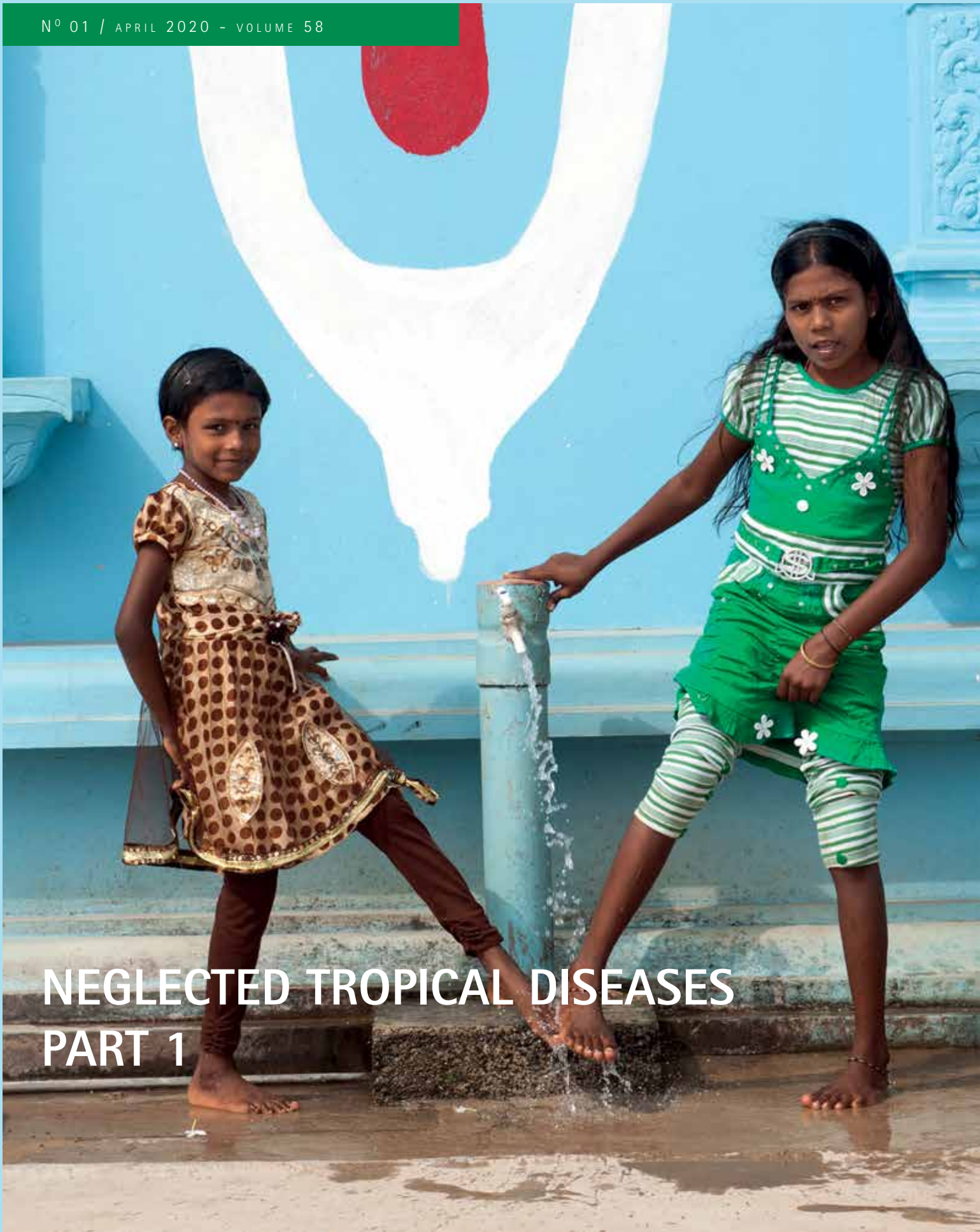
MTb

BULLETIN of the NETHERLANDS SOCIETY for TROPICAL MEDICINE and INTERNATIONAL HEALTH

Nº 01 / APRIL 2020 - VOLUME 58



NEGLECTED TROPICAL DISEASES PART 1

CONTENT

Competing interests:
Ed Zijlstra is consultant to the Drugs for Neglected Diseases initiative, Geneva, Switzerland

Do you feel like joining the MT*b* Editorial Board?

The Bulletin of the Netherlands Society for Tropical Medicine and International Health (NVTG) aims to expand the Editorial Board to further develop the Bulletin.

We are therefore looking for enthusiastic new members to supplement the current Editorial Board and specifically to expand our communication channels, including use of social media. We are particularly looking for young professionals with an interest in exploring and further developing this route.

The positions are available immediately and attractive for those who would like to be in the forefront of publishing relevant contributions in tropical medicine and international health for our readership, or who would like to develop good skills in writing and editing, as well as expanding their network. All those who have affinity with tropical medicine and international health in whatever capacity are welcome to apply.

In addition, we are looking for a new **CHIEF EDITOR** from 1 January 2021. The Chief Editor is the overall coordinator of each of the 4 annual editions and as such oversees all aspects of the quality and suitability of contributions, their coherence and observation of the timelines. Those who are interested would ideally already join the Board as an Editor at an earlier stage.

For enquiries and expression of interest, please contact us at MTredactie@nvtg.org

Global solidarity and collaboration are key to understanding and curbing the COVID-19 pandemic

The COVID-19 epidemic currently has Europe and the United States in a firm and nasty grip. There is a widespread sense of concern, uncertainty and fear now that the virus has reached these continents after causing havoc in China, South Korea and Iran, to name a few countries. And it spreads like wildfire. For example, in the Netherlands, the first case was diagnosed on 27 February 2020 and the first death on 6 March 2020; to date (30 March 2020 – only one month later!), there are 11,750 people reported infected, and 864 people have died. In addition, there are major, and unprecedented, social, economic and political consequences: people's movements are restricted; restaurants, theatres, schools and universities are closed; sport activities are suspended, and many small companies and private enterprises are out of work. For the health sector, it means scaling up of hospital beds for COVID-19 patients who need admission, particularly ICU bed capacity, which has already expanded two-fold and is still under stress as the demand for ICU beds is still growing. In some countries, triage is being used to give preference to those with better chances of a favourable outcome. An additional problem is that regular care is under strain as most of the available resources are absorbed by the COVID-19 pandemic.

Solidarity within Europe is also under strain. The European Union does not seem to be playing a major role in terms of coordination, harmonization, or providing leadership in research. There is friction in intercountry relationships because of lack of financial support for the hardest hit countries in Southern Europe (Italy, Spain). Another problem that the EU is not able to solve is the migrant crisis in Greece and Italy where people live in crowded camps in desperate conditions with poor hygiene: the ideal scenario for COVID-19 to cause havoc. The Moria camp on Lesbos is an example, but outside EU borders the crisis in Idlib, Syria, is of similar magnitude. The G20 in its recent meeting did pledge 5,000 billion US dollars in economic support, but there is no clarity on the way forward.

The USA is heading towards a major disaster, and the number of infections has already exceeded those in other countries. Precious weeks of preparation were lost because of President Trump's initial denial of the problem and the unfortunate faulty diagnostic test developed by the Centers for Disease Control (CDC). Similar denial is demonstrated by Brazil's President Bolsonaro. But our major concern is with the prospects of low- and middle-income countries. The sheer numbers of people at risk are staggering: in India 1.3 billion people are going through a nation-wide lockdown, directly affecting people's survival as many depend on day-to-day income.

In Africa, the number of confirmed cases is still limited, and there is some hope that the combination of higher temperatures and a younger population may restrict the spread of the virus. On the other hand, it is uncertain what effect COVID-19 will have on those who have HIV, tuberculosis or malnutrition, which are common in Africa.

There is no doubt that in many countries, resources will be insufficient to cope with the COVID-19 epidemic. Capacity for diagnostic testing is of paramount importance to guide any intervention. The impact is likely to be high; for example, health systems may be overloaded, and this will also affect regular care. Protective personal equipment may not be available, and intensive care capacity is limited.

A major concern is that high-income countries are preoccupied with their own COVID-19 related problems. However, we do not live on an island. Globalization has two faces: it caused the spread of the virus in an unprecedented way, but at the same time it is also part of the solution.

This is why collaboration and solidarity are essential. As Abiy Ahmed, Prime Minister of Ethiopia and 2019 Nobel Peace Prize laureate, wrote in the *Financial Times* (25 March 2020), 'Global leadership is needed and if the COVID-19 epidemic is not addressed in Africa, the epidemic may bounce back from there once it is brought under control in Europe and North America'. He points out that social distancing is quasi incompatible with African communal lifestyles.

Also, agricultural activities have fixed timeframes and interruption could result in widespread famine. The expected economic decline is likely to preclude governmental measures to purchase hospital equipment and supplies from abroad, let alone to protect vital industries and people who lose their jobs or informal sources of income.

We are deeply concerned about the situation in low- and middle-income countries and among migrant populations. We call for coordinated action – nationally and internationally – to help contain the spread of COVID-19, provide appropriate health care for those affected by the virus, increase universal access to diagnosis, continue the regular (not COVID-19 related) health care and, last but not least, promote clinical and epidemiological research.

The explosive way in which COVID-19 is spreading and has brought high-income countries to a standstill means there is no time to waste.

The Editorial Board of MT*b*

NEGLECTED TROPICAL DISEASES, PART 1

Neglected tropical diseases (NTDs) represent a group of conditions that originally by and large represent the classical tropical diseases other than malaria. They were recognized around 2000, a time when most of the research and funds in tropical medicine went to 'the big three': malaria, tuberculosis and HIV/AIDS. The NTDs are characterized by their tendency to affect poor populations who have no access to appropriate health care or safe and effective drugs and are severely neglected in terms of research. For example, sleeping sickness was still being treated by intravenous administration of toxic drugs based on heavy metals (arsenic) that could actually kill the patient. More than a billion people worldwide are infected with one or more NTDs. The World Health Organization (WHO) currently has twenty diseases in its portfolio, and these now also include relative newcomers such as mycetoma and scabies. The full list of NTDs is much longer (see table on page 5). The WHO policy on NTDs can be found in the recently published roadmap for 2021 - 2030. [1]

In this issue of MT bulletin, we address some of the more classical NTDs in which major progress has been made. The Drugs for Neglected Disease *initiative* (DND*i*) Geneva, Switzerland features in three articles illustrating how new and safe treatments can be delivered using a bench to bedside approach. This has been achieved for sleeping sickness and leishmaniasis, while new (badly needed) approaches are planned for onchocerciasis to supplement mass drug administration (MDA). DND*i* has received support for many years, among other donors, from the Netherlands Ministry of Foreign Affairs; this is money well spent! More new treatments will be delivered in the years to come (www.dndi.org), and there is no other option than going full speed ahead with this successful model.

Admit it: you have not been paying much attention recently to leprosy and thought it was eliminated. Think again: the disease is still with us and needs continuous monitoring to avoid complacency. Luckily, major progress has been made in prevention by post-exposure prophylaxis using a single dose of rifampin. Another relatively new condition on the NTD list is Buruli ulcer, and the first drug studies are underway.

Besides improved drug treatment, mathematical modelling has become essential for control efforts, being of great value in giving insight into disease development and predicting the effects of interventions. This is now available for a wide range of tropical diseases.

In summary, major progress has been made in the field of NTDs. The challenge lies in ensuring ongoing support for the various efforts and providing for the sustainability of all programs and achievements.

Ed Zijlstra & Olga Knaven

MAJOR PROGRESS HAS BEEN MADE IN THE FIELD OF NTDS. THE CHALLENGE LIES IN ENSURING ONGOING SUPPORT FOR THE VARIOUS EFFORTS AND PROVIDING FOR THE SUSTAINABILITY OF ALL PROGRAMS AND ACHIEVEMENTS

REFERENCE

1. World Health Organization. Ending the neglect to attain the sustainable development goals: a road map for neglected tropical diseases, 2021-2030. Geneva: World Health Organization; 2020. 55 p.

OVERVIEW OF NEGLECTED TROPICAL DISEASES[a]

	MAIN RESERVOIR	MODE OF TRANSMISSION	GLOBAL BURDEN[b]
VIRAL DISEASES			
Dengue and Chikungunya fevers*	Human	Vector-borne	2920
Japanese encephalitis	Zoonotic	Vector-borne	
Jungle yellow fever	Zoonotic	Vector-borne	314
Other arboviral infections	Zoonotic	Vector-borne	
Rabies*	Zoonotic	Direct contact	634
Rift Valley fever	Zoonotic	Vector-borne	
Viral haemorrhagic fevers	Zoonotic	Oral/food-borne, vector-borne, direct contact	
BACTERIAL DISEASES			
Bartonellosis	Human, zoonotic	Vector-borne, direct contact	
Bovine tuberculosis in humans	Zoonotic	Oral/food-borne	
Buruli ulcer*	Zoonotic and/or environmental	Unknown	
Cholera	Environment	Oral/food-borne	
Diarrhoeal diseases (Shigella, Salmonella, E. coli)	Human	Oral/food-borne	39600
Leprosy*	Human, (zoonotic)	Direct contact	31.5
Leptospirosis	Zoonotic	Oral/food-borne	
Trachoma*	Human	Direct contact	303
Treponematoses (Yaws, Endemic syphilis, Pinta)*	Human	Direct contact	
HELMINTHIC DISEASES			
Dracunculiasis*	Human	Oral/food-borne	
Echinococcosis*	Zoonotic	Oral/food-borne	100
Food-borne trematodiases (Chlonorchiasis, Fascioliasis, Opisthorchiasis, Paragonimiasis)*	Zoonotic	Oral/food-borne	1870
Loiasis	Human	Vector-borne	
Lymphatic filariasis (LF)*	Human	Vector-borne	1360
Onchocerciasis*	Human	Vector-borne	1340
Schistosomiasis*	Human, zoonotic	Direct contact	1430
Soil-transmitted helminthiases (Ascariasis, Hookworm disease, Trichuriasis, Strongyloidiasis)*	Human	Oral/food-borne, direct contact	1920
Taenia solium (Neuro)Cysticercosis/Taeniosis*	Zoonotic (only taeniosis)	Oral/food-borne	1610
Toxocariasis and other larva migrans diseases	Zoonotic	Oral/food-borne, direct contact	
PROTOZOAN DISEASES			
Amoebiasis	Human	Oral/food-borne	
Balantidiasis	Zoonotic	Vector-borne	
Chagas disease*	Zoonotic	Vector-borne, fetal-maternal, blood	232
Giardiasis	Human	Oral/food-borne	
Human African trypanosomiasis (HAT)*	Human, zoonotic	Vector-borne	79.0
Leishmaniasis*	Human, zoonotic	Vector-borne, fetal-maternal, blood	774
ECTOPARASITIC DISEASES*			
Myiasis		Vector-borne	
Scabies	Human	Direct contact	
Snake bite envenoming*	Environment	Direct contact	
Mycetoma, chromoblastomycosis and other deep mycoses*	Environment	Direct contact	

a) combination of neglected tropical diseases categorized by WHO and PLOS Neglected Tropical Diseases (source: Klohe K, Amuasi, J, Kaducu JM, et al. The 2017 Oslo conference report on neglected tropical diseases and emerging/re-emerging infectious diseases: focus on populations underserved. Infect Dis Poverty. 2018 May;8(1):40. DOI: 10.1186/s40249-019-0550-8.

b) the average in all-age DALYs (thousands) in 2017 (source: GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018 Nov 10;392(10159):1859-1922.

** indicates the 20 diseases categorized by WHO as belonging to the neglected tropical diseases.*

Latest advances in control of sleeping sickness: towards elimination

Sleeping sickness or human African trypanosomiasis (HAT) is a parasitic disease present in sub-Saharan Africa caused by two subspecies of the kinetoplastid protozoan *Trypanosoma brucei (T.b.)*. *T.b. gambiense* is prevalent in Central and West Africa whereas *T.b. rhodesiense* is present in Eastern and Southern Africa (Figure 1). Other *T.b.* subspecies are only infective to animals. Trypanosomes show a characteristic movement *in vivo* due to the presence of an undulating membrane and a trailing flagellum. [1] *T.b.* is mainly transmitted through the bite of several species of tsetse fly, which are found in distinctive habitats, mainly riverine forests and savannah shrublands. [2] Other transmission modes include mother to child during pregnancy and by blood transfusion or sexual contact, but these are much less frequent or are subject to controversy.

T.b. gambiense is most prevalent, has a higher geographical spread, and evolves chronically over months to years. Its main reservoir is humans, although it has been detected in wild and domestic animals. *T.b. rhodesiense* evolves acutely over weeks to months, is mainly zoonotic (cattle and game), and humans are accidental hosts. The clinical manifestations of *T.b. rhodesiense* are more severe, with higher parasitaemia and quicker clinical progression; the heart is commonly affected (pericarditis, myocarditis).

CLINICAL FEATURES

After inoculation through the skin, the clinical presentation of trypanosomiasis is through haemolymphatic spread with rather unspecific symptoms of irregular long-lasting fever, weakness, headache, and weight loss, and may show characteristic lymph node enlargement in posterior cervical angle (Winterbottom's sign). The sleep-wake rhythm may be disrupted before progression to meningo-encephalitic infection, with neuropsychiatric symptoms of advanced disease, including tremor, reappearance of archaic reflexes (palm-chin), walking difficulty, extrapyramidal syndrome, and a frontal syndrome including aggressivity, disinhibition, depression, or apathy. If untreated, this almost always progresses to coma, cachexia, and death. [4] Recently, healthy carriers have been detected, but their role in disease transmission is unknown. [5] Other research has described trypanosomes in the skin, but the clinical relevance is yet to be determined. [6]

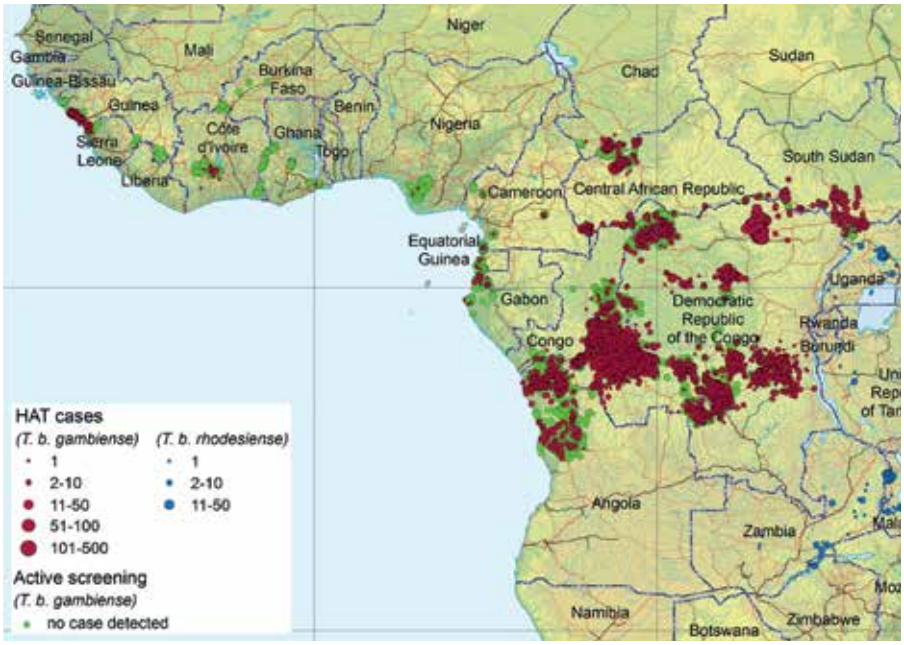


Figure 1: HAT cases detected between 2014 and 2016. (Source WHO/FAO HAT Atlas) [3]

HISTORY

After widespread epidemics in the early twentieth century, there was a steep decrease in the number of cases by the end of the colonial period, with the lowest number by the 1960s. This was related to the intensification of active case detection activities that, for certain countries during the 1940s and 1950s, included systematic chemoprophylaxis with pentamidine and a generally strongly organized vertical control model, which remains largely unchanged today. With the independence of endemic countries, other issues took priority and the colonial health systems were disrupted. It took time for the national governments to replace them, partly due to a widespread lack of trained health professionals. As a consequence, there was an increase in the number of cases, with a peak of detected cases in 1998 (almost 38,000).

Since then, a concerted effort on the part of the World Health Organisation (WHO), the national control programmes, bilateral cooperation (especially Belgian), drug producers (Sanofi and Bayer), and international NGOs such as Médecins Sans Frontières/ Doctors Without Borders (MSF) has led to a steep reduction in the number of

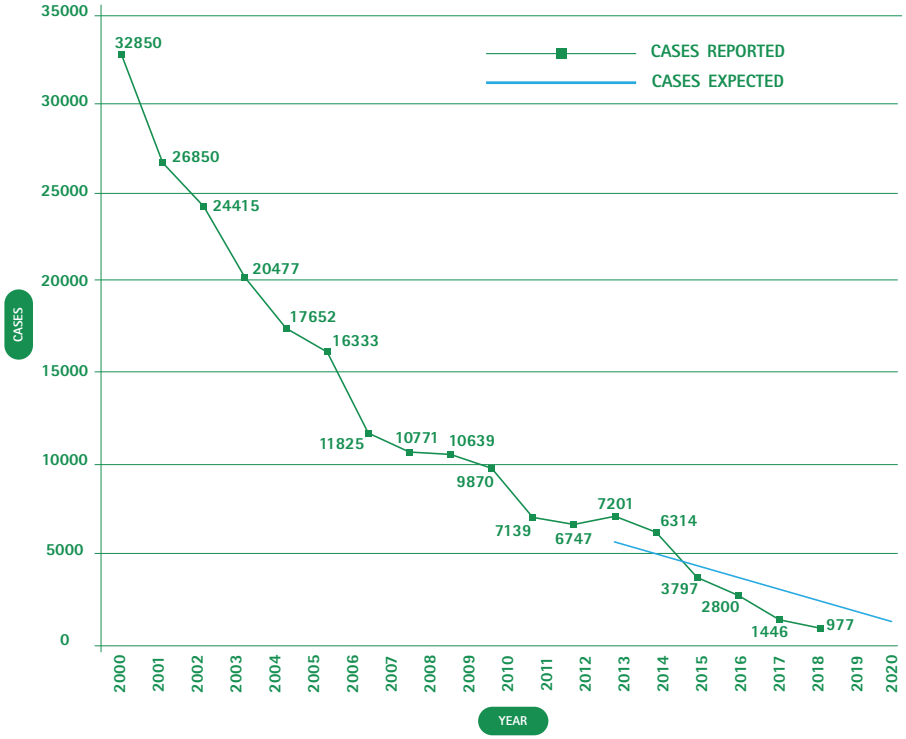


Figure 2: HAT elimination, progress towards WHO roadmap target. (Source WHO) [8]

cases. In 2012, the WHO defined a roadmap with specific targets for neglected disease elimination. International partners, including the Bill & Melinda Gates Foundation, UK AID/DFID, and the Drugs for Neglected Diseases *initiative* (DND*i*), among other partners supporting HAT elimination, signed the London Declaration on Neglected Tropical Diseases (NTDs), improving international partnership under the WHO coordination towards the roadmap goals for HAT and other NTDs. [7]

In 2018 for the first time the total number of reported cases worldwide was less than 1,000 (Figure 2). Of these, 97.5% were caused by *T.b. gambiense*. The country with the highest prevalence is the Democratic Republic of Congo (DRC). While sleeping sickness used to be endemic in 36 countries, during the last five years only 14 countries detected at least one case of *T.b. gambiense* and only five countries detected at least one case of *T.b. rhodesiense*. [8]

CASE DETECTION

Two case-detection strategies have been used since the 1920s: active case search, involving the deployment of mobile teams in endemic areas to examine the entire available population, and passive case search, which is conducted in specially equipped and staffed health structures where suspected symptomatic patients are examined. The main advantage of the active case search strategy is finding cases in initial development of the disease. However, as the number of cases rapidly diminishes, the classic 8- to 10-person mobile teams become too costly per case detected. In an attempt to address this issue, alternative light 'mini' mobile teams have been tested and deployed in the DRC. In most endemic areas, passive case detection and treatment remains concentrated in specialized units, separated from the mainstream primary health care system.

DIAGNOSIS

Disease diagnosis relies on a complex algorithm, with serological screening as the first step followed by microscopic examination of fresh samples to detect motile parasites in blood, lymph and, if positive, further examination of cerebrospinal fluid to determine invasion of the central nervous system. Other tests, such as trypanolysis, [9] detecting human antibodies that lyse cloned trypanosomes expressing specific surface glycoproteins, and several DNA/RNA detection tests need highly specialized laboratory structures and are unsuitable for quick field diagnosis, but rather for confirmation of suspected cases or for surveillance purposes. [10]

Serological screening was dependent on the card agglutination trypanosomiasis test (CATT) for a long time. However, this test requires cold chain for optimal performance and is produced in packs of 50 tests. This format is adapted to mobile teams, which perform a series of tests in community interventions. The recently developed rapid diagnostic tests, however, are oriented towards passive case searching at health care structures as they are individually packed and thermostable.

TREATMENT

For a long time, intravenous melarsoprol was the only treatment for the advanced stage of the disease, a very toxic arsenic derivative developed in 1949. [11] Even now, it remains the reference treatment for advanced *T.b. rhodesiense* infection. In 1981, the first HAT patient was treated with eflornithine, a much less toxic drug with a very short plasmatic half-life that requires four intravenous infusions per day for two weeks. Its use was thus confined to specialized teams with adequate nursing capacity, most often in general reference hospitals. In 2009, nifurtimox eflornithine combination therapy (NECT) was made available. By adding nifurtimox tablets for ten days, the administration of eflornithine could be reduced to twice a day for seven days, [12] but this remained restricted to a hospital setting (Table 1).

By the end of 2018, fexinidazole, a new, oral-only drug developed by the DND*i* [13] was registered in the DRC for the treatment of *T.b. gambiense* HAT. Fexinidazole will allow the treatment of both early and advanced stage HAT under close supervision in peripheral health structures once staff have been trained, with the exception of those patients with severe neurological or psychiatric symptoms who will still need to be hospitalized and treated with NECT. Specific training of trainers has been conducted by the WHO. This will be followed by an extended training

HAT STAGE	DRUG	YEAR INTRODUCED	INDICATION	USE
EARLY	Suramine	1917	T.b. rhodesiense	5 intramuscular injections 5 days (total duration) 21 days)
	Pentamidine	1940	T.b. gambiense T.b. rhodesiense (2nd line)	Intramuscular injection once a day 7-10 days
ADVANCED	Melarsoprol	1949	T.b. rhodesiense T.b. gambiense (3rd line rescue)	Slow intravenous infusion once a day for 10 days
	Eflornithine	1981	T.b. gambiense	4 intravenous infusions/day for 14 days.
	NECT	2009	T.b. gambiense (2nd line)	7 days eflornithine (2 infusions/day) and 10 days oral nifurtimox. First line for severe neuropsychiatric advanced disease
BOTH	Fexinidazole	2019	T.b. gambiense (1st line) T.b. rhodesiense (in phase III trial)	10 days once a day oral treatment. First line except for severe neuropsychiatric advanced disease
	Acoziborole	2022	T.b. gambiense (in Phase III trial)	Single oral dose

Table 1: Current and prospective treatments for hat.

programme targeting 250 hospitals and health centres in all *T.b. gambiense* endemic countries in 2020 to facilitate access to this simplified treatment and contribute towards treatment availability in areas where patients live. A DND*i* study on fexinidazole in *T.b. rhodesiense* infection is on-going.

A new chemical entity, single oral dose acoziborole, is in a phase 3 clinical trial, in which all study participants have been treated and are in the 18-month follow-up phase. The study is expected to be completed by September 2020. This latest drug in development may be a definitive game changer, [14] contributing to disease elimination as targeted by the WHO roadmap for 2030, possibly allowing for a simplified test and treat strategy.

SUMMARY

HAT is at the verge of elimination due to a collective case detection and treatment effort from many stakeholders, coordinated by the WHO and led by the national control programmes in the field. Because of rigorous research carried out in endemic areas under difficult conditions, the management of HAT has changed considerably over the years with old, toxic and intravenous drugs being replaced by patient-friendly regimens with safe, oral short-course drugs.

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THE MANAGEMENT OF **HAT** HAS CHANGED CONSIDERABLY OVER THE YEARS WITH OLD, TOXIC AND INTRAVENOUS DRUGS BEING REPLACED BY **PATIENT-FRIENDLY** REGIMENS WITH SAFE, ORAL SHORT-COURSE DRUGS

REFERENCES

1. Cayla M, Rojas F, Silvester E, et al. African trypanosomes. Parasit Vectors. 2019 Apr;12(1):190. DOI:10.1186/s13071-019-3355-5.
2. Attardo GM, Abd-Alla AMM, Acosta-Serrano A, et al. Comparative genomic analysis of six Glossina genomes, vectors of African trypanosomes. Genome Biol. 2019 Sep 2;20(1):187.
3. Franco JR, Cecchi G, Priotto G, et al. Monitoring the elimination of human African trypanosomiasis: update to 2016. PLoS Negl Trop Dis. 2018 Dec;12(12). DOI:10.1371/journal.pntd.0006890.
4. Kennedy PG. Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping sickness). Lancet Neurol. 2013 Feb;12(2):186-94.
5. Jamonneau V, Ilboudo H, Kaboré J, et al. Untreated human infections by Trypanosoma brucei gambiense are not 100% fatal. PLoS Negl Trop Dis. 2012 Jun;6(6). DOI:10.1371/journal.pntd.0001691.
6. Capewell P, Cren-Travaillé C, Marchesi F, et al. The skin is a significant but overlooked anatomical reservoir for vector-borne African trypanosomes. Elife. 2016 Sep 22;5. DOI:10.7554/eLife.17716.
7. World Health Organization. Accelerating work to overcome the global impact of neglected tropical diseases: a roadmap for implementation. Geneva: World Health Organization; 2012.
8. World Health Organization. Global Health Observatory data repository. Human African trypanosomiasis. [updated 2019 Jun 19] [consulted 2020 Feb 9]. Available from: http://apps.who.int/gho/data/node.main.A1635?lang=en.
9. Jamonneau V, Bucheton B, Kaboré J, et al. Revisiting the immune trypanolysis test to optimise epidemiological surveillance and control of sleeping sickness in West Africa. PLoS Negl Trop Dis. 2010 Dec;4(12). DOI:10.1371/journal.pntd.0000917.
10. Mumba Ngoyi D, Ali Ekangu R, Mumvemba Kodi MF, et al. Performance of parasitological and molecular techniques for the diagnosis and surveillance of gambiense sleeping sickness. PLoS Negl Trop Dis. 2014 Jun;8(6). DOI:10.1371/journal.pntd.0002954.
11. Mpanya A, Hendrickx D, Baloji S, et al. From health advice to taboo: community perspectives on the treatment of sleeping sickness in the Democratic Republic of Congo, a qualitative study. PLoS Negl Trop Dis. 2015 Apr;9(4). DOI: 10.1371/journal.pntd.0003686.
12. Eperon G, Balasegaram M, Potet J, et al. Treatment options for second-stage gambiense human African trypanosomiasis. Expert Rev Anti Infect Ther. 2014 Nov;12(11):1407-17.
13. Mesu VKBK, Kalonji WM, Bardonneau C, et al. Oral fexinidazole for late-stage African Trypanosoma brucei gambiense trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. Lancet. 2018 Jan 13;391(10116):144-154.
14. Bottieau E, Clerinx J. Human African Trypanosomiasis: progress and stagnation. Infect Dis Clin North Am. 2019 Mar;33(1):61-77.

The future of leprosy: opportunities and challenges

Leprosy (also called Hansen's Disease) is a communicable disease caused by *Mycobacterium leprae*. It has a long incubation time, on average around five years, but it can also be up to twenty years or more. The disease affects the skin and peripheral nerves and can cause permanent damage to the skin, nerves, face, hands and feet. Untreated leprosy can lead to impairment, disabilities and social exclusion. Stigma and discrimination are often associated with leprosy and define the disease to a large extent.

Transmission is most likely through droplets from the nose and mouth during prolonged and close contact with untreated leprosy patients, but zoonotic sources are also possible, notably armadillos in South America and the southern states of the United States of America. [1] Diagnosis of leprosy is primarily clinical. Early detection of cases is important to interrupt spread of infection and prevent disability. Multidrug therapy (MDT) is available for six or twelve months combining dapsone, rifampicin and clofazimine, depending on the classification of the disease. Paucibacillary leprosy (PB) is treated for six months and multibacillary leprosy (MB) for twelve months.

Case management includes periodic monitoring, detection and treatment of leprosy reactions, which are immunological phenomena including inflammation of peripheral nerves, fever and skin eruptions causing substantial morbidity and nerve damage. Prevention of disability, wound care, and management of disability (including self-care) are essential components of the care for those affected by the disease. In addition, rehabilitation services provide improved functioning of the individual in the community. Counselling, psychological aid, and health education are crucial to support leprosy patients, their families, and the communities they live in. For comprehensive information about all aspects of leprosy, refer to the online *International Textbook of Leprosy*. [2]

CURRENT EPIDEMIOLOGICAL SITUATION

In 2018, the number of new leprosy cases was 208,619 of which approximately 16,000 were children younger than fifteen years of age. [3] Also, over 11,000 of the new cases had visible deformity of hands, feet and face (indicated as grade 2 disability). Cases were reported from 159 countries, with 80% of the burden occurring in India, Brazil and Indonesia. Figure 1 shows the geographical distribution of new leprosy cases in 2018.

The global trend in leprosy new case detection since 1985 is presented in Figure 2. The trend was remarkably static up to the year 2001, with a peak around the year 2000, then fell dramatically between 2001 and 2005, and has levelled off since 2006. The most important factor contributing to the fast downwards trend between 2001 and 2005 was the decline in leprosy control activities following the declaration by the World Health Organization (WHO) in 2000 that leprosy was eliminated. The official term was "elimination as a public health problem", [4] defined as a prevalence of less than one per 10,000 population at the world level. But most people, including governments, conveniently concluded that leprosy had disappeared altogether and did not need further attention (and funds). Hence the sharp reduction in case finding. The stabilization of the new case detection at just over 200,000 cases annually indicates that transmission of *M. leprae* is continuing unabated, posing an enormous challenge to leprosy control.

THE WAY FORWARD

The declaration by the WHO in the year 2000 that leprosy was 'eliminated' was counterproductive. Since then, the WHO has introduced more concrete and attainable targets which focus on impact of the disease in terms of grade 2 disability in new cases, in particular among children, and on legal issues, such as abolishment of laws allowing discrimination of the basis of leprosy. [5] For 2030, the WHO is setting an ambitious target of reducing the incidence (new case detection) of leprosy by 70%, with emphasis on

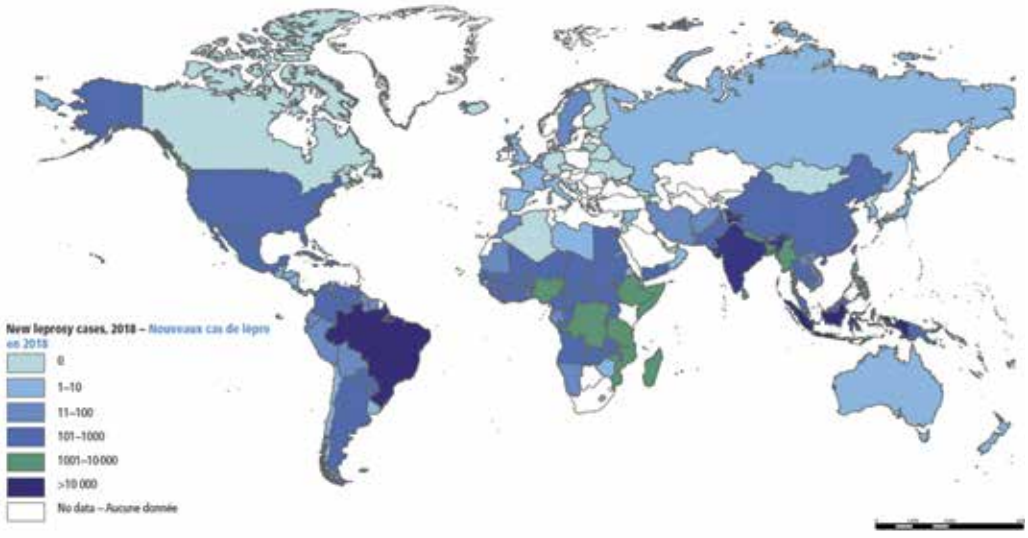

Figure 1: Geographical distribution of new leprosy cases in 2018. [3]

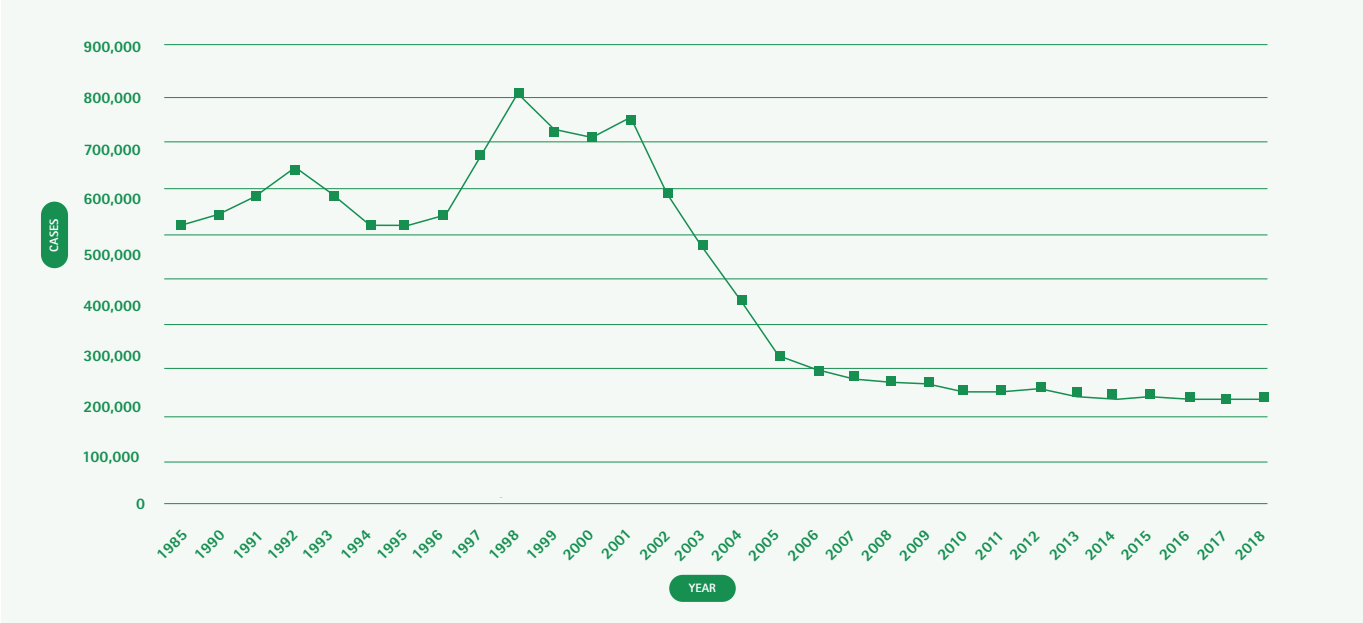

Figure 2: Global trend in leprosy new case detection 1985-2018.

substantially reducing new child cases (as a proxy for recent transmission) and new cases with grade 2 disability (as a proxy for detection delay). In the field of leprosy, an overall target of 'zero leprosy' has been embraced by the WHO, the International Federation of Anti-Leprosy Associations (ILEP), Novartis Foundation, the Sasakawa Health Foundation, and the International Association for Integration, Dignity and Economic Advancement (IDEA), indicating zero disease, zero disability, zero discrimination, and zero stigma (https://zeroleprosy.org/).

NEW PREVENTIVE STRATEGIES

Leprosy control has traditionally been based on early case detection and treatment with MDT. Apart from health education and leprosy awareness campaigns, there were no preventive measures available. It was hoped in the 1990s that through the strategy of timely detection of cases and provision of MDT for patients, the transmission of *M. leprae* in the community could be interrupted, leading to a decline in leprosy incidence. Unfortunately, this has not been the case, as shown in Figure 2. Vaccines for leprosy have not been successful to date, but fortunately the BCG vaccine against tuberculosis also provides some protection against leprosy. [6] An important innovation has been the introduction of post-exposure chemoprophylaxis (PEP) for household and other (close) contacts of leprosy patients. A randomized controlled trial had shown that single-dose rifampicin (SDR) given once to household contacts, neighbours and social contacts reduces their risk of leprosy by approximately 60%. [7] Implementation studies have shown that PEP with SDR is feasible and well-accepted by patients, contacts and health workers in different health care settings. [8] Modelling studies have indicated its potential impact on transmission of *M. leprae* in endemic populations. [9] This intervention was included in the 2018 WHO *Guidelines for the diagnosis, treatment and prevention of leprosy* and is currently being introduced in many countries. [10]

OPPORTUNITIES AND CHALLENGES IN LEPROSY

Leprosy is now included in the list of neglected tropical diseases (NTDs). This has drawn the attention of funding agencies outside the traditional field of leprosy, such as the Novartis Foundation, the Bill & Melinda Gates Foundation, and the European and Developing Countries Clinical Trials Partnership (EDCTP). This has invigorated research into new diagnostics for disease and infection, [11] vaccines, enhanced PEP regimens, epidemiological tools such as geographic information systems (GIS) for identifying leprosy 'hotspots', surveillance of anti-microbial resistance, and alternative drugs and drug regimens for MDT.

The outlook for achieving zero leprosy in the coming decades is better than ever before, but it is admittedly very ambitious. It can only be reached if all leprosy endemic countries enhance their leprosy control activities to include: 1) active case finding strategies such as improved diagnosis; 2) contact screening; and 3) implementation of PEP. The proposed reduction in new case detection of 70% in 2030 is theoretically attainable if these interventions are introduced widely. [12]

However, there is also an important threat. With the waning of interest in leprosy since the year 2000 and the integration of the disease into the regular health systems, the number of medical doctors and health workers at the primary care level with experience in diagnosing and treating leprosy has decreased substantially all over the world. Expertise is being lost and will be difficult to build up again. Seasoned leprologists and leprosy researchers are retiring and not being replaced sufficiently by young doctors and scientists with interest in leprosy. There is a need for fresh 'blood', and hopefully young tropical doctors will be encouraged by this article to take interest in

the fascinating topic of leprosy with its many challenges in the area of clinical medicine, public health, and social inclusion. The next generation needs to realize the ambition of a leprosy-free world in the decades to come.

Conflicts of interest: none

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REFERENCES

1. Truman RW, Singh P, Sharma R, et al. Probable zoonotic leprosy in the southern United States. N Engl J Med. 2011 Apr 28;364(17):1626-33.
2. International Textbook of Leprosy. 2018. Available from: https://internationaltextbookofleprosy.org/.
3. WHO. Global leprosy update, 2018: moving towards a leprosy-free world. Weekly epidemiological record. 2019 Aug 30;35/36(94):389-412.
4. World Health Organization. Guide to eliminate leprosy as a public health problem. Geneva: World Health Organization; 2000. 106 p. Available from: https://www.who.int/lep/resources/who_lep_97.7/en/.
5. World Health Organization. Global Leprosy Strategy 2016-2020: accelerating towards a leprosy-free world. Cooreman EA, editor. New Delhi: WHO SEARO/Department of Control of Neglected Tropical Diseases; 2016. 20 p. Available from: https://www.who.int/lep/resources/9789290225096/en/.
6. Duthie MS, Gillis TP, Reed SG. Advances and hurdles on the way toward a leprosy vaccine. Hum Vaccin. 2011 Nov;7(11):1172-83.
7. Moet FJ, Pahan D, Oskam L, et al. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. BMJ. 2008 Apr 5;336(7647):761-4.
8. Steinmann P, Cavaliero A, Aerts A, et al. The Leprosy Post-Exposure Prophylaxis (LPEP) programme: update and interim analysis. Lepr Rev. 2018;89(2):102-16.
9. de Matos HJ, Blok DJ, de Vlas SJ, et al. Leprosy new case detection trends and the future effect of preventive interventions in Pará State, Brazil: a modelling study. PLoS Negl Trop Dis. 2016 Mar;10(3). DOI:10.1371/journal.pntd.0004507.
10. World Health Organization. Guidelines for the diagnosis, treatment and prevention of leprosy. New Delhi: World Health Organization, Regional Office for South-East Asia; 2018. 106 p. Available from: https://apps.who.int/medicinedocs/en/m/abstract/Js23543en/.
11. Roset Bahmanyar E, Smith WC, Brennan P, et al. Leprosy diagnostic test development as a prerequisite towards elimination: requirements from the user's perspective. PLoS Negl Trop Dis. 2016 Feb;10(2). DOI:10.1371/journal.pntd.0004331.
12. Medley GF, Blok DJ, Crump RE, et al. Policy lessons from quantitative modeling of leprosy. Clin Infect Dis. 2018 Jun 1;66(suppl_4):S281-S5.

Buruli ulcer

Buruli ulcer (BU) is a disease affecting mostly poor people living in neglected parts of the world. The disease is caused by *Mycobacterium ulcerans* and leads to nodules or plaques which eventually break down in ulcers with undermined edges (Figure 1). The limbs are the most frequently involved areas; other areas involved are the head, neck, trunk and genital regions. Though prevalent in 33 countries, the disease is endemic mainly in West Africa and is currently showing a steep increase of incidence in Australia. [1,2] Even though it is difficult to measure exact incidence and prevalence numbers of BU, incidence is estimated at 150.8 per 100,000 in Ghana, and prevalence in some villages can be up to 12%. [3] Another study in Ghana in 2014 showed that in a typical hospital the annual burden for treating BU patients amounted to US$ 121,000, with which 75 patients were helped. The financial cost per capita was US$ 1,616. [4] BU frequently leads to long-term disabilities, especially if patients report late to the health care facilities with an advanced stage of the disease. [5] The delay in seeking treatment at the hospital is a major challenge in BU control since it heavily influences the physical problems and stigma caused by the disease. [6]

DIAGNOSIS

Over the past years, diagnostic tools have been improved to help health care workers diagnose BU. Currently, health care workers can send materials to referral laboratory centres to perform staining for acid-fast bacilli and polymerase chain reaction (PCR). Techniques currently under development include the loop-mediated isothermal amplification (LAMP) technique, [7] fluorescent thin layer chromatography (fTLC) for detection of mycolactone, the toxin produced by *M. ulcerans*, and a point-of-care diagnostic test based on monoclonal antibodies against

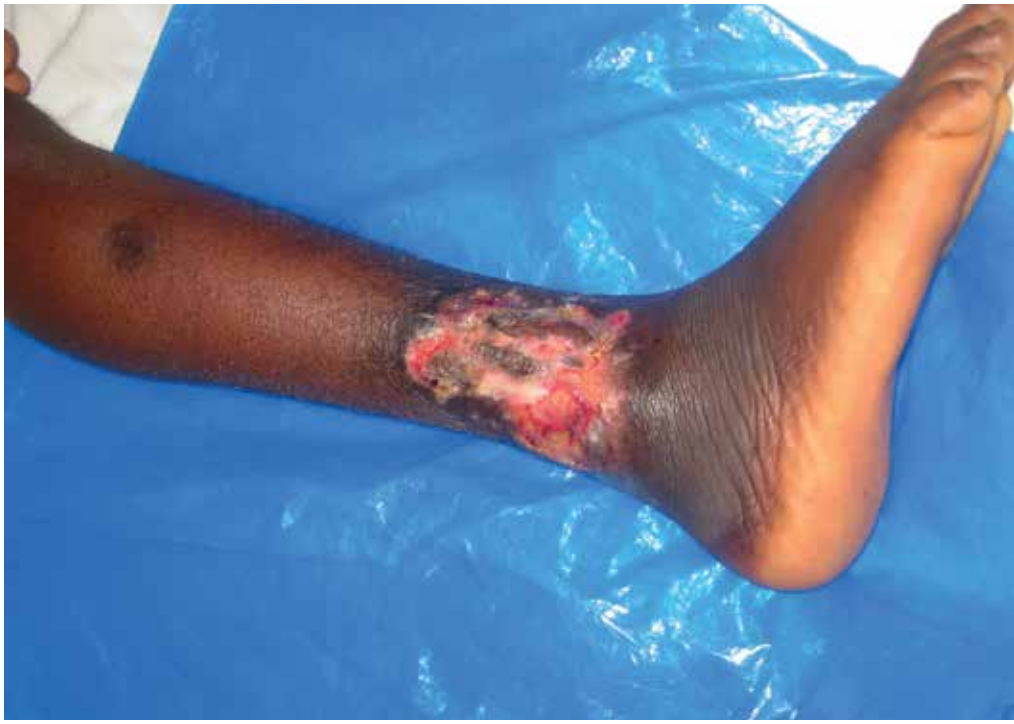

Figure 1: A typical example of Buruli ulcer.

M. ulcerans. [8] These new diagnostic tests will further reduce the doctor's delay in diagnosis – if available at low cost.

Nevertheless, the main cause of advanced stages of the disease at start of treatment is not the doctor's delay, but the patient's delay in seeking treatment at the hospital. This delay is due to financial difficulties, self-treatment and traditional medicine, and the uncertainty about the severity of the skin disease. A practical way to influence such delays is to develop a new diagnostic tool (rapid test) especially for use by the general public living in rural areas. Such a diagnostic tool can inform community member of the most likely diagnosis – BU or another skin disease – and the need to report to health care workers.

ANTIMICROBIAL TREATMENT

The antimicrobial treatment of BU consists of eight weeks of rifampicin combined with streptomycin intramuscularly. This regimen showed high cure rates in a clinical trial. [9] However, daily intramuscular injections are painful, especially for children, who are most affected. Moreover patients frequently have to travel several hours to access a health facility in order to receive their injection. Prolonged streptomycin administration can also cause oto-, vestibular and/or nephrotoxicity. [10]
A recently published randomized clinical trial performed in Ghana and Benin fortunately confirmed that a full oral antimicrobial treatment for early, limited BU with rifampicin and an extended release formulation of clarithromycin is not inferior to the treatment with rifampicin and injected streptomycin. [11]

Based on the findings of this trial, the WHO Technical Advisory Group decided to replace rifampicin and streptomycin by an oral regimen of rifampicin and clarithromycin as the advice for standard treatment for BU. Yet, this advice poses a challenge to national programs and local services in terms of compliance and prevention of misuse of the drugs.

Earlier research on treatment compliance in BU showed poor results during the eight weeks of treatment with rifampicin and streptomycin; in one centre in Ghana, only 46% of the patients completed antimicrobial therapy. [12] Another challenge is to prevent misuse of the new regimen. Clarithromycin can be used for many different infectious diseases and especially its potential in the treatment of respiratory tract infections is liable to lead to misuse of this drug by local trading. This drains the resources for BU treatment and will contribute to development of resistance to clarithromycin and other macrolides in the community. [13]

WOUND CARE

The poor quality of wound care is directly related to serious challenges in the management of BU. Despite the antimicrobial treatment, disabilities are still common, healing takes too much time (median from 18 to 21 weeks), and long hospital stays are still frequently needed and include painful changes of wound dressings. The limited attention given to wound care is illustrated by our previous study on BU wound care in Ghana and Benin which showed a variety in wound care practices among health care personnel and health care facilities; adherence to the WHO guidelines was found to be low. [14] Wound care frequently is accompanied by pain, which is mainly caused by removal of the gauze sticking to the wound without access to adequate pain medication. [15]

Improved wound care has the potential to prevent disabilities and has a direct impact on healing time, length of hospital stays, and long-term consequences of the disease such as contractures.

This need for improved wound care is not unique to BU. The disease burden of skin diseases in general is high in areas where BU is endemic. Patients present with burn wounds, sickle cell and diabetic ulcers or other skin lesions such as those caused by cutaneous leishmaniasis, leprosy or yaws.

SUMMARY

Case detection, community education, and wound care as applied in Buruli ulcer management are examples of activities which can be designed to target multiple neglected skin diseases. Such integration of neglected tropical skin disease activities allows for optimal use of limited resources.

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REFERENCES

1. World Health Organization. Investing to overcome the global impact of neglected tropical diseases: third WHO report on neglected diseases 2015. Geneva: World Health Organization/Department of Control of Neglected Tropical Diseases; 2015. 191 p. Available from: https://www.who.int/neglected_diseases/9789241564861/en/.
2. Carson C, Lavender CJ, Handasyde KA, et al. Potential wildlife sentinels for monitoring the endemic spread of human buruli ulcer in South-East Australia. PLoS Negl Trop Dis. 2014 Jan 30;8(1):13.
3. Amofah G, Bonsu F, Tetteh C, et al. Buruli ulcer in Ghana: results of a national case search. Emerg Infect Dis. 2002 Feb;8(2):167–70.
4. Asare KH, Aikins M. Health facility cost of buruli ulcer wound treatment in Ghana: a case study. Value Heal Reg Issues. 2014 Sep;4:14–8.
5. Barogui Y, Johnson RC, van der Werf TS, et al. Functional limitations after surgical or antibiotic treatment for buruli ulcer in Benin. Am J Trop Med Hyg. 2009 Jul;81(1):82–7.
6. de Zeeuw J, Omansen TF, Douwstra M, et al. Persisting social participation restrictions among former buruli ulcer patients in Ghana and Benin. PLoS Negl Trop Dis. 2014 Nov;8(11). DOI:10.1371/journal.pntd.0003303.
7. Beissner M, Phillips RO, Battke F, et al. Loop-mediated isothermal amplification for laboratory confirmation of buruli ulcer disease. Towards a point-of-care test. PLoS Negl Trop Dis. 2015 Nov;9(11). DOI:10.1371/journal.pntd.0004219.
8. Sakyi SA, Aboagye SY, Darko Otchere I, et al. Clinical and laboratory diagnosis of buruli ulcer disease: a systematic review. Can J Infect Dis Med Microbiol. 2016;2016. DOI:10.1155/2016/5310718.
9. Nienhuis WA, Stienstra Y, Thompson WA, et al. Antimicrobial treatment for early, limited Mycobacterium ulcerans infection: a randomised controlled trial. Lancet. 2010 Feb 20;375(9715):664–72.
10. Klis S, Stienstra Y, Phillips RO, et al. Long term streptomycin toxicity in the treatment of buruli ulcer: follow-up of participants in the BURULICO drug trial. PLoS Negl Trop Dis. 2014 Mar;8(3). DOI:10.1371/journal.pntd.0002739.
11. Phillips, R.O., Robert J, Abass KM, et al. Rifampicin and clarithromycin (extended release) versus rifampicin and streptomycin for limited buruli ulcer lesions: a randomised, open-label, non-inferiority phase 3 trial. Lancet. 2020 Mar; in press.
12. Klis S, Kingma RA, Tuah W, et al. Compliance with antimicrobial therapy for buruli ulcer. Antimicrob Agents Chemother. 2014 Oct;58(10):6340.
13. George DP. The Macrolide Antibiotic Renaissance. Br J Pharmacol. 2017 Jun. DOI:10.1111/bph.13936.
14. Velding K, Klis SA, Abass KM, et al. Wound care in buruli ulcer disease in Ghana and Benin. Am J Trop Med Hyg. 2014 Aug;91(2):313–8.
15. de Zeeuw J, Alferink M, Barogui YT, et al. Assessment and treatment of pain during treatment of buruli ulcer. PLoS Negl Trop Dis. 2015 Sep;9(9). DOI:10.1371/journal.pntd.0004076.

Onchocerciasis elimination: what`s left to do?

Onchocerciasis is a filarial disease caused by infection with *Onchocerca volvulus*, a vector-borne parasitic nematode transmitted via the bites of several Simulium black fly species. The disease is also known as river blindness because black flies breed in and bite near fast-flowing rivers, and because the most devastating sequela is irreversible loss of vision. High infection load, measured by the density of microfilariae (the larval progeny of adult worms) in the skin, is associated both with blindness incidence and excess human mortality. In addition to ocular sequelae, onchocerciasis is also responsible for skin disease and troublesome itching, which disturbs sleep and work patterns. Onchocerciasis represents a major public health problem in affected countries with up to 1.34 million disability adjusted life years (DALYs) lost in 2017. [1] This high number is driven by disease-induced disability and overall loss of economic productivity. The introduction of ivermectin in mass drug administration (MDA) has been extremely successful in reducing transmission and human morbidity. [2] However, treatment must be repeated at regular intervals (6 or 12 months) for 10-15 years and limitations exist in zones where *Loa loa* is co-endemic [3] due to severe adverse events, including fatalities, that may result from microfilaricidal treatment of individuals heavily infected with *L. loa*.

MASS DRUG ADMINISTRATION: LIMITATIONS

MDA with ivermectin has been extremely successful in reducing the onchocerciasis microfilarial burden resulting in reduction of clinical manifestations and interrupting transmission in some areas. The adult worm however is not permanently affected, and with a worm's life span being 10-15 years, MDA campaigns need to continue for many years. Success of MDA is strongly related to 1) coverage of the population and 2) pre-intervention prevalence, making implementation of a sustainable MDA program extremely challenging in some areas. Thus, elimination of transmission appears feasible in low to moderate endemic areas with long-term MDA at high coverage (≥75%). [4] However, in other areas, this may be less successful because of high endemicity, low adherence, and lack of financial resources or political engagement.

Members of the NTD Modelling Consortium have used two mathematical models of onchocerciasis transmission dynamics and control (EPIONCHO and ONCHOSIM) to provide predictions of the elimination goals. [4] ONCHOSIM for example predicts there will be around fourteen million infected cases in the areas covered by the African Programme for Onchocerciasis Control (APOC) in 2025 with >4 million cases remaining with clinical manifestations. The total population at risk will be approximately 200 million in the countries formerly covered by APOC. [5] Success of MDA however continues to require extensive logistical efforts and financial commitments to ensure that treatment reaches all target recipients. Other drawbacks of MDA are inconvenience, loss of confidence in the elimination campaign, and possible drug resistance as described for ivermectin use in livestock. The effectiveness of MDA will therefore likely deviate from the model predictions and further delay the timeline to elimination.

The cost-effectiveness of current elimination strategies is currently being reconsidered and economic analyses are being conducted, [4] factoring in the expansion into currently untreated areas and prospects of more frequent rounds of MDA. This also includes support by additional tools such as the recently registered moxidectin, [6] the triple therapy with ivermectin, albendazole and diethylcarbamazine, [7] as well as a hypothetical macrofilaricide, enhanced surveillance or test and treat strategies. Given the current elimination goals, the additional benefit of optimized strategies and full engagement into a drug development pipeline for new treatments needs to be seriously considered.

Another aspect of MDA is that treatment of the entire population requires a careful risk-benefit analysis. In combatting infectious diseases, drug administration campaigns are important strategies for dealing with public health issues. There is however a balance between making MDA compulsory, which potentially limits the autonomy of an individual, and the possibility of opting out, which could jeopardize the entire effort of the campaign as onchocerciasis may be re-introduced to the treated community. [8] Unlike a vaccine, MDA does not provide an immediate benefit for an uninfected person. An individual may find repeated MDA inconvenient or may lose confidence in the MDA campaign. With effective MDA, the benefits for the entire population clearly exceed the risk, but if prevalence has been reduced, the risk/benefit ratio may be different.

ALTERNATIVE APPROACHES ARE NEEDED

A macrofilaricidal drug that kills the adult worm or has a long-term sterilizing effect offers the advantage of reducing the number of MDA cycles and would be a powerful addition to the global strategy for eliminating onchocerciasis. A new and registered macrofilaricide or long-term sterilizing treatment would have considerable advantages and could be used for:

1. MDA, provided it is safe and well tolerated;

2. Test-and-treat (TNT) strategies for treatment of patients in endemic areas outside MDA campaigns if diagnostic tools are available, especially in "mop-up" campaigns after the disease burden has been reduced by MDA programs rendering them no longer cost

effective, or in areas where regular ivermectin distribution is difficult;

3. Test-and-not-treat (TaNT) campaigns in areas where *L. loa* is co-endemic;

4. Appropriate case management.

The Drugs for Neglected Diseases *initiative* (DND*i*) is a non-profit research and development organization based in Geneva, Switzerland that is committed to developing new treatments for patients with neglected tropical diseases, including those infected with onchocerciasis.

In general, helminth infections affect mostly poor and marginalized populations. Whereas the development of new treatment options is commercially not attractive, the development of anthelmintic drugs for animal health is lucrative. Commercially available animal health products should therefore be considered and evaluated for human indications to shorten drug development timelines. Two potential pathways are being considered, targeting the filarial parasite directly (a macrofilaricidal drug) or its endosymbiont (Wolbachia bacteria).

In collaboration with the Bayer AG pharmaceutical company, DND*i* is currently developing emodepside, an anthelmintic veterinary product for cats and dogs. It inhibits parasite development and elicits profound impairment of neuromuscular function with broad-spectrum efficacy against gastrointestinal [9] as well as filarial nematodes, [10] which results in rapid paralysis (inhibition of locomotion, feeding and slowed development). The mechanism of action of emodepside is complex and not fully understood, but it predominantly exerts its anthelmintic activity through selective activation of the nematode isoform of a potassium channel called slowpoke (Slo-1). Emodepside has proven antifilarial potential in preclinical models, [10] warranting its further development.

Adult filarial worms causing onchocerciasis carry an obligate symbiotic endobacterium, Wolbachia, which is essential for development, fecundity, and ultimate survival. Clinical studies with doxycycline show that it depletes these endobacteria. Although it has no immediate effect on the adult worms, they will die in time. [11] It is effective in lowering microfilarial load in regions with suboptimal response to ivermectin. [3]

Although doxycycline is effective as a macrofilaricide via its anti-Wolbachia activity, it is contraindicated in pregnant women and children through the age of eight due to developmental toxicities. Furthermore, four to six weeks of daily therapy with doxycycline are required to lower the Wolbachia population sufficiently to produce a cidal effect in the adult worm. Consequently, doxycycline is unsuitable for MDA and far from ideal for patient management. Improved treatments are warranted.

The pharmaceutical company AbbVie has developed a tylosin analogue that has potent anti-Wolbachia and antifilarial activity. [12,13] In pre-clinical models, the compound (ABBV-4083) has demonstrated equal or superior efficacy to doxycycline with a shorter duration of treatment. In a collaboration with AbbVie, the DND*i* and the Liverpool School of Tropical Medicine, ABBV-4083 is now further progressing into proof-of-concept studies in infected volunteers.

SUMMARY

Years of experience have shown that current MDA with ivermectin has severe shortcomings in onchocerciasis control. New approaches are needed, such as development of macrofilarial drugs, to supplement current MDA in order to meet the sustainable development goals.

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REFERENCES

1. GBD DALYs 2017 and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018 Nov 10;392(10159):1859-1922.
2. Campbell, WC. Ivermectin: a reflection on simplicity (nobel lecture). Angew Chem Int Ed Engl. 2016 Aug 22;55(35):10184-9.
3. Lenk EJ, Moungui HC, Boussinesq M, et al. A test-and-not-treat strategy for onchocerciasis elimination in Loa loa co-endemic areas: cost analysis of a pilot in the Soa health district, Cameroon. Clin Infect Dis. 2019 Jun. DOI:10.1093/cid/ciz461. [Epub ahead of print].
4. NTD Modelling Consortium Onchocerciasis Group. The World Health Organization 2030 goals for onchocerciasis: insights and perspectives from mathematical modelling: NTD Modelling Consortium Onchocerciasis Group. Gates Open Res. 2019 Sep 26;3:1545.
5. Vinkeles Melchers NVS, Coffeng LE, Boussinesq M et al. Projected number of people with onchocerciasis-loiasis co-infection in Africa, 1995 to 2025. Clin Infect Dis. 2019 Jul. DOI:10.1093/cid/ciz647. [Epub ahead of print].
6. Opoku NO, Bakajika DK, Kanza EM, et al. Single dose moxidectin versus ivermectin for Onchocerca volvulus infection in Ghana, Liberia, and the Democratic Republic of the Congo: a randomised, controlled, double-blind phase 3 trial. Lancet. 2018 Oct 6;392(10154):1207-1216.
7. Fischer PU, King CL, Jacobson JA, et al. Potential value of triple drug therapy with ivermectin, diethylcarbamazine, and albendazole (IDA) to accelerate elimination of lymphatic filariasis and onchocerciasis in Africa. PLoS Negl Trop Dis. 2017 Jan;11(1). DOI:10.1371/journal.pntd.0005163.
8. Cheah PY, White NJ, Antimalarial mass drug administration: ethical considerations. Int Health. 2016 Jul;8(4):235-8.
9. Kulke D, Krücken J, Harder A, et al. Efficacy of cyclooctadepsipeptides and aminophenylamidines against larval, immature and mature adult stages of a parasitologically characterized trichurosis model in mice. PLoS Negl Trop Dis. 2014 Feb;8(2). DOI:10.1371/journal.pntd.0002698.
10. Zahner H, Taubert A, Harder A, et al. Effects of Bay 44-4400, a new cyclodepsipeptide, on developing stages of filariae (Acanthocheilonema viteae, Brugia malayi, Litomosoides sigmodontis) in the rodent Mastomys coucha. Acta Trop. 2001 Sep 1;80(1):19-28.
11. Hoerauf A, Specht S, Büttner M, et al. Wolbachia endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study. Med Microbiol Immunol. 2008 Sep;197(3):295-311.
12. Taylor MJ, von Geldern TW, Ford L, et al. Preclinical development of an oral anti-Wolbachia macrolide drug for the treatment of lymphatic filariasis and onchocerciasis. Sci Transl Med. 2019 Mar;11(483).
13. von Geldern TW, Morton HE, Clark RF, et al. Discovery of ABBV-4083, a novel analog of Tylosin A that has potent anti-Wolbachia and anti-filarial activity. PLoS Negl Trop Dis. 2019 Feb;13(2). DOI:10.1371/journal.pntd.0007159.

NEW APPROACHES ARE NEEDED, SUCH AS DEVELOPMENT OF MACROFILARIAL DRUGS, TO SUPPLEMENT CURRENT MDA IN ORDER TO MEET THE SUSTAINABLE DEVELOPMENT GOALS

Cystic echinococcosis: a neglected tropical disease with increasing importance in migrants

Echinococcosis is one of twenty neglected tropical diseases (NTDs) defined as such by the World Health Organization (WHO). In 2015, an estimated loss of 641,430 disability adjusted life years (DALYs) globally were reported, ranking the disease in the 12th place out of seventeen reported NTDs. [1] There are various endemic regions for echinococcosis worldwide where prevalence can reach up to 5-10% of the population, such as South America, North Africa and parts of the Middle East (Figure 1). [2] Although several attempts to control the disease have been made, it still remains a public health problem in numerous countries, with about two to three million cases worldwide and 19,300 deaths annually. [3,4]
The prevalence depends on various factors such as education, economy, medical treatment and culture. In the Amsterdam University Medical Center (UMC), a centre of expertise for treatment of cystic echinococcosis (CE) in the Netherlands, an increase in new patients was seen in the last two decades among migrants, mainly from Morocco and Turkey and more recently also from Iraq, Iran, Afghanistan and Syria (Figure 2). There are two forms of echinococcosis in humans: cystic echinococcosis (CE), also called hydatidosis, and the alveolar form of echinococcosis. CE is a zoonosis caused by a tapeworm of the genus *Echinococcosis granulosus*. This article will focus on CE.

PATHOGENESIS

Human echinococcosis is caused by the larval stages of the Echinococcus tapeworm. Infection of humans occurs in a peculiar way and is not part of the natural cycle of the parasite. The normal intermediate host, cattle and other herbivores, are infected by the ingestion of food or water contaminated with eggs that develop into larvae in the viscera. The definitive host, usually dogs, are infected by eating the viscera of infected intermediate hosts. [5] The cycle is completed in the intestines of the definitive host as the larvae develop into mature tapeworms and produce eggs. [3] However, humans can become an accidental intermediate host, infected in the same way but not transmitting the disease to the definitive host. In the viscera of an intermediate host, the eggs hatch and hooked larvae (oncospheres) are released. They pass through the intestinal wall and enter the portal system, through which they colonize mainly the filtering organs such as liver and lungs. Here the oncospheres develop into larval echinococcal cysts. Most cysts are found in the liver (75%), with the majority of cysts localized in the right lobe (85%). Other affected organs include the lungs and the brain (Figure 3). The cyst steadily grows larger and infective protoscolices are produced inside the cyst. [4-8]

CLINICAL PRESENTATION

In 80% of cases, the cysts formed by the larvae are restricted to one organ and remain solitary in most patients. Besides lungs and liver, the cysts can sporadically occur in any other organ or tissue. [7,9] The majority of patients never develop symptoms and the disease remains clinically silent. It usually takes 5-20 years before the slowly growing cyst is large enough to cause symptoms. The most frequently seen clinical features are abdominal pain, usually in the right upper quadrant, hepatomegaly, hepatitis and/or cholangitis. [10] A serious complication is anaphylactic shock after rupture of a cyst. Other clinical presentations of patients are caused by pressure of the abdominal mass, on stomach, duodenum or biliary tree resulting in jaundice. [5]

DIAGNOSIS

Because of the long asymptomatic period

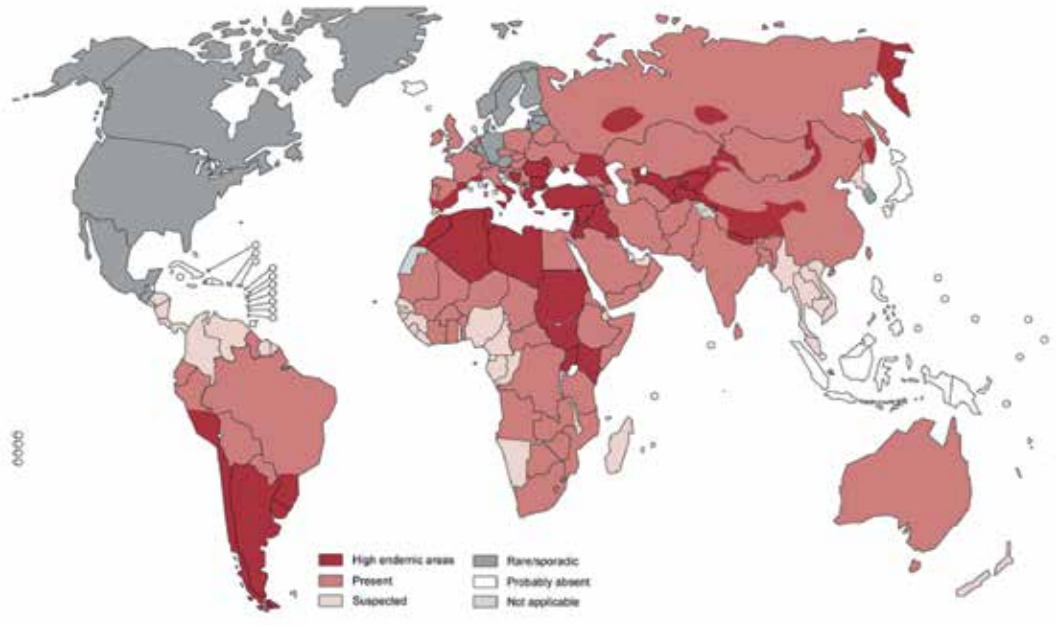


Figure 1: Geographical distribution of CE. [4]

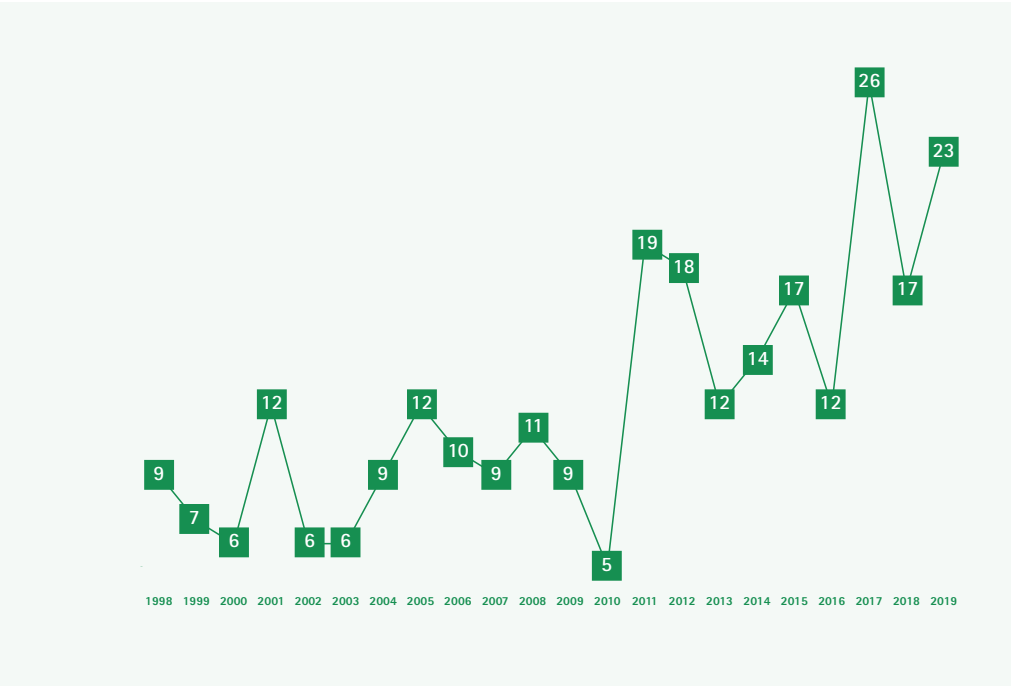


Figure 2: Number of new patients per year treated at the Amsterdam UMC, location AMC.

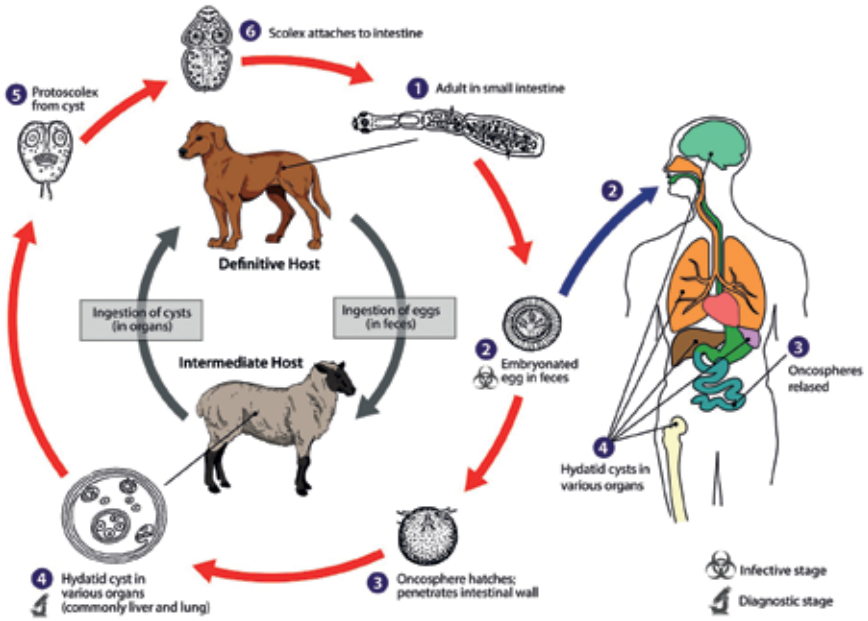
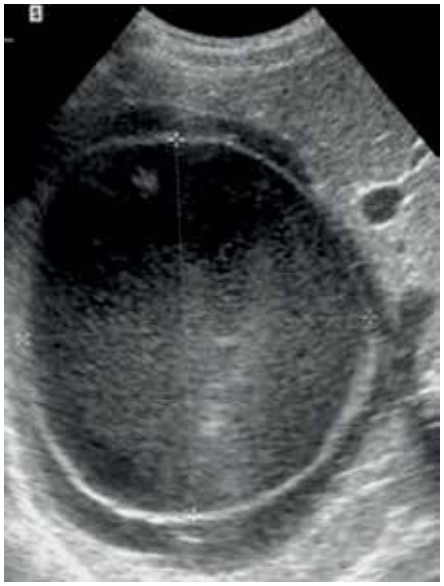


Figure 3: Life cycle of Echinococcus granulosus and infection of humans. [8]

mentioned before, the diagnosis is often made coincidentally or when first complications occur, usually in adults. It is important to take the background of patients into account, focusing on visits to endemic regions or living in rural areas as well as living in close contact with definitive or intermediate hosts. Sometimes travellers to endemic countries can become infected by drinking water or eating undercooked food contaminated with eggs. Especially hikers, trekkers and hunters are at greater risk of coming into contact with infected animals or their stools.

A combination of epidemiological and clinical findings, serological and



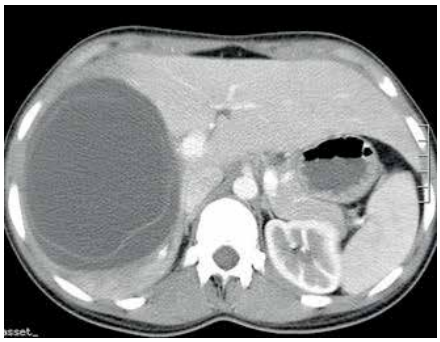


Figure 4: Ultrasound and CT-scan in a patient with type 2 Gharbi cyst.

immunological tests, and imaging is used to confirm the diagnosis of CE. Serology is helpful in detecting CE, but as a result of an undetectable immune response it misses about 30-40% of cases. Furthermore, many endemic countries lack the resources to use serology as a diagnostic tool. [11] Therefore, ultrasonic imaging is seen as the cornerstone in diagnosing CE. The accuracy is almost 90%, depending on the experience of the clinician. [12] Alternatively, a CT- or MRI-scan may be performed (Figure 4). [11]

CLASSIFICATION

Two classifications have been developed, based on ultrasound: the Gharbi and the WHO 2001 classification. The latter is a modification of the Gharbi classification made by the WHO Informal Working Group on Echinococcosis (WHO-IWGE); [13] it is recommended as the imaging reference standard, for guiding treatment and for use in follow-up (Table 1).

CLASSIFICATION TYPE GHARBI ET AL.	WHO-IWGE	CLASSIFYING FEATURES	STAGE
I	CE 1	Univesicular fluid collection/simple cyst	Active
III	CE 2	Multivesicular fluid collection with multiple daughter cysts or septae (honeycomb)	Active
II	CE 3 A	Fluid collection with membranes detached (water lily sign)	Transitional
III	CE 3 B	Daughter cysts in solid matrix	Transitional
IV	CE 4	Cysts with heterogenous matrix, no daughter cysts	Inactive/degenerative
V	CE 5	Solid cystic wall	Inactive/degenerative

Table 1: Overview of the two classifications and biological activity. [11]

TREATMENT AND CONTROL

Treatment should be given to all patients with vital cysts, as complications may be fatal or lead to morbidity with prolonged hospitalization. Furthermore, CE might pose a large social and economic burden on patients. Several treatment options are at hand: chemotherapy, surgery, percutaneous drainage and wait-and-see.

Chemotherapy consists of anthelmintic drugs, such as albendazole and mebendazole. It is mostly effective in the very early stages of uncomplicated CE and pre- and/or perioperatively, reducing the chance of dissemination and anaphylaxis. The surgical approach has long been the gold standard in treatment of CE and can consist of a conservative, radical, or laparoscopic technique. The PAIR technique (puncture, aspiration, injection, reaspiration) uses ultrasound to puncture the cyst, destruction of the protoscolices using a scolicidal fluid, and re-aspiration of this fluid after 15-20 minutes. PAIR is effective in early stages of the disease with clear cyst content (CE 2). At the Amsterdam UMC, a modified percutaneous technique was developed and frequently used, called PEVAC (percutaneous evacuation of cyst content). PEVAC may serve as a less invasive alternative to surgery in mature cysts (CE 3), reducing complications and hospital stay with a similar recurrence rate. [14] In an ongoing literature review, similar recurrence rates were found after percutaneous techniques vs. surgery in more mature cysts, while percutaneous techniques led to less complications and shorter hospital stay. This is in agreement with UMCA's experience with percutaneous treatment of almost 300 CE patients over a period of more than twenty years (unpublished data). The last treatment option is the wait-and-see approach, usually in patients with CE 4 or CE 5 type cysts. [15] In various previously endemic countries, CE has been eliminated by implementing effective CE control strategies, primarily using a One Health approach. According to the WHO, the combination of deworming dogs, vaccination of lambs, and culling of older sheep could eliminate CE globally in less than ten years. However, as for many NTDs, data on CE are scarce. [4]

CONCLUSION

Cystic echinococcosis is one of the WHO's twenty neglected diseases. In high-income countries, it is increasingly important as an imported disease in migrants and other travellers from endemic countries. In low- and middle-income countries, it may cause significant morbidity and mortality if left untreated, posing an important burden on local health facilities. CE is a typical example of how animal and human health are interrelated, underlining the One Health approach as recommended by the WHO.

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REFERENCES

1. Mitra AK, Mawson AR. Neglected tropical diseases: epidemiology and global burden. Trop Med Infect Dis. 2017 Aug 5;2(3):36.
2. Pakala T, Molina M, Wu GY. Hepatic echinococcal cysts: a review. J Clin Transl Hepatol. 2016 Mar 28;4(1):39-46.
3. Craig P, McManus D. Prevention and control of cystic echinococcosis. Lancet Infect Dis. 2007 Jun;35(6):385-94.
4. World Health Organization. Echinococcosis. 2019 May 24. Available from: https://www.who.int/news-room/fact-sheets/detail/echinococcosis.
5. Mandal S, Mandal MD. Human cystic echinococcosis: epidemiologic, zoonotic, clinical, diagnostic and therapeutic aspects. Asian Pac J Trop Med. 2012 Apr;5(4):253-60.
6. Yagci G, Ustunsoz B, Kaymakcioglu N, et al. Results of surgical, laparoscopic, and percutaneous treatment for hydatid disease of the liver: 10 years experience with 355 patients. World J Surg. 2012 Dec;29(12):1670–1679.
7. Medscape. Echinococcosis hydatid cyst. Brunetti CF; Updated 2015 Dec 05. Available from: https://emedicine.medscape.com/article/216432-overview#a5.
8. CDC. Echinococcosis. Biology. 2012 [updated 2019 July 16]. Available from: https://www.cdc.gov/parasites/echinococcosis/biology.html.
9. Filippou D, Tselepis D, Filippou G. Advances in liver echinococcosis: diagnosis and treatment. Clin Gastroenterol Hepatol. 2007 Feb;5(2):152-59.
10. Mihmanli M, Idiz UO, Kaya C. Current status of diagnosis and treatment of hepatic echinococcosis. World J Hepatol. 2016 Oct 8;8(28):1169-81.
11. Pakala T, Molina M, Wu GY. Hepatic echinococcal cysts: a review. J Clin Transl Hepatol. 2016 Mar 28;4(1):39-46.
12. Macpherson CNL, Milner R. Performance characteristics and quality control of community based ultrasound surveys for cystic and alveolar echinococcosis. Acta Trop. 2003 Feb;85(2):203-9.
13. WHO Informal Working Group. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. Acta Trop. 2003 Feb;85(2):253-61.
14. Shera TA, Choh NA, Gojwari TA. A comparison of imaging guided double percutaneous aspiration injection and surgery in the treatment of cystic echinococcosis of liver. Br J Radiol. 2017 Apr;90(1072). DOI:10.1259/bjr.20160640.
15. Stojkovic MJ, Rosenberger KD, Steudle F, et al. Watch and wait management of inactive cystic echinococcosis – Does the path to inactivity matter – Analysis of a prospective patient cohort. PLoS Neglected Tropical Diseases 2016 Dec;10(12). DOI:10.1371/journal.pntd.0005243.

Visceral leishmaniasis: towards control

Visceral leishmaniasis (VL or kala-azar) is a neglected tropical disease caused by *Leishmania spp.*, a protozoal parasite that is transmitted by the bite of a Phlebotomine sand fly (*Phlebotomus spp.* in the Old World, *Lutzomyia spp.* in the New World). It is estimated that 200,000 to 400,000 new cases of VL occur worldwide each year. The most endemic regions are the Indian subcontinent and East Africa. [1] Over 90% of new cases occur in six countries: Bangladesh, Brazil, Ethiopia, India, South Sudan and Sudan. The global data on incidence in all endemic countries are available. [2] VL runs a fatal course if untreated.

EPIDEMIOLOGY

In endemic areas VL is a disease of childhood, often occurring below the age of five. In outbreaks all ages may be affected. [3] In Asia, *Leishmania donovani* is the causative parasite; there is no known animal reservoir (anthroponotic transmission). India (Bihar), Bangladesh and Nepal are most endemic. In Africa, VL occurs in Sudan, South Sudan, Ethiopia, Kenya, Uganda and Somalia; here also *L. donovani* is the parasite involved, but it is genetically very different from that found in Asia. [4] The transmission is mixed anthroponotic and zoonotic, although the exact animal reservoir and its contribution has not been identified.

All countries in the Mediterranean basin are endemic. Here, and in South and Central America, VL is caused by *L. infantum*, and dogs are known reservoirs. In endemic and non-endemic countries, VL may occur among travellers, ecotourists, immigrants or military personnel. There is a risk that imported cases in endemic areas may introduce new strains. [5] This may be particularly relevant given

Figure 1: Typical VL patient presenting with weight loss, hepatomegaly and a huge spleen. Cautery marks are seen in the skin overlying the spleen as the result of traditional medicine.

the mass migration of people from VL-endemic countries in the Middle East, East Africa and Asia that started in 2015. Immunosuppression is a major risk factor for VL. This includes patients with HIV/AIDS, or those who have other conditions associated with immunosuppression such as haematological malignancies. [6] Not all infections lead to clinical disease; the number of asymptomatic or subclinical infections usually outnumber the clinical cases by a ratio of 1:5.

CLINICAL PRESENTATION

The incubation period is 2-6 months. The patient usually presents with fever >3 weeks; in endemic areas there is often a history of fever not responding to antimalarials. Weight loss and abdominal left quadrant upper pain caused by spleen enlargement are common symptoms; on physical examination fever, hepatosplenomegaly and malnutrition are commonly found (Figure 1). In HIV co-infected VL patients, the clinical presentation is similar but unusual presentations occur, such as dermal lesions.

POST-KALA-AZAR DERMAL LEISHMANIASIS (PKDL)

PKDL is characterized by a skin rash that may develop after treatment of VL (Figure 2). It is most common in areas where *L. donovani* is the causative agent of VL (Africa, Asia). Most patients are well except for the rash.

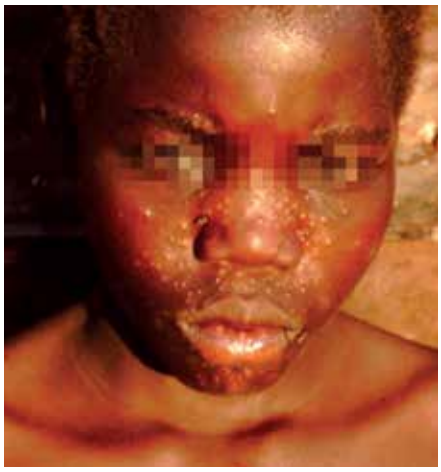

Figure 2: A patient with post-kala-azar dermal leishmaniasis (PKDL), with papules mainly in the face as the result of inflammation around leishmania parasites that persist after VL.

There are important regional differences. While in Africa a predominantly papular rash occurs in up to 50% of patients after VL treatment, in Asia the rash is often macular and occurs only after 1-3 years after VL, in up to 20% of patients. It is thought that PKDL patients may play an important role in outbreaks of VL because leishmania parasites may be found in the skin lesions and sand flies may become infected after feeding on PKDL patients.

Images of PKDL can be found in *The Post Kala-azar Dermal Leishmaniasis (PKDL) Atlas: A Manual for Health Workers*, published by the World Health Organization (WHO). [7]

LABORATORY AND RADIOLOGICAL DIAGNOSIS

Laboratory tests typically show pancytopenia. Other features include low albumin and high gamma globulin levels. Ultrasound examination may be useful for differential diagnosis and to confirm hepatosplenomegaly and lymphadenopathy.

PARASITOLOGICAL

Parasites may be demonstrated by classical microscopic examination of

aspirates of lymph node, bone marrow or spleen, with increasing sensitivity (approximately 55%, 70% and 95%, respectively). [8] Molecular diagnosis involves detection of leishmanial DNA by PCR that has the highest sensitivity and specificity. qPCR quantifies the parasite load and may be used as a biomarker to monitor treatment. Field adapted formats are being developed.

SEROLOGICAL

Serological tests including direct agglutination test (DAT), immunofluorescence tests or ELISA that take advantage of the high gamma globulin levels (anti-leishmania antibodies). The rK39 rapid diagnostic (RDT) test is easy to use in the field and widely accepted for first line diagnosis in the Indian subcontinent. Other tests detect leishmania antigens in the urine.

IMMUNOLOGICAL

The leishmanin skin test (LST) measures cell-mediated immunity; killed Leishmania promastigotes are injected intradermally and the skin induration is read after 48-72 hours. The LST is mainly used for screening purposes; a positive test indicates past exposure (clinical or asymptomatic infection).

TREATMENT

Guidelines for treatment have been published by the WHO according to the strength of available data. [9] Sodium stibogluconate (SSG) has long been the mainstay of treatment; it is given for 30 days by IM or IV injections that are painful. There is concern about side-effects, mainly cardiotoxicity.

In Asia, SSG is no longer effective because of resistance. Single dose AmBisome (liposomal amphotericin B) (SDA) in a dose of 10 mg/kg is the current standard treatment with cure rates of 96-98% in India and Bangladesh. [10]

Globally, miltefosine is the only oral drug available; currently it is given as treatment for PKDL patients for 90 days. [11]

In Africa, combination therapy with stibogluconate and paromomycin for seventeen days is currently the standard regimen, and this has replaced SSG monotherapy given for 30 days. [10]

In the Mediterranean countries and South America, AmBisome (multiple doses) is used as first-line treatment. HIV co-infected patients are treated with AmBisome combined with miltefosine. Because of the immunodeficiency, these patients often relapse, and maintenance treatment (secondary prophylaxis) is needed with injections of an anti-leishmanial drug (e.g. AmBisome) every 3-4 weeks, in addition to antiretroviral therapy. [10]

CURRENT NEEDS

There is a need for new, oral, short course regimens for both VL and PKDL. The Drugs for Neglected Diseases *initiative* (DND*i*), Geneva, (www.dndi.org) is a not-for-profit organisation committed to research and development of new drugs for neglected tropical diseases (NTDs) and has delivered new treatment options in Asia and Africa, including options for HIV-VL co-infected patients. [10]

In addition to new drugs, a better understanding of the pathophysiology of VL and PKDL is needed to identify biomarkers for diagnosis and disease progression and as entry points for immune manipulation.

CONTROL

Clearly, control strategies depend on regional characteristics of the disease.

The South-East Asia region kala-azar elimination program (KAEP) adopted a multi approach strategy aiming to reach the elimination target of less than one kala-azar case per 10,000 people per year by 2015. The program focuses on active case finding of kala-azar using rapid point-of-care diagnostic tests (rK39 strip test) and treatment with SDA with combination therapies as alternative treatments. Sand fly vector control completes the approach. [12] In India, good progress has been made. Increased awareness, less stigma, use of mosquito nets and SDA has resulted in a three-fold reduction of cases and mortality in Bihar alone. However, it is doubtful if the elimination target will reached in 2015. [13] Among threats to the program are the detection and management of PKDL patients, the role of asymptomatic patients, and concerns about quality assurance and resistance of sand flies to DDT. [14,15]

In Africa, there is currently no control strategy, mainly because of lack of political commitment and the unstable situation in South Sudan and Somalia. This is complicated by the lack of information on the sand fly vector regarding biting habits and habitat. [16] Long-lasting insecticidal bed nets were associated with reduced disease incidence in Eastern Sudan. [17] Several animals have been identified as potential reservoirs, but the contribution of each has not been established. Active and passive case finding of VL and PKDL cases may reduce the human reservoir. PKDL patients are a likely reservoir, but currently only chronic and severe cases are treated.

In the Mediterranean area, dogs may be protected by insecticide-containing collars; sick dogs are culled as they do not respond well to treatment. Currently there is no vaccine for human use; dogs can be vaccinated.

SUMMARY

Visceral leishmaniasis continues to be an important neglected tropical disease despite considerable progress in understanding the pathophysiology and improved management. In Asia, the control program seems successful so far, but the role of PKDL and asymptomatic infection needs to be clarified. VL control in Africa is problematic. Vigilance of health authorities in non-endemic areas for VL as an imported disease continues to be appropriate in view of increased migration and travel.

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REFERENCES

1. World Health Organization. Leishmaniasis. 2020 Mar 2. Available from: http://www.who.int/mediacentre/factsheets/fs375/en/.
2. Alvar J, Velez ID, Bern C, et al. Leishmaniasis worldwide and global estimates of its incidence. PLoS One. 2012 May;7(5) DOI:10.1371/journal.pone.0035671.
3. Seaman J, Mercer AJ, Sondorp E. The epidemic of visceral leishmaniasis in western Upper Nile, southern Sudan: course and impact from 1984 to 1994. Int J Epidemiol. 1996 Aug;25(4):862-71. Epub 1996 Aug 1.
4. Lukes J, Mauricio IL, Schonian G, et al. Evolutionary and geographical history of the Leishmania donovani complex with a revision of current taxonomy. Proc Natl Acad Sci U S A. 2007 May 29;104(22):9375-80. Epub 2007 May 21.
5. Di Muccio T, Scalone A, Bruno A, et al. Epidemiology of imported Leishmaniasis in Italy: implications for a European endemic country. PLoS One. 2015 Jul;10(6). DOI:10.1371/journal.pone.0134885.
6. Komitopoulou A, Tzenou T, Baltadakis J, et al. Is leishmaniasis an "unusual suspect" of infection in allogeneic transplantation? Transpl Infect Dis. 2014 Dec 16;16(6):1012-8. Epub 2014 Nov 21. DOI:10.1111/tid.12316.
7. WHO/Department of control of neglected tropical diseases. The post Kala-azar dermal leishmaniasis (PKDL) atlas: a manual for health workers. 2012. 214 p. Available from: http://apps.who.int/iris/bitstream/10665/101164/1/9789241504102_eng.pdf.
8. Zijlstra EE, el-Hassan AM. Leishmaniasis in Sudan. Visceral leishmaniasis. Trans R Soc Trop Med Hyg. 2001 Apr;95 Suppl 1:S27-58. Epub 2001 May 24.
9. World Health Organization. Control of the Leishmaniases: report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22-26 March 2010. Geneva. World Health Organization. 2010. 202 p. World Technical Report Series No. 949.
10. Alves F, Bilbe G, Blesson S, et al. Recent development of visceral leishmaniasis treatments: successes, pitfalls, and perspectives. Clin Microbiol Rev. 2018 Aug;31(4). DOI:10.1128/CMR.00048-18.
11. Sundar S, Sinha P, Jha TK, et al. Oral miltefosine for Indian post-kala-azar dermal leishmaniasis: a randomised trial. Trop Med Int Health. 2013 Jan;18(1):96-100. Epub 2012 Nov 8. DOI:10.1111/tmi.12015.
12. World Health Organization, Regional Office for South-East Asia. Regional strategic framework for elimination of kala azar from the South-East Asia Region (2005-2015). WHO Regional Office for South-East Asia. 2005. 22 p. Available from: https://apps.who.int/iris/handle/10665/205825.
13. Cousins S. India makes good progress in combating kala-azar. Lancet. 2015 May;385(9979):1716. DOI:10.1016/S0140-6736(15)60877-7.
14. Coleman M, Foster GM, Deb R, et al. DDT-based indoor residual spraying suboptimal for visceral leishmaniasis elimination in India. Proc Natl Acad Sci U S A. 2015 Jul;112(28):8573-8. DOI:10.1073/pnas.1507782112.
15. Le Rutte EA, Zijlstra EE, de Vlas SJ. Post-kala-azar dermal leishmaniasis as a reservoir for visceral leishmaniasis transmission. Trends Parasitol. 2019 Aug;35(8):590-2. Epub 2019 Jun 29 DOI:10.1016/j.pt.2019.06.007.
16. Elnaiem DE. Ecology and control of the sand fly vectors of Leishmania donovani in East Africa, with special emphasis on Phlebotomus orientalis. J Vector. 2011 Mar;36 Suppl 1:S23-31. DOI:10.1111/j.1948-7134.2011.00109.x.
17. Ritmeijer K, Davies C, van Zorge R, et al. Evaluation of a mass distribution programme for fine-mesh impregnated bednets against visceral leishmaniasis in eastern Sudan. Trop Med Int Health. 2007 Mar;12(3):404-14. Epub 2007 Feb 23.

Using mathematical modelling in the fight against human parasitic worm infections

BACKGROUND

Helminths, parasitic worms, are a common cause of disease in tropical and subtropical regions worldwide, disproportionately affecting people living under poor conditions (lack of safe water, poor sanitation, sub-standard housing). Major helminthic diseases in humans include soil-transmitted helminthiases (STH: ascariasis, trichuriasis, hookworm), schistosomiasis (or bilharzia), lymphatic filariasis (LF), and onchocerciasis (or river blindness). They are characterized by the chronic nature of infection and slow development of severe, debilitating consequences such as visual impairment, skin changes, limb and genital deformities, growth retardation, and limited cognitive functioning. The clinical manifestations are often associated with stigma, reduced ability to learn, or reduced worker productivity, ultimately causing impoverishment. [1] The huge health and socio-economic impact of helminthic infections had for long been underestimated, resulting in insufficient attention in public health policy, research, and drug development. These diseases are therefore commonly referred to as neglected tropical diseases (NTDs).

Fortunately, international commitment to fight helminthic diseases has increased markedly over the last decades. The first major public health initiative was the Onchocerciasis Control Programme (OCP) in West Africa, which was set up in 1974 to fight onchocerciasis in eleven countries through vector control. A decade later, mass drug administration (MDA) of the new drug ivermectin was introduced as a new complementary or stand-alone strategy, following the demonstration of its safety and effectiveness and Merck's pledge in 1987 to donate the drug "for as long as needed for the treatment and control of onchocerciasis".

New large-scale programmes were set up in the 1990s, expanding ivermectin MDA into other endemic regions (African Programme for Onchocerciasis Control; Onchocerciasis Control Programme for the Americas). MDA also became the mainstay of control for filariasis and – more recently – for schistosomiasis and STH. Indeed, MDA programmes have expanded at an unprecedented pace thanks to the enormous effort of affected countries [2] and spurred by the World Health Organization's (WHO) roadmap on NTDs 2012-2020 [3] as well as medicine donations by several pharmaceutical companies. [4] Much has been achieved. In 2018, over one billion people received preventive chemotherapy for at least one of the four main helminthic diseases: 552 million people were treated for LF, 149 million for onchocerciasis, 572 million school-aged children were treated for STH, and 94 million school-aged children were treated for schistosomiasis. [2] In some countries or subnational areas, MDA is no longer required as elimination targets have been met.

AMBITIOUS GOALS FOR 2030

There is great policy momentum to continue the fight against helminths as well as other NTDs, and global aspirations are high, as evidenced by Sustainable Development Goal (SDG) 3.3: to end the epidemic of neglected tropical diseases by 2030. Later this year, the WHO will present its new roadmap on NTDs for the period 2021-2030, with new disease-specific targets for 2030 aligned with SDG 3.3. Helminthic diseases are targeted

for elimination as a public health problem (LF, schistosomiasis, STH) or elimination of transmission (onchocerciasis), defined as follows: [5]

Elimination (interruption of transmission): Reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographical area, with minimal risk of reintroduction, as a result of deliberate efforts; continued action to prevent re-establishment of transmission may be required. Documentation of elimination of transmission is called verification.

Elimination as a public health problem: A term related to both infection and disease, defined by achievement of measurable targets set by WHO in relation to a specific disease. When reached, continued action is required to maintain the targets and/or to advance interruption of transmission. Documentation of elimination as a public health problem is called validation.

The question is to what extent the set targets can be achieved and which strategies are most effective to this end. Mathematical modelling is increasingly being accepted as an important source of evidence to answer this question.

MATHEMATICAL MODELLING OF HELMINTHIC DISEASES

Mathematical models for infectious diseases describe key processes involved in transmission, disease development, and control measures in mathematical terms. They can be used to elucidate mechanisms of transmission, predict future trends in infection, and assess the likely impact (and costs) of interventions. The application of mathematical models to policy question on helminths has slowly increased over the past decades. [6] It was further boosted in 2014 by the formation of the Bill & Melinda Gates Foundation funded NTD Modelling Consortium, which aims to support ongoing efforts to control and eliminate NTDs by modelling and improving model quality by stimulating collaboration between different modelling groups. [7] Erasmus MC is a pioneer in NTD modelling. It started modelling onchocerciasis control before 1990, expanded its activities since then to include five other NTDs, and is the largest partner in the NTD Modelling Consortium.

INSIGHTS FROM MODELLING ON REACHING THE 2030 TARGETS

Several modellers, clustered around the NTD Modelling Consortium, have recently published a collection of open research letters summarizing lessons learned from modelling regarding the impact of interventions, the feasibility of proposed WHO 2030 targets, and possible strategy adjustments that can help to maximize the gains in the coming years. [8] Below we briefly describe the main findings for the four helminthic infections.

LF is targeted for 'elimination as a public health problem', which is said to be achieved if 1) transmission assessment surveys show that infection is sustained below a predefined threshold for at least four years after stopping MDA, and 2) an essential package of care is available for all patients suffering from filarial hydrocele (enlarged scrotum) or lymphoedema (swollen limbs or external genitalia). Twenty-four countries have already stopped MDA and are now under post-MDA or even post-validation surveillance. [9]

Modelling suggests that achieving the epidemiological target is feasible with MDA, but the required MDA duration depends on baseline endemicity. [10] Also, poor coverage and systematic non-adherence can severely impede elimination programmes, and programmes need to ensure good coverage to be successful. [10] Late starting programmes and programmes in high-endemicity settings could consider increasing the frequency of MDA (e.g. from yearly to 6-monthly) or switching to more effective treatment regimens. Low-level transmission can continue after stopping MDA and even after validating elimination as a public health problem, which entails a risk of resurgence. Vector control could mitigate this risk but is sometimes very difficult to implement, depending on the vector species.

Onchocerciasis is targeted for elimination of transmission using MDA of ivermectin. The WHO has formulated guidelines for stopping MDA and verifying elimination. Four countries in the Americas have already achieved country-wide elimination of onchocerciasis transmission, and a few others have stopped MDA in certain areas. [9] Due to the biology of the parasite and the limited effect of ivermectin (it kills the microfilariae offspring, not the adult worms), the timeline to elimination is long, easily spanning 15-20 years, and model results are uncertain about the feasibility of elimination in high-endemic settings. [11] Most of the 34 endemic countries will likely not achieve country-wide elimination by 2030.

To maximize the success probability and reduce the timeline to elimination, countries should consider acceleration strategies, e.g. increasing the frequency of mass treatment from annual to biannual (i.e. 6-monthly, see Figure 1), or complementing MDA by vector control where most needed and feasible. [11] Using more efficacious drugs (e.g. moxidectin) could also be an option if donated or made available at low cost. Furthermore, alternative strategies are required in *Loa loa* co-endemic areas, where the use of ivermectin is not safe due to a risk of very serious (sometimes lethal) side effects in people with heavy *L. loa* infections. Further research is needed on the risk and dynamics of resurgence after verification of elimination.

STH is targeted for elimination as a public health problem by reducing the prevalence of medium-to-high intensity infections through chemotherapy targeted at high-risk groups (initially only school-aged children 5-12 year old, but in the latest WHO guidelines also preschool-age children and women of reproductive age) with treatment frequency dependent on the baseline endemicity. Models confirm that infection targets can be met if the latest guidelines are followed, and that the

inclusion of women of reproductive age (or even better, all adults) and biannual treatment of risk groups are needed in highly endemic areas. [12] Yet, how this translates to actual morbidity levels is not entirely certain. Models have clearly shown that resurgence will soon occur if treatment programs are stopped unless water, sanitation, and hygiene conditions are improved in compensation. Where hookworm is the dominant prevailing STH species, community-wide MDA may be recommended.

Schistosomiasis is targeted for elimination as a public health problem. Based on current WHO treatment guidelines, chemotherapy is targeted at school-aged children and given once every 1-3 years depending on baseline endemicity. Model analyses show that the current guidelines are sufficient for achieving the goal in areas with low and moderate intestinal schistosomiasis, but the impact on morbidity may very well be less than desired in settings with higher baseline endemicity levels (≥50% infection in school-age children). In such areas, treatment has to be expanded to adults. [13] Achieving elimination as a public health problem does not necessarily imply interruption of transmission, and chemotherapy will likely have to be continued to prevent resurgence and maintain the achievements.

IMPLICATIONS FOR THE COMING DECADE

The ambitious SDG goal 3.3 challenges the NTD community not only to maximize the health impact of NTD interventions in the next decade, but also to ensure sustainability of the achievements. Enhanced country ownership and integration of treatment and surveillance into the broader health systems are key to maintaining interventions and health gains. [14] Ultimately though, we need to target the underlying factors that drive helminth transmission, by implementing integrated vector management, improving access to safe water, sanitation and hygiene, and – above all – tackling poverty. [15]

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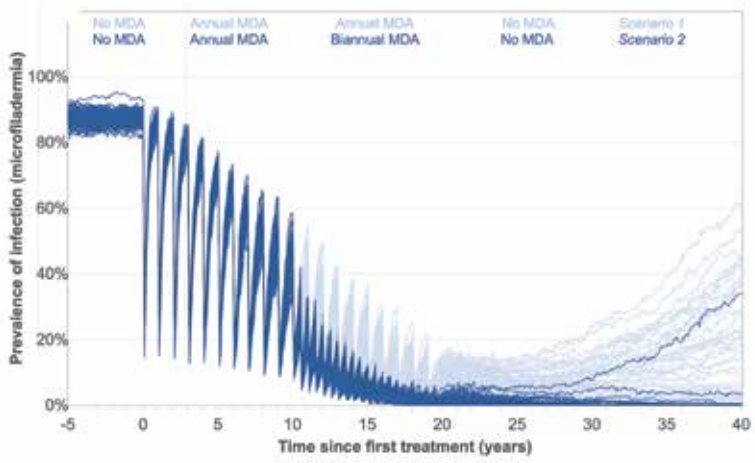

Figure 1. Model-predicted trend in the prevalence of onchocerciasis infection (microfiladermia) during and after 20 years of MDA for 100 high-endemic villages, assuming that 65% of the population is treated per round. In scenario 1 (light blue lines), MDA is provided annually for 20 years; in scenario 2 (dark blue lines), 10 years of annual MDA are followed by 10 years of biannual (6-monthly) MDA. Resurgence is predicted to occur in 30 of the 100 villages in scenario 1, and in only 1 village in scenario 2. Predictions were made with the ONCHOSIM simulation model. [11]

REFERENCES

1. Hotez, Fenwick A, Savioli L, et al. Rescuing the bottom billion through control of neglected tropical diseases. Lancet. 2009 May 2;373(9674):1570-5.
2. World Health Organization. Global update on implementation of preventive chemotherapy against neglected tropical diseases in 2018. Weekly Epidemiological Record. 2019;94(38):425-38.
3. World Health Organization. Accelerating work to overcome the global impact of neglected tropical diseases: a roadmap for implementation: executive summary. Geneva: World Health Organization; 2012. 22 p. Available from: https://apps.who.int/iris/handle/10665/70809.
4. World Health Organization. Essential medicines donated to control, eliminate and eradicate neglected tropical diseases. Geneva: World Health Organization; 2019 [cited 2020 February 7]. 3 p. Available from: https://www.who.int/neglected_diseases/Medicine-donation-04-march-2019.pdf.
5. World Health Organization. Generic framework for control, elimination and eradication of neglected tropical diseases. Geneva: World Health Organization; 2016 [cited 2020 Mar 13]. 6 p. Available from: https://apps.who.int/iris/handle/10665/205080.
6. Basáñez MG, McCarthy JS, et al. A research agenda for helminth diseases of humans: modelling for control and elimination. PLoS Negl Trop Dis. 2012 Apr;6(4). DOI:10.1371/journal.pntd.0001548.
7. Hollingsworth TD, Adams ER, Anderson RM, et al. Quantitative analyses and modelling to support achievement of the 2020 goals for nine neglected tropical diseases. Parasit Vectors. 2015 Dec;8:630. DOI:10.1186/s13071-015-1235-1.
8. Gates Open Research. 2030 goals for neglected tropical diseases. Open letters NTD Modelling Consortium. 2019 Sep 13-2020 Mar 4 [cited 2020 Feb 7]. Available from: https://gatesopenresearch.org/collections/ntd.
9. Uniting to Combat Neglected Tropical Diseases. Impact dashboard for preventive chemotherapy (PC) diseases. Cited 2020 Feb 7. Available from: https://unitingtocombatntds.org/impact-dashboards/pc-diseases-dashboard/.
10. Stolk WA, Prada JM, Smith ME, et al. Are alternative strategies required to accelerate the global elimination of lymphatic filariasis?: insights from mathematical models. Clin Infect Dis. 2018 Jun 1;66(suppl_4):S260-S266.
11. Verver S, Walker M, Kim YE, et al. How can onchocerciasis elimination in Africa be accelerated?: modeling the impact of Increased ivermectin treatment frequency and complementary vector control. Clin Infect Dis. 2018 Jun 1;66(suppl_4):S267-S274.
12. Farrell SH, Coffeng LE, Truscott JE, et al. Investigating the effectiveness of current and modified World Health Organization guidelines for the control of soil-transmitted helminth infections. Clin Infect Dis. 2018 Jun 1;66(suppl_4):S253-S259.
13. Toor J, Alsallaq R, Truscott JE, et al. Are we on our way to achieving the 2020 goals for schistosomiasis morbidity control using current World Health Organization guidelines? Clin Infect Dis. 2018 Jun 1;66(suppl_4):S245-S252.
14. Malecela MN. Reflections on the decade of the neglected tropical diseases. Int Health. 2019 Sep;11(5):338–40. DOI:10.1093/inthealth/ihz048.
15. Engels D, Zhou X. Neglected tropical diseases: an effective global response to local poverty-related disease priorities. Infect Dis Poverty. 2020 Jan;9(1):10. DOI:10.1186/s40249-020-0630-9.

Project reports from the Global Health Residency programme

The 27-month AIGT (medical doctor in global health and tropical medicine) training programme, offered by the OIGT training institute in the Netherlands with support from the **Netherlands Society for Tropical Medicine & International Health (NVTG)**, is concluded by a Global Health Residency of six months duration in a low-resource setting. Residents undertake two projects aimed at tackling locally relevant public health problems. Attaining knowledge of the social determinants of health as well as the epidemiology and burden of particular diseases and finding out how local health systems address these are some of the learning objectives. Since the introduction of the training programme in 2014, a large variety of public health research projects have been completed. In this new section, MT*b* offers a platform for AIGT trainees to present the findings of their projects.

ENDING PREVENTABLE NEONATAL DEATHS IN MALAWI: IMPLEMENTING NEONATAL DEATH AUDITS AT NKHOMA MISSION HOSPITAL

SETTING

Nkhoma Mission Hospital is a 104-year old district hospital in the southern region of Malawi, with 250 beds serving a catchment area of 460,000 people. Annually, an average number of 13,000 patients are admitted and approximately 46,000 outpatient cases seen. In 2016, Nkhoma Mission Hospital opened its own nursery, which received over 800 admissions in 2018. Primary reasons for admission were prematurity, low birth weight, birth asphyxia, neonatal sepsis and congenital abnormalities. [1]

BACKGROUND AND RATIONALE

It is estimated that annually a staggering 2.7 million neonatal deaths and 2.6 million stillbirths occur globally, of which the majority are preventable. To address this, the World Health Organization (WHO) launched the global Every Newborn Action Plan (ENAP) in 2014. [2]

Malawi successfully achieved millennium development goal 4, ahead of the 2015 deadline. However, as shown in Figure 1, most of the progress made has been due to a reduction in infant and under-5 mortality, as opposed to neonatal mortality. [3] Additionally, although the neonatal mortality rate (NMR) has indeed declined by about 2% per year since 2007, absolute numbers remain high, with a NMR of 23/1,000 live births in 2017. [4] In comparison, the global average NMR was 18/1,000 live births in 2017, and 2/1,000 in high-resource settings. [5,6]

The high NMR in Malawi persists despite an increase in the rate of deliveries in health institutions from 53% in 2000 to 90% in 2014, suggesting that neonatal mortality is not solely related to the location of delivery but — perhaps more importantly — to the quality of care provided in these facilities. [7]

In 2015, in response to the global ENAP, the government of Malawi developed its own Newborn Action Plan aimed at reducing the NMR to 15/1000 live births by 2035. [8] Crucial in this plan is the implementation of neonatal death and stillbirth audits in every health facility across the country. [8]

Although initial trainings had already been delivered and the necessary data management and surveillance systems implemented, neonatal death audits were not routinely conducted at Nkhoma Mission Hospital before September 2019. Therefore, at the request of, and in collaboration with, the hospital's management team, clinical officers and nursing staff, an initiative was undertaken to introduce these audits.

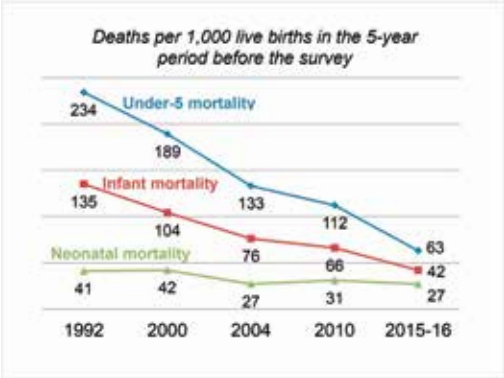

Figure 1: Under-5 infant and neonatal mortality between 1992 and 2016. Source: DHS 2015-2016. [3]

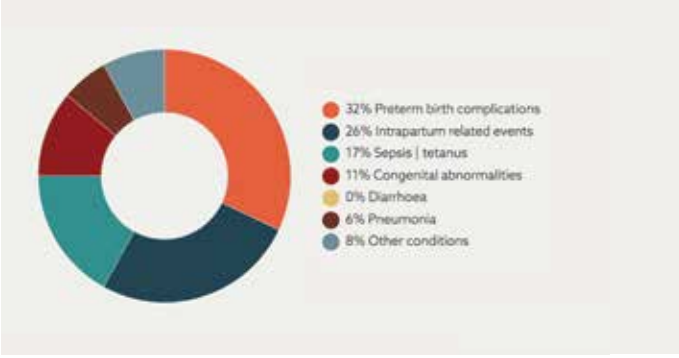

Figure 2: Causes of neonatal mortality in Malawi (2017). Source: Healthy Newborn Network. [9]

AIM

The aim of the Global Health Residency project was to reduce neonatal mortality in Nkhoma through the collection of neonatal death data and the introduction of a monthly audit.

METHODS

The neonatal death audit was organized on a monthly basis by the resident GHTM medical doctor, in collaboration with the responsible clinician of the nursery. Clinical staff from various departments also took part. During each meeting, an overview of the preceding months' mortality was presented and one case was audited using the national forms as a guideline. Modifiable factors were identified and possible solutions proposed with actionable tasks being delegated to team members.

RESULTS

Monthly neonatal death audits have been conducted in Nkhoma Mission Hospital since they were introduced in October 2019. The audit meetings led to the identification of various modifiable factors, of which the most important ones are described in Table 1. Solutions that were proposed and implemented included:

- introduction of an agreement on 4-hourly vital signs monitoring in all neonates in the nursery with documentation in specific charts
- guarantee of continuity of care during weekends and public holidays through daily ward rounds by the paediatric clinician on duty
- appointment of one nurse as team leader of the maternity ward during night shifts, who is responsible for critically-ill pregnant women and timely administration of prescribed drugs (for example nifedipine and dexamethasone)
- monitoring of feeding of premature babies through the use of feeding charts for every baby born with a birth weight of 1,500 grams or less
- optimal handover of neonates from the labour ward through optimizing completion of admission sheets with clinical details around delivery.

MODIFIABLE FACTOR
Poor monitoring of vital signs
Absence of ward rounds during weekend
Inadequate record-keeping in the ward
Essential medication not administered
Insufficient monitoring of feeds in critically ill neonates (e.g. very low birth weight babies, babies on ventilation support)
Insufficient (written) handover of babies admitted and transferred from labour ward to nursery ward

Table 1: Most important modifiable factors identified during neonatal death audit meetings.

	TOTAL LIVE BIRTHS	TOTAL NND	NMR PER 1000 LIVE BIRTHS
JANUARY	270	9	33
FEBRUARY	276	16	58
MARCH	212	6	28
APRIL	278	2	7
MAY	310	11	35
JUNE	264	6	23
JULY	316	13	41
AUGUST	310	8	26
SEPTEMBER	271	8	30
OCTOBER	315	5	16

Table 2: Neonatal mortality rate per month in 2019 at Nkhoma Mission Hospital. [1]

The impact of the audits and subsequent interventions can be evaluated via the NMR. In September 2019, the NMR in Nkhoma was 30/1,000 live births (271 babies born alive, 8 neonatal deaths). Of the eight neonatal deaths, four were due to birth asphyxia, three due to prematurity/low birth weight, and one due to neonatal sepsis. In October 2019, the NMR had shown an encouraging drop to 16/1,000 live births (315 babies born alive, 5 neonatal deaths). Of the five neonatal deaths, one was due to birth asphyxia and four due to prematurity/low birth weight. For comparison of NMRs before and after audits, see Table 2.

DISCUSSION

Neonatal death audits were successfully introduced at Nkhoma Mission Hospital in October 2019, with staff routinely filling in death audit forms and action plans being formulated and implemented. An encouraging drop in NMR has been observed since, but future data need to confirm this trend. A clear pattern in the most important causes of death and related modifiable factors has been identified. Insufficient monitoring of neonates by nursing staff and clinicians, inadequate response to emergency signs, and suboptimal record keeping were identified as areas of concern.

Based on the above, multiple interventions were initiated, of which several have been successfully implemented. In order for the audits to remain effective and prove sustainable, the following challenges need to be overcome:

- enhancing ownership of the audits by local staff
- motivating the staff of the wards outside of the nursery to attend the audits in order to achieve multi-disciplinary and widely supported solutions
- creating an open and respectful audit culture which prevents naming and shaming and invites participants to speak and contribute
- ensuring adequate follow-up of implementation and continuation of proposed solutions

CONCLUSION

The smooth and well-accepted introduction of neonatal death audits, the enthusiasm and involvement of local staff, and the initial reduction observed in neonatal deaths are promising signs for audit continuation and improved management of neonates at Nkhoma Mission Hospital.

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REFERENCES

1. Nkhoma Mission Hospital. Nkhoma Mission Hospital annual report 2018. Nkhoma: Nkhoma Mission Hospital; 2019.
2. World Health Organization. Making very Baby Count: Audit and review of stillbirths and neonatal deaths. Geneva: World Health Organization; 2016. p.136 Available from: https://www.who.int/maternal_child_adolescent/documents/stillbirth-neonatal-death-review/en/.
3. National Statistical Office. Malawi demographic and health survey 2015-16. Zomba and Rockville: National Statistical Office and ICF; 2017 February. p.658. Final report. Available from: https://dhsprogram.com/pubs/pdf/FR319/FR319.pdf.
4. UNICEF. Maternal and newborn health disparities: Malawi country profile report. UNICEF Data; 2016 November. p.108. Available from: https://data.unicef.org/wp- content/uploads/country_profiles/Malawi/country%20profile_MWI.pdf.
5. UNICEF. Neonatal mortality. UNICEF Data; 2019 September. Available from: https://data.unicef.org/topic/child-survival/neonatal- mortality/.
6. UNICEF, World Health Organization, World Bank Group, United Nations. Child mortality report: levels and trends in child mortality. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME) 2018; 2019 September. 48 p. Available from: https://www.unicef.org/media/47626/file/UN-IGME-Child-Mortality-Report-2018.pdf.
7. Leslie HH, Fink G, Nsona H, et al. Obstetric facility quality and newborn mortality in Malawi: a cross-sectional study. PLoS Med. 2016 Oct;13(10). DOI:10.1371/journal.pmed.1002151.
8. Government of Malawi. Every Newborn Action Plan: an action plan to end preventable neonatal deaths in Malawi. Malawi: World Health Organization; 2015. 38 p. Available from: https://www.who.int/pmnch/media/events/2015/malawi_enap.pdf.
9. Healthy Newborn Network. Leading causes on neonatal deaths in Malawi (2017). Malawi: Safe the Children Federation; 2017. Available from: https://www.healthynewbornnetwork.org/country/malawi/.

A neonate with an inside-out bladder

Case

An apparent birth defect caused a South Sudanese mother to seek help for her, otherwise healthy, 2-day-old son. An abdominal wall defect was seen just below the umbilical cord (Figure 1). The boy was breastfeeding well, and he passed urine and stool normally. No other signs of congenital abnormalities were found. The treating global health doctor in training asked Consult Online specialists for advice on diagnosis and surgical treatment options.

SETTING

This case was seen in an emergency setting hospital in South Sudan with 150 beds and basic surgical services.

SPECIALIST ADVICE

Within a day, the surgeons of Consult Online responded to the question, saying that a bladder exstrophy was the most likely diagnosis. They stated that unskilled treatment of this condition, which is not immediately life-threatening, might lead to complications, but the upper urinal tract (kidneys and ureters) will not be affected as long as there is a free flow of urine. Attempts to close the bladder can possibly lead to obstruction, which is difficult to handle in this particular hospital. The advice was to transpose the ureters into the sigmoid, with or without a pouch. Since this was not an emergency, it was advised not to intervene until a skilled surgeon would be available. In the meantime, the kidneys needed to be monitored by ultrasound imaging, since dilatation of the ureters or renal pelvis would indicate the need for an intervention. Furthermore, it was considered important to avoid or minimise trauma to the exposed inner surface of the bladder. In the absence of transparent adhesive dressings, clean cotton cloths would be a good alternative to protect against... Antibiotic prophylaxis was considered not necessary.

FOLLOW-UP

After two weeks, the mother reported for a follow-up consultation: her son was doing well and there was no hydronephrosis seen on ultrasound examination.

However, some granulation tissue had begun to appear (Figure 2). Surgery had not been scheduled yet, since a skilled surgeon was still not available.

Figure 1. Two days after birth, an abdominal wall defect and clear genital abnormalities were seen.

Figure 2: Two weeks after birth, some granulation tissue had formed.

BACKGROUND

Bladder exstrophy (exstrophy meaning 'inversion of a hollow organ') is a complex congenital disorder within the exstrophy-epispadias complex, which also covers epispadias and cloacal exstrophy. An overdeveloped cloacal membrane, preventing medial migration of mesenchymal tissue, appears to be the cause of the disorder. The incidence is 3-5 cases per 100,000 live births, with boys more likely to be affected than girls. [1]

CLINICAL FEATURES

The main characteristics of bladder exstrophy are protrusion and inversion of the urinary bladder through a defect in the lower abdominal wall, with an open exposed dorsal urethra (Figure 3). However, several other organ systems can also be affected. [2] In males, epispadias are seen, and additionally the penis is shortened and the dorsal foreskin is absent. In females, significant genital abnormalities are seen as well.

Furthermore, the umbilicus is situated in a more caudal position than normal, lying just above the abdominal wall defect. Outward malrotation of the pelvic bones may lead to diastasis symphysis pubis and consequently separation of the pubic bones, possibly causing an abnormal gait later in life. Another possible complication is faecal incontinence, due to an anteriorly displaced anus, in combination with associated abnormalities of pelvic floor muscles. [2]

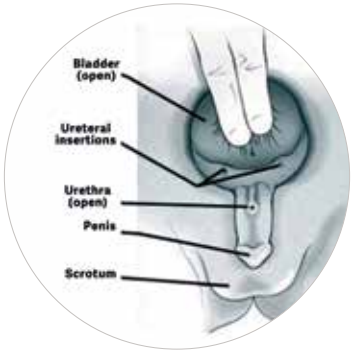

Figure 3. Schematic anatomy of bladder exstrophy in a male. Source: J.G. Borer,Clinical manifestations and initial management of infants with bladder exstrophy. [2]

TREATMENT AND PROGNOSIS

In high-income countries, affected infants undergo repair surgery early in life. [2] Little research has been done concerning management and prognosis of bladder exstrophy in low-resource settings. However, in settings marked by poverty, parental illiteracy, and limited access to health care facilities, first presentations in adulthood do occur. All documented adult cases presented with urine incontinence and had a normal renal function. [3] As can be expected, the risk of urinary tract infections is higher in people with bladder exstrophy.

Urinary diversion (creating a functional connection between the urinary and intestinal tracts) is not being done in high-resource settings anymore. However, if a skilled surgeon is not available or regular follow-up is not possible, it is the treatment of choice. The urine will enter the colon and leave the body via the stool. Even in adults, successful rehabilitation and improved quality of life have been shown to be possible. [3]

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REFERENCES

1. Jayachandran D, Bythell M, Platt MW, et al. Register based study of bladder exstrophy-epispadias complex: prevalence, associated anomalies, prenatal diagnosis and survival. J Urol. 2011 Nov;186(5):2056-2061. DOI:10.1016/j.juro.2011.07.022.
2. Borer JG. Clinical manifestations and initial management of infants with bladder exstrophy. UpToDate. Updated 2019 Dec 2. Available from: https://amc-literatuur.amc.nl/f5-w-687474707733a2f2f7777772e7570746f6461746652e636f6d$$/contents/clinical-manifestations-and-initial-management-of-infants-with-bladder-exstrophy?search=bladder.
3. Venkatramani V, Chandrasingh J, Devasia A, et al. Exstrophy-epispadias complex presenting in adulthood: a single-center review of presentation, management, and outcomes. Urology. 2014 Nov;84(5):1243-1247. DOI:10.1016/j.urology.2014.06.063.

EVEN IN ADULTS, SUCCESSFUL REHABILITATION AND IMPROVED QUALITY OF LIFE HAVE BEEN SHOWN TO BE POSSIBLE

Tropical medicine point-of-care testing: supporting the UN 2030 agenda

By Monica Cheesbrough
Published by Tropical Health Technology, first published 2020
Priced £15.00

This is another welcome contribution to the field of tropical medicine by Monica Cheesbrough, who is author of various other texts and books on laboratory medicine in the tropics. The title of this new book appropriately mentions point-of-care testing in the context of supporting the UN 2030 agenda with reference to the sustainable development goals (SDGs) 3 (health and well-being) and 6 (clean water and sanitation).

It has three sections. In the first section, strengthening the quality of district laboratory services is explained, with all the pitfalls of running and maintaining a laboratory in a tropical setting.

Section 2 contains 'Laboratory investigations of communicable diseases'. In each paragraph, a short summary of the condition is given, followed by a detailed description of the appropriate laboratory tests. Boxes highlight the main issues and there are multiple figures and drawings as well as plates in black-and-white or colour showing how to use test devices and how to read the result, as well as microscopy slides and other test results.

Section 3 has 'Laboratory investigation of non-communicable diseases', a most welcome addition to the classical laboratory that often focuses on infectious diseases. This section includes investigation of anaemia, diabetes mellitus, lipid abnormalities and liver and renal disease.

This book is an excellent contribution to the practice of tropical medicine. The author is to be congratulated with this achievement. The book is not only useful for laboratory workers but also for doctors and students from tropical countries as well as those who want to work in the tropics for some time. The price is quite reasonable and should be no restriction for wide use. It is not clear if an electronic copy will become available or an app that would allow quick reference in the lab, at the bedside, or in the classroom.

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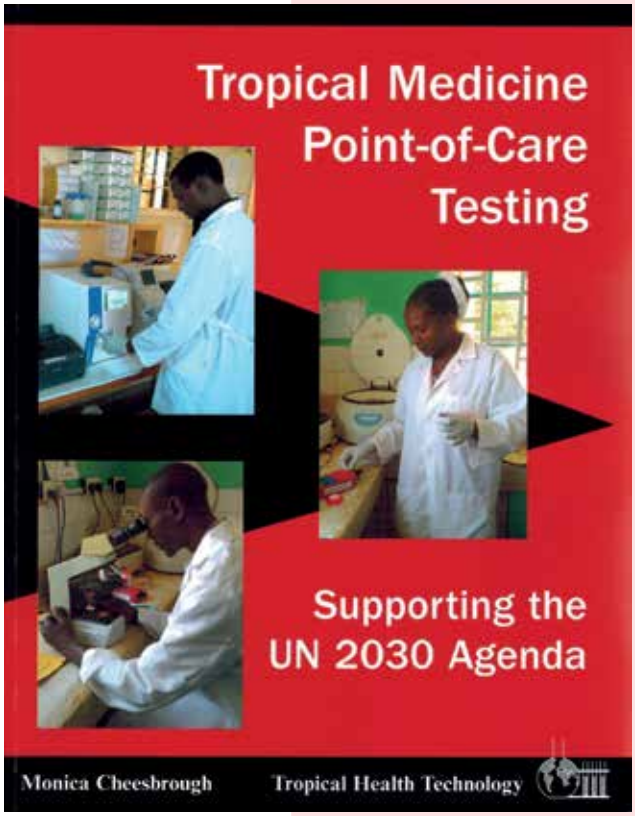
THE BOOK IS NOT ONLY USEFUL FOR LABORATORY WORKERS BUT ALSO FOR DOCTORS AND STUDENTS FROM TROPICAL COUNTRIES AS WELL AS THOSE WHO WANT TO WORK IN THE TROPICS FOR SOME TIME



Robert Sauerwein medal for junior researchers in tropical infectious diseases

Robert Sauerwein's retirement in 2020 marks the end of an important era in malaria research in the Netherlands. Robert Sauerwein pioneered the use of controlled human infections for malaria and led a productive research group that profoundly improved our understanding of the biology of malaria parasites as well as the clinical, immunological and epidemiological consequences of infection. Under his guidance, the malaria research group of the Radboud university medical center became one of the world-leading hubs for research into *Plasmodium falciparum* with strong collaborations in the Netherlands and worldwide.

To honour his legacy, the Robert Sauerwein medal will be awarded every two years to junior researchers in the field of tropical infectious diseases. The prize consists of a medal and €500 and is jointly awarded by Radboudumc and Uniting Streams. For the 2020 award, candidates can be nominated until the 1st of September 2020. Nominees should be junior researchers (PhD students or within three years after PhD graduation) who have made major contributions to our understanding of tropical infectious diseases and are affiliated to a university or research institute in the Netherlands. Information on the nomination process and eligibility criteria can be found on the websites of NVTG and Uniting Streams.

Robert Sauerwein and Teun Bousema admiring the first medal

nvtg verenigt global health professionals

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COLOPHON
MT Bulletin of the Netherlands Society for Tropical Medicine and International Health
ISSN 0166-9303

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