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EDITORIAL

How many neglected tropical diseases can we eliminate by 2030?

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In 2012, the year of the London Declaration, the World Health Organization (WHO) published a roadmap for the elimination of neglected tropical diseases (NTDs). Guinea worm and yaws were targeted for global eradication and trachoma and lymphatic filariasis for global elimination as public health problems by 2020. Regional elimination targets were set for onchocerciasis, Chagas disease, rabies and visceral leishmaniasis. Impressive progress has been made in the control of NTDs since 2012. At least one NTD has been eliminated from 40 countries, territories or areas and 500 million fewer people require interventions against NTDs,[1] but unfortunately none of the targets will be met by 2020.

Since 2018 the WHO NTD Department, in consultation with the wider NTD community, has been developing a roadmap for 2030. The 2030 roadmap, which is awaiting endorsement by the World Health Assembly, sets the following overall targets:

- A 90% reduction in the number of people requiring interventions against NTDs
- 100% of the population at risk will be protected from out-of-pocket payments for NTDs
- At least one NTD will have been eliminated from 100 countries
- Disability-adjusted life years lost to NTDs will have been reduced by 75%.

Integrated approaches and multisectoral collaboration are recommended to achieve these targets, with increased emphasis on country ownership of NTD programmes, which can play an important role in achieving the Sustainable Development Goal of universal health coverage by 2030. Increased emphasis should be placed on measuring the impact of interventions against NTDs rather than simply reporting the number of treatments given. Guinea worm and yaws are targeted for global eradication by 2030 and trachoma is targeted for global elimination as a public health problem. How likely is it that these targets will be met?

The Guinea worm eradication programme was initiated in 1984 by the WHO and the Centers for Disease Control and Prevention (CDC), at which time the WHO estimated there were 3.5 million cases globally in 20 countries. Former president Jimmy Carter was a powerful advocate, and the Carter Center has played a central role in the eradication programme since 1986. The programme aimed to interrupt transmission by containing cases identified by village health workers; improving water supplies or, where that was not possible, advising people to filter drinking water through a cloth; and treating open water sources with temephos to kill the copepod vector. This has been a hugely successful programme, as 16 countries have eliminated the disease.[2] In 2014 only 126 cases were reported; but that year a paper was published reporting a number of new cases in previously unaffected districts in Chad, where large numbers of infected dogs had been identified.[3] Since then, several hundred infected dogs have been identified annually in Chad and infected dogs, cats and baboons have been identified in Ethiopia, Mali and South Sudan. Dogs are thought to acquire the infection by eating fish entrails or infected paratenic hosts such as frogs rather than by drinking from infected water sources.[4]

The identification of an animal reservoir poses new challenges for the Guinea worm eradication programme. Interventions to address this that have been implemented in Chad include health education to encourage safe cooking and disposal of fish entrails, rewards of $20 per infected dog tethered and increased use of temephos to treat contaminated water sources. In 2018, 28 human cases were reported worldwide: 17 in Chad, 10 in South Sudan and 1 in Angola, a country that had never previously reported a case, which was a concern. In 2019, 54 human cases were reported: 48 in Chad, 4 in South Sudan and 1 each in Angola and Cameroon. In 2020, seven cases have so far been reported from the Gambella region of Ethiopia, a country that had not reported a human case in the previous 3 years.

Will Guinea worm be eradicated by 2030? The remarkable progress made in the past 30 years, and the fact that it has been eliminated from 16 countries, suggest that this should be possible, but a number of challenges remain. The target is confirmed absence of the emergence of adult female worms in humans and animals for 3 consecutive years at the global level. Some of the remaining endemic areas are conflict zones, making access difficult; ensuring adequate funding for eradication programmes is increasingly challenging as the number of cases fall to very low levels and the impact of the coronavirus disease 2019 (COVID-19) pandemic on NTD programmes remains to be seen.

Yaws was first targeted for eradication by the WHO in 1952. Active case-finding was followed by treatment with a single intramuscular dose of long-acting benzathine penicillin. Whole communities were treated where the prevalence was >10%; all children, active cases and their contacts were treated where the

prevalence was between 5 and 10%; and active cases and their contacts were treated where the prevalence was <5%. Surveillance was by clinical examination and serology, to ensure that latent as well as active cases were identified. Between 1952 and 1964, 460 million people were examined for yaws, >50 million people were treated and the global prevalence was reduced by >95%. Unfortunately, surveillance was discontinued and yaws later re-emerged in a number of countries.[5]

In 2012, the results of a randomised controlled trial conducted in Papua New Guinea (PNG) were published, showing that a single oral dose of azithromycin 30 mg/kg (maximum 2 g) was equivalent to intramuscular benzathine penicillin for the treatment of yaws.[6] The following year the WHO convened a meeting in Morges, Switzerland, a small town on the shores of Lake Geneva, to discuss the implications of this study. Soon afterwards the Morges strategy for the eradication of ~~trachoma~~ by 2020 was published, which recommended an initial round of community mass treatment with azithromycin, followed by subsequent surveys every 3–6 months at which all cases and their contacts would be treated with azithromycin. Once no further cases were found, post-elimination surveillance would be implemented, consisting of serological surveys in children 1–5 y of age to ensure that transmission had been interrupted.

The dose of azithromycin used in the trial in PNG was higher than that used for the control and elimination of trachoma and caused significantly more side effects. A second study carried out in Ghana and PNG compared the treatment efficacy of lower-dose azithromycin (20 mg/kg, maximum 1 g) with the higher dose (30 mg/kg, maximum 2 g). The primary outcome was cure at 6 months, defined as healing of skin lesions and a fourfold reduction in rapid plasma reagin (RPR) titre. This was achieved in 61/76 patients in the low-dose treatment group (80%) and 68/81 in the high-dose group (84%), suggesting that mass treatment for trachoma was likely to have a significant impact on yaws in communities where the two diseases coexist.[7] Unfortunately, a follow-up survey of patients in PNG included in the original azithromycin trial identified three subjects infected with a strain of *Treponema pallidum* carrying the 23SrRNA mutation that confers resistance to azithromycin and other macrolide antibiotics.[8]

Will yaws be eradicated by 2020? There are a number of challenges ahead. First, there is little recent information on its geographical distribution. A number of formerly endemic countries have reported no cases for many years, but the clinical signs of yaws are not specific and latent infection is common. Serological testing is needed to confirm the absence of transmission. So far this has only been confirmed in India and Ecuador. Second, there appears to be an animal reservoir; non-human primates infected with *T. pallidum* have been found in a number of African countries.[9] Third, the emergence of macrolide resistance has been documented in PNG.[8] To meet the ambitious target of global eradication by 2030, strong advocacy will be needed to raise the funds required and secure a substantial drug donation.

The target for elimination of trachoma as a public health problem is to reduce the prevalence of active trachoma to <5% in children 1–9 y of age, and the prevalence of trachomatous trichiasis to <2 per 1000 in adults ≥15 y of age in every formerly endemic district in the world. Active trachoma is diagnosed clinically by identifying follicles in the conjunctiva of the everted upper eyelid. Trichiasis is diagnosed clinically if at least one lash from the upper eyelid is touching the globe. Elimination is to be achieved by implementing the SAFE strategy: Surgery to correct trichiasis, mass treatment with Antibiotics (single-dose azithromycin) to treat ocular *Chlamydia trachomatis* infection and promotion of Facial cleanliness and Environmental improvement to reduce transmission.[10]

Impressive progress has been made since the World Health Assembly passed a resolution calling for the elimination of trachoma as a public health problem in 1998. The estimated number of people with trichiasis has been reduced from >10 million to <3 million and >80 million people have received azithromycin mass treatment annually since 2016. Nine countries have been validated by the WHO as having met the elimination targets (Cambodia, China, Ghana, Iran, Laos, Mexico, Morocco, Nepal and Oman) and a further four countries report having met the targets. The number of people requiring azithromycin has been reduced from an estimated 232 million in 2013 to 142 million in 2019. Thanks to the Global Trachoma Mapping Project, which was completed in 2016, we know exactly where our efforts should be focussed. This was the largest disease mapping project ever undertaken, in which 2.6 million people were examined in 29 countries, and the data on trachoma prevalence are continually updated through the ongoing Tropical Data programme.[11]

Using the most recent data on prevalence and coverage of mass drug administration, assuming that as-yet untreated districts that qualify for azithromycin mass treatment will start without delay, that there will be no funding constraints and no disruptions to programming due to insecurity or other factors, the WHO estimates that the target of global elimination as a public health problem will be met before 2030.[12] How reasonable are these assumptions? Pfizer, the manufacturer of azithromycin, has agreed to continue to donate it to trachoma control programmes until at least 2025, and the funding requirements should be reduced as more countries meet the elimination targets. It will be important to implement plans for post-elimination surveillance to ensure that trachoma does not re-emerge as yaws did. Insecurity remains a problem in trachoma-endemic countries such as South Sudan and the Central African Republic, and the impact of the COVID-19 pandemic on NTD programmes remains to be seen, but this should be an achievable goal. Q6

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