

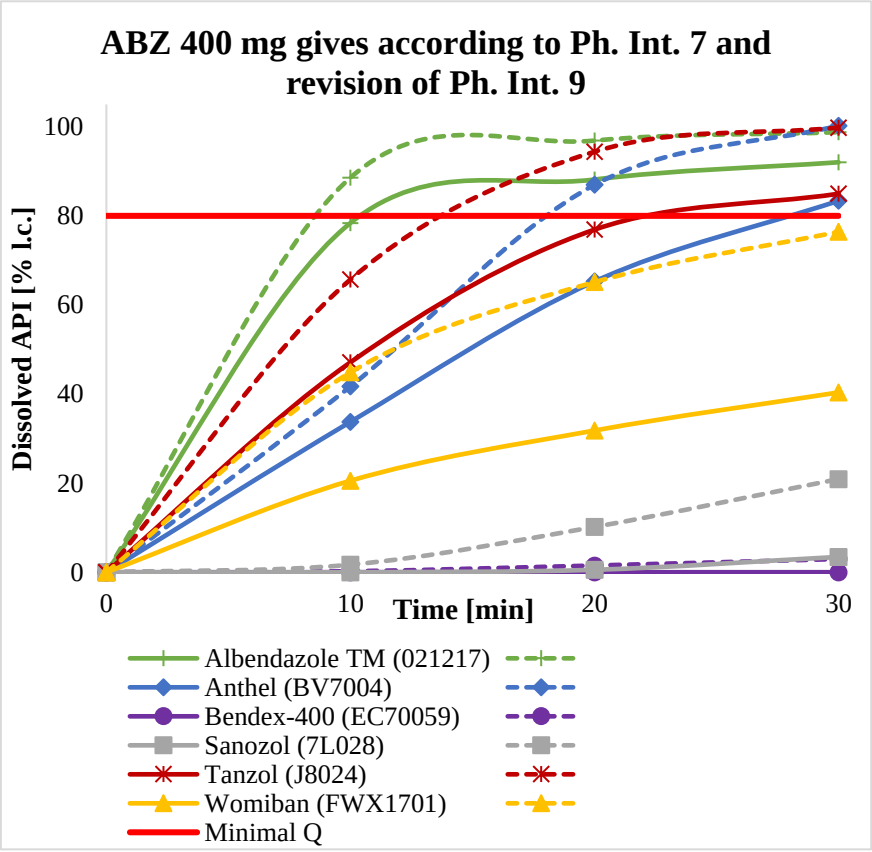

Figure 53: ABZ 400 mg gives according to Ph. Int. 7 and revision of Ph. Int. 9 (dotted lines). The red horizontal line indicates the specific minimal Q of each API.

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VI Curriculum vitae

Nicht in der elektronischen Version enthalten.

VII Publikationen und Konferenzbeiträge

Seitzer M, Klapper S, Mazigo HD, Holzgrabe U, Mueller A. Quality and composition of Albendazole, Mebendazole and Praziquantel available in Burkina Faso, Côte d'Ivoire, Ghana and Tanzania. *PLoS Negl Trop Dis*. 2021;15(1):e0009038. doi:10.1371/journal.pntd.0009038.

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VIII Eidesstattliche Erklärung (Affidavit)

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation „Quality and composition of anthelmintic medicines available in Eastern and Western Africa: an *in-vitro* analysis of Albendazole, Mebendazole and Praziquantel“ eigenständig, d. h. insbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben. Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Würzburg, 08.05.2023

Moritz Seitzer

Affidavit

I hereby confirm that my thesis entitled ‘Quality and composition of anthelmintic medicines available in Eastern and Western Africa: an *in-vitro* analysis of Albendazole, Mebendazole and Praziquantel’ is the result of my own work. I did not receive any help or support from commercial consultants. All sources and / or materials applied are listed and specified in the thesis. Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

Würzburg, 8th May 2023

Moritz Seitzer