Neglected tropical diseases: elimination and eradication

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ABSTRACT

The term neglected tropical diseases (NTDs) describes a disparate group of diseases which affect populations living in poverty and are important causes of morbidity and mortality worldwide. Global programmes for the control of NTDs benefit large-scale donations made by pharmaceutical companies. A number of NTDs have internationally agreed targets for their control, elimination and eradication. Eradication is defined as the permanent reduction to zero of the worldwide incidence of infection. Elimination is defined as the reduction to zero of the incidence of infection in a specified geographic area. Considerable progress has been made towards elimination and eradication of some NTDs but unexpected new challenges have emerged which threaten the eventual achievement of these goals.

Neglected tropical diseases

In the early 2000s the term neglected tropical diseases (NTDs) emerged to describe a disparate group of diseases which disproportionately affect populations living in poverty; cause important morbidity and mortality – including stigma and discrimination – in such populations, justifying a global response; are amenable to broad control, elimination or eradication through mass treatment, intensified or innovative case management, vector control or veterinary public health; and are relatively neglected by research.[1,2] The World Health Organization (WHO) currently recognises 20 diseases which meet these criteria (Table 1).

NTD programmes benefit from some of the largest pharmaceutical donation programmes ever made. Several pharmaceutical companies agreed to donate unlimited supplies of medication for as long as it was needed to support global programmes. These donations, supported by substantial funds for implementation from partners, including the UK Department for International Development, have allowed substantial progress to be made in reducing morbidity from these conditions.[3] Despite this progress, considerable challenges remain in the control, elimination and eradication of NTDs. In this article we outline the principles of disease elimination and eradication as they apply to NTD programmes and illustrate some of the challenges in achieving the aim of disease eradication.

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Principles of elimination and eradication

A common feature of many of the NTDs is the existence of international targets for their control, elimination and eradication (see Table 1). These terms are often used interchangeably and sound similar but in fact have specific definitions. The terms were first well defined at the Dahlem Workshop in 1997.[4]

Eradication is defined as the permanent reduction to zero of the worldwide incidence of infection. Elimination is defined as the reduction to zero of the incidence of infection in a specified geographic area. These definitions also highlight other important points. Firstly, eradication is by definition a global term – a disease cannot be eradicated at the national level. Secondly, even following elimination of a disease, ongoing control efforts are required to avoid re-introduction. For example, polio has been eliminated in the Americas but vaccination is still required until the goal of global eradication is achieved.

The Dahlem Workshop also highlighted criteria to be considered when assessing the feasibility of disease eradication. These criteria consist of both biological and political factors and are outlined in Table 2.

Key points

There are 20 conditions currently recognised by the World Health Organization as neglected tropical diseases

Ten of these diseases are targeted for either elimination or eradication

Considerable progress has been made towards guinea worm eradication but the occurrence of disease in dogs is a major challenge to its eventual eradication

Mass treatment with azithromycin is a promising strategy for the eradication of yaws but drug resistance is a significant concern

Progress has been made towards the control, elimination and eradication of many neglected tropical diseases supported by large scale drug donations

KEYWORDS: Neglected tropical diseases, guinea worm, yaws, trachoma, lymphatic filariasis ■

Table 1. The World Health Organization neglected tropical diseases

Neglected tropical diseases	Control strategy	Elimination target
Schistosomiasis	MDA (praziquantel), sanitation, snail control	Yes (in China)
Onchocerciasis	MDA (ivermectin), vector control	Yes (in Americas)
Lymphatic filariasis	MDA (ivermectin, albendazole), vector control	Yes
Trachoma	MDA (azithromycin), water, sanitation, education	Yes
Yaws	MDA (azithromycin)	Yes – eradication
Soil transmitted helminths	MDA (albendazole)	No
Guinea worm	Safe water, health education	Yes – eradication
African trypanosomiasis	Case finding and treatment, vector control	Yes (for *Trypanosoma brucei gambiense*)
Visceral leishmaniasis	Case finding and treatment	Yes (subcontinent)
Leprosy	Case finding and treatment	Yes
Taeniasis/cysticercosis	Sanitation, meat inspection, vaccination of pigs	No
Echinococcosis	Abbattoir control, treatment of dogs, education	No
Foodborne trematodes	Treatment of sheep, health education	No
Chagas disease	Vector control, blood screening	Yes (some countries)
Buruli ulcer	Case finding and treatment	No
Rabies	Vaccination of dogs, health education	No
Dengue and chikungunya	Vector control	No
Mycetoma	Case finding and treatment	No
Scabies	Not yet defined. Possibly MDA (ivermectin)	No
Snakebite	Not yet defined	No

MDA = mass drug administration.

Table 2: Criteria and requirements for disease elimination and eradication

Biological criteria	Social and political criteria
Availability of an effective intervention ie a drug or vaccine.	Disease must be recognised to be of public health importance.
Diagnostic test with adequate sensitivity and specificity.	Eradication must be widely perceived to be a worthy goal.
Absence of an environmental or animal reservoir.	Technically feasible intervention must be found to be effective in a geographical region.
	Political commitment must be gained at the highest level including potentially a World Health Assembly resolution.
	There must be an advocacy plan for the global, regional and national level.

A number of NTDs have neither an 'eradication' nor an 'elimination' target. Instead they have a target of 'elimination as a public health problem'. This term is not well defined but broadly can be considered to mean reduction in the prevalence and/or incidence of a disease to such a level that it no longer contributes significantly to morbidity (or mortality) at the population level. The closeness of the terms 'elimination as a public health problem' and 'elimination' risks creating confusion in the minds of policymakers for whom the terms may appear to be analogous. This risk is compounded by the absence of a standard definition for 'elimination as a public health problem' – instead the definitions used vary between disease programmes. The targets for each disease have also tended to shift over time most commonly from less challenging (elimination) to more challenging (eradication) targets.

The London Declaration

Individual targets for neglected tropical disease eradication and elimination have emerged over a period of years. In 2012, WHO published a roadmap for neglected tropical diseases[5] and this was followed by a landmark meeting in London which culminated in the 'London Declaration' for neglected tropical diseases. This meeting bought together policymakers, pharmaceutical companies, non-governmental organisations and academics to agree a common set of disease targets and priorities.

Progress and challenges – case studies in NTD eradication

Guinea worm

Guinea worm disease is caused by infection with *Dracunculus medinensis*. Infection occurs when humans ingest contaminated water containing cyclops (microscopic crustaceans) which act as vectors for the Guinea worm larvae. Once in the digestive tract, larvae escape from the cyclops and penetrate the subcutaneous soft tissues where they mate. Over the following year, the female

worms migrate to the legs and feet where a small painful blister forms and the worm emerges. It then releases its larvae into water sources allowing the cycle of infection to repeat.

In the 1980s, the control and eventual elimination of Guinea worm were adopted as targets by the World Health Assembly (WHA) as part of the United Nation's International Drinking Water Supply and Sanitation decade.[6] In 1991, the WHA formally committed to global eradication of Guinea worm.[7]

The strategy for eradication is based primarily on behaviour change. Health education, combined with filter distribution, vector control, safe water provision and case containment, enables affected communities to break the cycle of transmission.[8] These methods, spearheaded by the Carter Center, have had considerable success. In 1986, there were an estimated 3.5 million cases in 20 countries;[9] in 2017 only 30 cases of Guinea worm were reported in two countries, Ethiopia and Chad.[10]

Despite the progress, significant challenges remain. Continuing civil war in South Sudan has disrupted surveillance activities. Following 19 consecutive months without a case being reported, three have been detected there since May 2018.[11] Chad remains a reservoir of the disease largely due to the significant number of cases in dogs, 830 of which were detected in 2017.[10] The hypothesised model of transmission in dogs involves consumption of Guinea worm larvae contained in the fresh entrails of fish.[12] Finally, the recent discovery of a human case of Guinea worm in Angola, a country that has never previously documented a case of the disease, serves as a reminder of the surprises that eradication programmes can produce.[11] The source of the worm, identified in April 2018, remains a mystery and extensive investigations are ongoing. These developments call the imminent success of the eradication programme into question.

Yaws

Yaws, caused by *Treponema pallidum* subsp *pertenue*, is one of two NTDs currently targeted for global eradication. Yaws is closely related to syphilis but predominantly affects children living in remote tropical communities. If untreated the disease may cause destructive and disfiguring lesions of the skin, bones and soft tissues. During the mid-twentieth century the disease was widespread throughout the tropics and was considered a major public health problem.[13,14]

In 1949, the WHA passed a resolution supporting efforts for the control and elimination of yaws. Between 1952 and 1962, WHO and the United Nations International Children's Emergency Fund led a joint global campaign to eradicate yaws.[14] More than 300 million individuals were assessed as part of the campaign and more than 50 million treated, a monumental effort at the time. However, these efforts were ultimately not successful. Whilst the programme did significantly reduce the global prevalence of yaws, by as much as 98%, the incidence of the disease rebounded in a number of countries in the 1970s. Interest in yaws eradication then waned and the disease fell off the global health agenda. Interest in yaws eradication was restarted by a landmark study conducted in Papua New Guinea which demonstrated that a single oral dose of azithromycin was non-inferior to intramuscular benzathine benzylpenicillin.[15]

Mass drug administration (MDA) with azithromycin has been widely used as part of the WHO strategy for the elimination of trachoma as a public health problem.[16] Given the evidence of the safety of MDA with azithromycin and the efficacy of azithromycin for the treatment of yaws, WHO developed a revised strategy for the eradication of yaws (the Morges strategy). This strategy emphasises an initial round of MDA using azithromycin in endemic communities. Following this it may be appropriate to conduct further MDA or to switch to a strategy of treating active cases and their contacts (total targeted treatment).[17] Initial assessments of the efficacy of azithromycin MDA were conducted in both the Pacific and west Africa and demonstrated considerable impact of MDA on the prevalence of yaws. However, despite these initial successes, interruption of transmission was not achieved.[18–20] Furthermore resistance to azithromycin emerged in the pilot study in Papua New Guinea. Although subsequent treatment with benzathine benzylpenicillin was used to successfully ring-fence this outbreak, these data highlight the risk of emerging azithromycin resistance threatening yaws eradication efforts.[21]

Finally, there is also evidence that non-human primates are also infected with *Treponema pallidum* subsp *pertenue*.[22,23] While no evidence currently exists for zoonotic transmission, the existence of a possible animal reservoir highlights the challenges that may emerge during an eradication campaign.

Conclusions

Enormous progress has been made towards the control, elimination and eradication of neglected tropical diseases. These achievements have been based on unprecedented levels of support from pharmaceutical companies, governments and private donors. Despite this, challenges remain towards the eventual attainment of the London Declaration 2020 targets and the eventual elimination and eradication of these diseases remains uncertain. ■

References:

1 Hotez PJ, Fenwick A, Savioli L, Molyneux DH. Rescuing the bottom billion through control of neglected tropical diseases. *Lancet* 2009;373:1570–5.
2 Hotez PJ, Alvarado M, Basáñez M-G *et al*. The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. *PLoS Negl Trop Dis* 2014;8:e2865.
3 Hotez PJ, Fenwick A, Ray SE, Hay SI, Molyneux DH. 'Rapid impact' 10 years after: The first 'decade' (2006–2016) of integrated neglected tropical disease control. *PLoS Negl Trop Dis* 2018;12:e0006137.
4 Dowdle WR. The principles of disease elimination and eradication. *Bull World Health Organ* 1998;76:22–5.
5 World Health Organization. *Accelerating work to overcome the global impact of neglected tropical dieases – a roadmap for implementation*. Geneva: WHO, 2012. www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf.
6 World Health Organization. *World Health Assembly Resolution 34.25: International drinking water supply and sanitation decade*. WHO, 1981. www.who.int/neglected_diseases/mediacentre/WHA_34.25_Eng.pdf?ua=1.
7 World Health Organization. *World Health Assembly Resolution 42.29: Eradication of dracunculiasis*. WHO, 1989. www.who.int/neglected_diseases/mediacentre/WHA_42.29_Eng.pdf?ua=1.
8 Biswas G, Sankara DP, Agua-Agum J, Maiga A. Dracunculiasis (Guinea worm disease): eradication without a drug or a vaccine. *Philos Trans R Soc B Biol Sci* 2013;368:20120146.
9 Watts SJ. Dracunculiasis in Africa in 1986: Its geographic extent, incidence, and at-risk population. *Am J Trop Med Hyg* 1987;37:119–25.

10 World Health Organization Collaborating Center for Dracunculiasis Eradication. *Guinea worm wrap-up #253*. Atlanta: The Carter Center, 2018. www.cartercenter.org/resources/pdfs/news/health_publications/guinea_worm/wrap-up/253.pdf
11 World Health Organization Collaborating Center for Dracunculiasis Eradication. *Guinea worm wrap-up #256*. Atlanta: The Carter Center, 2018. www.cartercenter.org/resources/pdfs/news/health_publications/guinea_worm/wrap-up/256.pdf
12 Sreenivasan N, Weiss A, Djiatsa J-P *et al*. Recurrence of Guinea worm disease in Chad after a 10-year absence: risk factors for human cases identified in 2010–2011. *Am J Trop Med Hyg* 2017;97:575–82.
13 Urrutia RP, Merisier D, Small M *et al*. Unmet health needs identified by Haitian women as priorities for attention: a qualitative study. *Reprod Health Matters* 2012;20:93–103.
14 Asiedu K, Amouzou B, Dhariwal A *et al*. Yaws eradication: past efforts and future perspectives. *Bull World Health Organ* 2008;86:499-499A.
15 Mitjà O, Hays R, Ipai A *et al*. Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial. *Lancet* 2012;379:342–7.
16 Emerson PM, Burton MJ, Solomon AW, Bailey R, Mabey DC. The SAFE strategy for trachoma control: using operational research for policy, and implementation. *Bull World Health Organ* 2006;84:613–9.
17 The World Health Organization. Eradication of yaws - the Morges Strategy. *Wkly Epidemiol Rec* 2012;87:189–194.
18 Abdulai AA, Agana-Nsiire P, Biney F *et al*. Community-based mass treatment with azithromycin for the elimination of yaws in Ghana – Results of a pilot study. *PLoS Negl Trop Dis* 2018;12:e0006303.
19 Marks M, Vahi V, Sokana O *et al*. Impact of community mass treatment with azithromycin for trachoma elimination on the prevalence of yaws. *PLoS Negl Trop Dis* 2015;9:e0003988.
20 Mitjà O, Houinei W, Moses P *et al*. Mass treatment with single-dose azithromycin for yaws. *N Engl J Med* 2015;372:703–10.
21 Mitjà O, Godornes C, Houinei W *et al*. Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study. *Lancet* 2018;391:1599–1607.
22 Knauf S, Gogarten JF, Schuenemann VJ *et al*. Nonhuman primates across sub-Saharan Africa are infected with the yaws bacterium *Treponema pallidum* subsp *pertenue*. *Emerg Microbes Infect* 2018;7:157.
23 Chuma IS, Batamuzi EK, Collins DA *et al*. Widespread *Treponema pallidum* infection in nonhuman primates, Tanzania. *Emerg Infect Dis* 2018;24:1002–9.

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