An economic evaluation of the global strategy to eradicate yaws

Christopher Fitzpatrick

Supervisors:
Prof. Dr. Patrick van der Stuyft
Dr. Filip Meheus

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACER</td>
<td>Average cost-effectiveness ratio</td>
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<tr>
<td>CEA</td>
<td>Cost-effectiveness analysis</td>
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<tr>
<td>CEAC</td>
<td>Cost-effectiveness acceptability curve</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
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<tr>
<td>ERR</td>
<td>Economic rate of return</td>
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<tr>
<td>FTA-ABS</td>
<td>Fluorescent treponemal antibody absorption test</td>
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<tr>
<td>GCP</td>
<td>Gross cell product</td>
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<tr>
<td>GDP</td>
<td>Gross domestic product</td>
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<td>GNI</td>
<td>Gross national income</td>
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<tr>
<td>GWD</td>
<td>Guinea worm disease</td>
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<td>GWEP</td>
<td>Guinea Worm Eradication Programme</td>
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<tr>
<td>ICCDE</td>
<td>International Commission for Certification of Dracunculiasis Eradication</td>
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<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
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<tr>
<td>ICT</td>
<td>International Certification Team</td>
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<td>IPT</td>
<td>Intermittent preventive treatment</td>
</tr>
<tr>
<td>ITFDE</td>
<td>International Task Force for Disease Eradication</td>
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<tr>
<td>IVD</td>
<td>In vitro diagnostic</td>
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<tr>
<td>KOICA</td>
<td>Korea International Cooperation Agency</td>
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<tr>
<td>LF</td>
<td>Lymphatic filariasis</td>
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<tr>
<td>MDA</td>
<td>Mass drug administration</td>
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<tr>
<td>NTD</td>
<td>Neglected Tropical Disease</td>
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<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
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<td>PC</td>
<td>Preventive chemotherapy</td>
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<td>PCR</td>
<td>Polymerase chain reaction</td>
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<td>PI</td>
<td>Prediction interval</td>
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<tr>
<td>POC</td>
<td>Point-of-care</td>
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<td>PPP</td>
<td>Purchasing power parity</td>
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<td>PSA</td>
<td>Probabilistic sensitivity analysis</td>
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<tr>
<td>RDT</td>
<td>Rapid diagnostic test</td>
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<tr>
<td>RPR</td>
<td>Rapid plasma reagin</td>
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<tr>
<td>SIDS</td>
<td>Small island developing state</td>
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<tr>
<td>STH</td>
<td>Soil-transmitted helminthiasis</td>
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<tr>
<td>TCC</td>
<td>The Carter Center</td>
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<tr>
<td>TCT</td>
<td>Total community treatment</td>
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<td>TTT</td>
<td>Total targeted treatment</td>
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<td>Abbreviation</td>
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<tr>
<td>TPHA</td>
<td><em>T. pallidum</em> hemagglutination assay</td>
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<td>TPPA</td>
<td><em>T. pallidum</em> particle agglutination assay</td>
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<tr>
<td>UHC</td>
<td>Universal Health Coverage</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<tr>
<td>VDRL</td>
<td>Venereal Disease Research Laboratory</td>
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<tr>
<td>WB</td>
<td>World Bank</td>
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<tr>
<td>WHA</td>
<td>World Health Assembly</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WTP</td>
<td>Willingness to pay</td>
</tr>
<tr>
<td>YLD</td>
<td>Years lost due to disability</td>
</tr>
<tr>
<td>YLL</td>
<td>Years of life lost</td>
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Part 1 General introduction
Chapter 1.1 Background

Yaws belongs to a group of bacterial diseases known as treponematoses, including also bejel, pinta and syphilis.[1] It is caused by the treponemal spirochete (cork-screw shaped) Treponema pallidum subsp. pertenue. The disease is known regionally by other names, such as buba (Spanish), pian (French), parangi or paru (Malay). It is also known as frambesia (from “framboise”, or raspberry in French), due to its appearance. The name “yaws” may have originated from an African word for berry (yaw).[1]

In 1948, when the World Health Organization (WHO) was established, yaws was among the major public health problems that the new health agency chose to prioritize. In 1949, the second World Health Assembly (WHA) adopted resolution WHA 2.36, “realiz[ing] the importance of treponematoses other than syphilis”. [2] The extensive geographical range and the high morbidity and disability cause by yaws justified international attention. In 1950, WHO estimated that 160 million people were infected with yaws.[3]

Yaws was found primarily in poor rural communities lacking improved water and sanitation, specifically in warm, humid, and tropical forest areas of Africa, Asia, and the Pacific. Transmission between humans occurs through direct skin contact with the fluid from an infected lesion.[1] Yaws-like lesions and infective agents resembling T. pallidum subsp. pertenue have been detected in primates in jungles in Africa.[4] However, it remains unclear whether non-human primates can transmit the disease to humans.[5]

The incubation period lasts an average of 21 days. Early clinical manifestations are seen primarily in children under the age of 15. The disease first appears as a solitary papule. The lesion grows into a papilloma of up to 5 cm in diameter, causing itching but no pain (Figure 1). This primary lesion, called “mother yaw” (buba madre or mamapian) is often found on the lower body, but can also occur on the patient's arms or face. The mother yaw is highly contagious and persists for weeks or months before healing spontaneously.[1]

Figure 1. Infectious papilloma occurring during active, primary yaws.

In most cases, the primary lesion heals before the onset of secondary lesions (Figure 2), which occurs as much as 2 years after the initial exposure. “Daughter yaws” may resemble the mother yaw or may appear as scaly macules (skin patches) of irregular shape. Fever, malaise, and cracks in palms and soles are common. “Crab yaws” refers to the painful crab-like gait
that can result. Periostitis and osteitis may affect the tibia, fibula, and forearm and the proximal phalanges (Figure 3), with pain and swelling.[1]

**Figure 2. Infectious papilloma occurring during active, secondary yaws.**


**Figure 3. Non-infectious periostitis occurring during active, secondary yaws.**


Active secondary cases include both infectious cases with skin lesions and non-infectious cases with swelling of the bone but no skin lesions. Secondary lesions also heal spontaneously, and within weeks or months the patient enters the latent stage of the infection. Latent cases do not have any lesions, and are detectable only by serology. Recurrences might be seen up to 5 years after the initial infection.[1]

Unless treated, approximately 10% of cases will develop tertiary yaws.[1] Manifestations include: subcutaneous gummatous nodules; chronic periostitis causing bowing of the tibia, known as “saber shin” (Figure 4); collapse of the palate and nasal septum, known as “gangosa” (Figure 5); and bilateral hypertrophic periostitis of the paranasal maxilla and nasal bridge, known as “goundou”.


There is no vaccine to prevent yaws. However, it responds to treatment with injectable benzathine penicillin. WHO and United Nations Children’s Fund (UNICEF) piloted yaws elimination campaigns using injectable penicillin in ten countries over 1948–1953. Success in these initial pilot projects led to support for similar intervention in 46 countries from 1953–1963. These mass treatment campaigns reduced the estimated global prevalence of infection to 2.5 million by 1964.

At the time, there was no formal certification process in place to confirm local elimination. Vertical yaws programmes were subsequently integrated into national primary health care systems. It has not been verified whether the countries that stopped reporting yaws cases did so due to the interruption of transmission or simply the interruption of reporting systems. In 1995, WHO estimated the global prevalence at 460,000 infectious cases.

During 2008–2015, over 450,000 new cases were reported to WHO. These cases were reported from 14 countries in Africa and Asia. A systematic review of the literature provided
The population at risk in these 11 countries is estimated at 89 million. In spite of the continued high number of cases, there are no published estimates of the burden of yaws in terms of Disability-Adjusted Life Years (DALYs). Similarly, there are no known estimates of the economic cost of the disease in terms of health care costs or productivity losses.

Figure 6. Cumulative number of yaws cases by subnational regions in the WHO Africa region, 2010-2013

Figure 7. Cumulative number of yaws cases by subnational regions in the WHO southeast Asia and western Pacific regions, 2010-2013
In 2012, a WHO-convened meeting of experts resulted in the Morges Strategy for yaws eradication.[11] Eradication is the “permanent reduction to zero of the worldwide incidence of an infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed.”[12] In 2013, the sixty-sixth WHA (2013) adopted resolution 66.12, with a target to eradicate yaws by 2020.[2] Of the three diseases currently targeted for eradication by WHO, two are so-called Neglected Tropical Diseases (NTDs) – guinea worm disease (GWD) and yaws. The third, poliomyelitis, is not a tropical disease.

Smallpox is the only human disease to have been eradicated. The smallpox eradication programme is estimated to have cost a total of about US$ 300 million in the period 1959-1979.[13] Eradication was formally declared in 1980. It avoided 1.5 million deaths annually. In developing countries, it saved about US$1070 million per year due to averted productivity losses.[14] In developed countries, the economic benefit to developed countries of avoided vaccination costs alone amounted to about US$350 million per year.

There are three major components of the yaws eradication strategy: mass treatment, surveillance, and certification. There are also some remaining unknowns about how each of these components will be implemented in practice, which we review here.

Mass treatment
Mass treatment involves the large-scale, single-dose administration of medicines free-of-charge to entire populations at risk, without the need for diagnosis.

The Morges Strategy is centred on 100% coverage at the village- or community-level with a single dose of azithromycin at 30 mg/kg (maximum 2 g).[11] Because of its simplicity and convenience, oral azithromycin is now preferred to injectable benzathine penicillin. One or two rounds of mass treatment at high levels of population coverage have been shown to reduce the prevalence of yaws near to elimination levels.[15] The approach is known as total community treatment (TCT) – treatment of an entire endemic community irrespective of the number of active clinical cases. Under the strategy, treatment is to be repeated 3-6 monthly until zero cases are reported in a given year.

In the case of other NTDs, namely lymphatic filariasis, schistosomiasis, soil-transmitted helminthiasis, onchocerciasis, and trachoma, mass treatment is known as Preventive Chemotherapy (PC) or Mass Drug Administration (MDA). The cost per person treated has usually been estimated less than US$ 0.50 per person, excluding the cost of medicines, which are typically donated by the pharmaceutical industry.[16] However, this unit cost is expected to vary significantly across settings and the total cost of eradicating yaws is unknown.

Surveillance
Public health surveillance is “the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice.”[17] Active surveillance involves visiting communities and health facilities, talking to household members, health-care providers and patients, implementing population surveys or testing suspected cases, often in the context of disease eradication or elimination. Passive surveillance, by contrast, involves regular reporting of disease data by facilities where patients are examined or specimens are tested.

The Morges Strategy calls for yearly serological surveys in children aged 1–5 years, starting one year after zero cases, and continued for three years.[11] Serological diagnosis of clinically active yaws requires the detection of two distinct sets of antibodies: one against treponemal antigens and one against non-treponemal antigens released due to cellular damage.
during infection. A reactive treponemal test result indicates current or past infection; the non-treponemal-test is required to diagnose active infection. In practice, surveillance can be carried out using a rapid diagnostic test (RDT) for the dual detection of treponemal and non-treponemal serological markers at or near to point-of-care.

However, use of the treponemal/non-treponemal (trep/non-trep) RDT alone in low endemicity settings may not be the most economical option. In yaws eradication pilot projects undertaken in 2013-2014, WHO negotiated a price of US$ 2.50 for the dual trep/non-trep RDT and only US$0.45 for a treponemal RDT alone. For surveys in which a large number of people are non-reactive to the treponemal test, such as in low endemicity settings, a strategy combining two rapid tests (treponemal RDT for screening, and trep/non-trep RDT for confirmation) should be evaluated for possible cost-savings.

Surveillance will need to be undertaken in the 14 countries still reporting yaws cases to WHO. However, a larger but (as yet) unknown number of countries with a history of yaws that will also at some point require some surveillance, to certify that all countries are in fact free from yaws. A cost-effective and affordable surveillance strategy, including active surveillance, is required.

Certification

Certification is the process by which WHO, through an International Commission established by World Health Assembly resolution, certifies that a country has successfully eliminated a disease targeted for global eradication; only once all countries have been certified is the disease officially declared eradicated.[18]

The Morges Strategy recognizes that a global eradication programme requires a global structure and process for certification. For GWD (dracunculiasis), WHO established the International Commission for Certification of Dracunculiasis Eradication (ICCDE) in 1995, “to evaluate the status of countries applying for certification of dracunculiasis eradication and to recommend whether a particular country should be certified as free of transmission.”[19] WHO has been formally certifying every individual country even if no transmission has ever been recorded in that particular country.

It is not clear what the cost of certification will be, or what impact it will have on the overall cost-effectiveness and affordability of the yaws eradication programme.
Chapter 1.2 A review of historical efforts leading up to the updated global strategy to eradicate yaws

Extracted and adapted from:


Historical eradication efforts

In 1948, when WHO was established, endemic treponematoses were among the major public health problems that the new health agency had to deal with. The large geographical distribution and high burden of yaws before the mass treatment campaigns justified the urgency and actions taken. For example, in 1936 in the then Gold Coast (now Ghana), yaws constituted 63% of all infectious diseases treated in government health facilities compared with 20% for malaria [20]. Similarly, in Nigeria in 1935, among infectious diseases treated at government health facilities, yaws constituted 48% compared with 16% for malaria [21]. The World Health Assembly resolution WHA2.36 in 1949 to support control of endemic treponematoses was therefore timely and appropriate. The initial WHO-assisted pilot projects to introduce penicillin in mass treatment campaigns in Bosnia, Haiti, Indonesia, the Philippines, and Thailand were rapid and remarkably successful [7]. The spectacular and visible results achieved with single-dose treatment (Figure 1) helped to reinforce community cooperation in the campaigns.

Figure 1. Results of treatment with a single injection of benzathine penicillin in the 1950s. Panel A shows a patient with yaws lesions (papilloma) on the face before treatment. Panel B shows the same patient two weeks after treatment with a single injection of benzathine penicillin.

In March 1952, WHO organized the first international conference on yaws in Bangkok, Thailand, attended by 23 countries [22]. The objectives of this meeting were to assess the global status of yaws and to share the experiences gained in pilot countries with other endemic countries. In November 1955, WHO convened a second international conference on yaws in Enugu, Nigeria, attended by 30 countries [23]. Africa was chosen as the venue because it was the home to about half of the estimated 50 million yaws cases in the world at that time. The venue in the eastern part of Nigeria was also chosen because of active and successful yaws control activities [24]. The objectives of the conference were to review the progress made and provide guidance to health authorities of the endemic countries. Basic
operational principles to guide yaws eradication were established, noting that success would depend on 100% treatment coverage of both active clinical disease and latent infections; anything below 90% was considered inadequate. In 1956, the Pan American Sanitary Bureau, now Pan American Health Organization (PAHO), organized a seminar on the eradication of endemic treponematoses in the Americas at Port-au-Prince, Haiti [25]. At this meeting, the practicability of yaws eradication was stressed, and a plan for a coordinated implementation in the region was agreed upon.

By 1963, WHO and UNICEF supported mass treatment campaigns using injectable penicillin in 46 countries. About 300 million people were screened, and over 50 million cases and contacts were treated. By the end of the campaign, the global burden of cases of endemic treponematoses was estimated to have reduced by 95%, to just 2.5 million cases. The implementation of this highly vertical programme also contributed to delivering much needed healthcare to affected communities [26]. Where possible, other diseases common in the communities—such as malaria, sleeping sickness, leprosy, smallpox, and yellow fever—were addressed by the yaws team, highlighting the historic concept of integrated public health interventions at the community level. Based on the experiences gathered in the field, Hackett and Guthe summarized the principles of yaws eradication to guide all those involved in the planning and implementation of yaws eradication campaigns [27].

The success of these campaigns in significantly reducing the global prevalence of yaws and other endemic treponematoses was credited as one of the greatest public health achievements in the history of WHO [28]. For UNICEF, yaws eradication was characterized as one of the most profitable investments it made, considering the per capita cost and amount of suffering alleviated [7]. The vertical programmes were gradually dismantled in favor of integration into (still weak) primary health care systems, in the hope that these would suffice to identify and treat the remaining 5% of cases. Ultimately, the lack of continued surveillance and waning of commitment and resources led to the resurgence of yaws in West Africa, Asia, and the Pacific in the late 1970s. The World Health Assembly consequently adopted resolution WHA31.58 in 1978 [29]. This resolution requested Member States 1) to formulate and implement integrated treponematoses control programmes with particular emphasis on active surveillance so as to interrupt transmission of the diseases at the earliest possible time in the areas where they are still endemic and to prevent their recurrence in areas from which they have been eliminated or where they have never been endemic, and 2) to report regularly to WHO on the current epidemiological situation of endemic treponematoses.

In response to this resolution, control activities were renewed in a number of countries, notably West Africa in the early 1980s. In Ghana, a combined yaws and yellow fever project was implemented in 1981 with funding from the United States Agency for International Development, WHO, UNICEF, and the European Economic Community [30]. Efforts were made to galvanize support from the international community and regional bodies for the eradication effort. In 1980, the Fogarty International Center convened an expert meeting to review different diseases and their suitability for eradication [31]. Three diseases—measles, poliomyelitis, and yaws—were considered suitable for eradication or at least elimination at the regional level. Yaws was considered to be the best candidate for eradication. As a follow-up to this 1980 meeting, the Fogarty International Center, together with ten other organizations, sponsored an international symposium on yaws and other endemic treponematoses in 1984 to review the status of these diseases, and to consider strategies, technologies, and research needed for their control and eventual eradication. This meeting, which was held at the Pan American Health Organization office in Washington, D.C. was attended by over 60 participants [3]. Regional meetings then followed in Cipanas, Indonesia (1985) [32], Brazzaville, the Congo (1986) [33], and Amman, Jordan (1986) [34] to draw up
plans for interrupting transmission. The regional meeting on yaws and pinta for the Americas was replaced by a consultant’s evaluation of the situation in 1987 (PAHO internal document) [35]. However, the organization of international and multiple regional meetings was not sufficient to revive global interest.

The historical mass treatment policies that formed the basis of yaws eradication were developed during the second international conference on yaws in Enugu, Nigeria in 1955. Experience had shown that it is only when active clinical cases and incubating and latent infections are simultaneously treated that interruption of transmission can be achieved. Treatment policies were based on the prevalence of clinically active yaws in the entire population of a village to determine the policy to apply, whereby (i) in areas where prevalence exceeds 10%, the entire population should be treated with benzathine penicillin, (ii) in places where prevalence is 5%–10%, all children aged under 15 years and close contacts should be treated, and (iii) in areas where prevalence is less than 5%, only household and other close contacts should be treated. Although contacts were defined as people having regular person-to-person interaction with patients with active infectious clinical yaws, it was difficult to fully define the extent of contacts and to treat all. Hence, the application of the second and third policies was unlikely to deal with all potential incubating and latent infections; and without very frequent resurveys (difficult and costly), it was impossible to interrupt transmission. The general consensus at the Enugu conference was to use total mass treatment even in areas where prevalence is lower than 10%.

Criteria for discontinuing mass treatment and routine population resurveys were established in 1960 to be when (i) at least 80% of the population has been seen in the last resurvey, (ii) the prevalence of active yaws is ≤2%, and (iii) the prevalence of infectious yaws is ≤0.5%. A surveillance system was then established through the local health facilities (rural health centers or health posts) supplemented by periodic school surveys with a focus on children who are at the highest risk of infection. Key problems that could be encountered during the post mass treatment surveillance phase were identified and possible solutions were also proposed (Figure 2) [7].
Figure 2. Yaws control: surveillance phase in the 1950s. The figure shows the steps taken in the 1950s to address factors and problems that could undermine the eradication effort during the post mass treatment surveillance phase.

Technical feasibility of yaws eradication

Following successful experience in pilot projects, the second international conference on yaws in Enugu, Nigeria in 1955 embraced an ambitious plan for scaling up yaws control to elimination, particularly in Africa, and the ultimate goal of global eradication. Experience in the 1940s and 1950s of eradicating yaws in Haiti and Nigeria and endemic syphilis in Bosnia and Yugoslavia had shown that a single injection of long-acting penicillin coupled with treatment coverage exceeding 90% rapidly reduces the burden of the disease within 12 months [36][24][37]. In Indonesia, where selective treatment policy of patients combined with regular resurveys was used, the rate of reduction in prevalence was not impressive, and it took 2–3 years to reach the same post-treatment prevalence that was achieved within one year in Nigeria.[38]

The experiences gathered were used to make informed, evidence-based choices to move from yaws control to progressive eradication. The WHO Expert Committee on Venereal Infections and Treponematoses in 1960 set two criteria for the eradication of yaws from a public health perspective [39].

1. Epidemiological eradication: was considered as the intermediate stage to complete eradication, defined as the absence of an indigenous infectious case in the population for three consecutive years. The basis of findings include information gathered from four sources: (i) all medical centers in the country where proper records of cases of the disease are kept, (ii)
biannual medical examinations of all schoolchildren, (iii) annual surveys of randomly selected villages remote from medical facilities, schools, and towns, and (iv) reported from any reliable source of information.

2. Complete eradication: was considered as the final stage of achievement of eradication (interruption of transmission), defined as the absence of an indigenous case in the population for three consecutive years, with information from all the above sources having been considered and no seroreactor in the age group under five years having been found.

After the successful eradication of smallpox in the 1970s, attention was again refocused on yaws eradication [40]. Many experts believed it to be an attainable goal that should be pursued. At the International Symposium on Yaws and Other Endemic Treponematoses in 1984, the feasibility of eradication of yaws was again considered to be technically feasible and achievable: “If the eradication of yaws can be accomplished, it should be done to reduce the suffering that is associated with the disease”, William Foege [41].

In 2011, the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases reviewed the 17 NTDs and their suitability for elimination or eradication. In considering the current knowledge and the available tools, it recommended that yaws be targeted for eradication, and this was included in the WHO NTD roadmap of 2012 [42].

In 2012, the 20th meeting of the International Task Force for Disease Eradication (ITFDE) examined the recent developments in yaws, including new tools – single-dose oral azithromycin, rapid dual platform point-of-care (POC) syphilis test, and polymerase chain reaction (PCR) technology to monitor resistance – and lent its support for the renewed yaws eradication effort [43].

Finally, in 2013, the World Health Assembly adopted resolution WHA66.12 on 17 NTDs, which targets the eradication of dracunculiasis (2015) and yaws (2020) [44].

The renewed eradication effort

In 2006, WHO created the Department of Control of Neglected Tropical Diseases. The initial list of diseases did not include yaws, bejel, and pinta [45]. However, following the reports of increasing cases from its African, South-East Asian, and Western Pacific regions, WHO organized a three-day meeting in 2007 to review the current situation and devise ways forward. The meeting recommended, as a first step, that the endemic treponematoses be included in the list of NTDs. This was done, and since then WHO has sought to highlight the problem of yaws on the international public health agenda. The interruption of transmission of yaws in India in 2003 and subsequent declaration of the elimination of the disease in 2006 provided an impetus to the renewed eradication initiative [46,47]. India is the second most populous country (>1 billion) in the world and one of the fastest growing economies. Together with smallpox and dracunculiasis, yaws and, recently, polio now belong to the public health history of the country. These achievements, despite its huge population, serve as a motivation for other countries to demonstrate that some carefully selected infectious diseases can be eradicated.

In January 2012, the Lancet published the results of the first study in Papua New Guinea, which showed that a single dose of azithromycin (Figure 3) was as effective in treating yaws as a single injection with benzathine penicillin [36]. This finding signaled a major advance in the history of yaws control in the past 60 years and further contributed to reviving interest in a global eradication campaign. Azithromycin has been used extensively in mass treatment campaigns in the elimination of blinding trachoma, and its safety is well documented.
In March 2012, WHO organized a first consultation in Morges, Switzerland to develop a new yaws eradication strategy based on azithromycin [11]. This meeting resulted in the recommendation of two new treatment policies to replace those of the 1950s. The rationale of the new policies is to simplify the criteria for determining the prevalence of active yaws to guide treatment and ensure that incubating and latent infections are adequately dealt with. The two treatment policies are:

1. Total community treatment (TCT): treatment of an entire endemic community, irrespective of the number of active clinical cases.

2. Total targeted treatment (TTT): treatment of all active clinical cases and their contacts (household, school, and playmates).

The new strategy recommends a first round of TCT with treatment coverage >90% (based on historic experience), followed by mop ups and active surveillance. Depending on the initial coverage, TTT rounds every six months may be adopted to actively detect and treat the remaining cases. Both theoretical and empirical studies are under way to validate the new strategy. Mathematical models will be useful to investigate the number of rounds of TCT that would need to be administered, and at what level of treatment coverage, in order to interrupt transmission.

In addition, to prove the feasibility of interrupting transmission using empirical data, the meeting recommended that pilot studies be conducted in one district each in six initial countries: Cameroon, Ghana, Indonesia, Papua New Guinea, the Solomon Islands, and Vanuatu. Later on, the Congo was added because of an intervention by Médecins Sans Frontières.

In March 2013, WHO organized a meeting of experts to prepare the guidelines for national programmes to implement the Morges Strategy and procedures for verification of transmission and eventual certification of countries [48,49].
As a first step in implementing the new eradication strategy, pilot treatment campaigns have been carried out in Congo (Bétou and Enyellé districts), Papua New Guinea (Lihir island), Vanuatu (Tafea Province), and Ghana (West Akyem district) in 2012 and 2013 to demonstrate the feasibility of eradicating the disease. About 90,000 people have been treated. Acceptability to the community, especially children, of oral azithromycin (to replace painful injections) has been high (unpublished results). As observed in the 1950s with penicillin, the rapid disappearance of yaws lesions after a single-dose treatment with azithromycin reinforced community cooperation and encouraged those who missed the initial treatment to come forward to take their medication. The preliminary serological results indicate that the underlying prevalence of *T. pallidum subsp. pertenue* infection (active and latent) in some of these communities may be quite high 10%–30%. The proposed use of TCT approach is strongly supported by this evidence. A prevalence serological and clinical survey in combination with trachoma was also completed in the Solomon Islands in November 2013. Plans are under way to start large-scale treatment in 2014 in Cameroon, Indonesia, and the Solomon Islands.

In March 2014, WHO convened a third consultative meeting on the Morges strategy at its headquarters in Geneva, Switzerland. Detailed reports of the pilot implementation showed that TCT with azithromycin is feasible and can be carried out in different geographical areas. The results of the evaluation of the new dual POC syphilis test in Ghana, Papua New Guinea, the Solomon Islands, and Vanuatu confirmed that the test can accurately diagnose active and untreated yaws [50]. The new POC test allows to screen and confirm the serological status of patients in the field and to reliably target yaws cases and contacts. Despite improved ability for diagnosis, programme managers still need to keep in mind that there are other causes of skin ulcers which may be confused with ulcerative yaws and which may not respond to azithromycin, giving the erroneous impression that the treatment did not work. Recent reports show that ulcers caused by *Haemophilus ducreyi* co-exist in yaws-endemic areas and are a possible confounder of yaws diagnosis [51]. Results of studies on baseline azithromycin resistance showed the absence of A2058G/A2059G point mutations on 23S rRNA in TPE strains, which implies no resistance, and azithromycin can be used. As recommended by the ITFDE in 2012, the meeting agreed to a proposal to conduct a clinical trial to clarify the different dosages of azithromycin for yaws and trachoma.

**Conclusion**

Since the 1950s, there have been seven eradication programs: hookworm and yellow fever (by the Rockefeller Foundation, before the existence of WHO), followed by yaws, malaria, smallpox, dracunculiasis, and poliomyelitis (by WHO) [52]. WHO has since abandoned the goal of malaria eradication in favor of control. Only smallpox eradication has been successful to date. Polio and dracunculiasis eradication programs are in their final stages but challenges remain [53].

Despite some concerns about eradication programs in general, the recent achievement in India has shown that eradication of yaws in modern times is technically and operationally feasible. The probability of finally succeeding in this endeavor is greatly increased by the availability of a new, easier, and more effective treatment option and new diagnostic tools. Single-dose treatment with azithromycin (oral) given in one or two rounds of large-scale treatment, depending on the initial coverage, may be sufficient to interrupt transmission. Post-treatment active surveillance will be enhanced by our ability to test any suspected case using the rapid dual POC treponemal and nontreponemal syphilis tests, which require only a finger prick drop of blood.
Lessons from the past and current eradication programmes, including challenges, will guide the renewed yaws eradication effort. All considered, what is needed to achieve the WHO 2020 eradication target and end the human suffering caused by this easily curable disease is to find the goodwill, commitment, and necessary resources.

Chapter 1.3 Aims, objectives and outline of the thesis

The strategy exists for WHO and its partners to follow the guinea worm eradication campaign in eliminating another NTD from every country of the world. And yet, at the time of writing, the effort is still not financed, with no cash or in-kind donations yet received for a global yaws eradication campaign.

Yaws-endemic villages and communities are among the poorest in the world. As a result, much of the resources required for the eradications of yaws globally will need to be mobilized by public institutions, both domestic and international. Decision-makers will have to be convinced that yaws eradication is cost-effective and affordable, before embarking on such a programme.

An economic evaluation of the yaws eradication strategy will help by informing the operationalization of the strategy, making it the most cost-effective possible, and demonstrating that it is affordable. This thesis aims to inform the strategy for yaws eradication focusing on health economic aspects of each of its major components: mass treatment, surveillance, and certification.

The main body of the thesis, containing the main published works, is contained within Part 2. Part 2 is composed of three chapters corresponding to the three major components of the yaws eradication strategy: mass treatment (Chapter 2.1), surveillance (Chapter 2.2), and certification (Chapter 2.3).

These three components are connected. Mass treatment is the intervention that leads to interruption of the transmission of yaws; surveillance determines where and for how long mass treatment is needed; certification is the process that establishes when mass treatment and surveillance can be stopped, and the eradication of yaws formally declared. Surveillance includes community surveillance, which will determine the need for rounds of mass treatment at the community level, and individual diagnosis, which will determine the need for subsequent rounds targeting case contacts. Surveillance can be more or less active depending on access to services and the quality of passive surveillance systems, and incidence of the disease. Certification is very much linked to the outputs of surveillance, in that certification is not possible as long as cases are being detected, but goes beyond those outputs to include assessment of the overall quality of surveillance systems.

Chapter 2.1, on the economics of mass treatment for yaws, consists of two papers.

In Paper 2.1.1, we establish benchmarks for the cost per capita of mass treatment for yaws, reviewing and synthesizing evidence on the cost of mass treatment campaigns for other NTDs. The objective is to understand what determines the cost of mass treatment and predict what unit cost (cost per person treated) one might expect during its implementation in different settings.

In Paper 2.1.2, we use those benchmarks to model the cost and cost-effectiveness of the yaws eradication strategy in the known endemic countries. We aim to evaluate the costs and effects in terms of DALYs averted by mass treatment in all countries known to be endemic for yaws.

Chapter 2.2, on the economics of yaws surveillance, also consists of two papers.
In Paper 2.2.1, we appraise the cost and cost-effectiveness of two alternative testing strategies using treponemal and dual trep/non-trep RDTs for yaws diagnosis and surveillance. The objective is to measure the costs and effects in terms of cases correctly diagnosed, and establish the conditions under which use of a sequential strategy of two rapid tests (treponemal RDT for screening, and trep/non-trep RDT for confirmation) would save costs or be more cost-effective relative to the trep/non-trep RDT alone.

In Paper 2.2.2, we examine the historical literature on yaws case reports by all countries since 1945 and develop a statistical model to better understand what factors were associated with some countries not reporting cases despite (likely) ongoing transmission. The group of countries with a history of yaws is both large and diverse; we set out to identify countries with a high probability of reporting cases passively, so that the limited available resources for active surveillance can be deployed efficiently.

Chapter 2.3, on the economics of certification, consists of a single paper.

In Paper 2.3.1, using evidence from (ongoing) efforts to eradicate GWD, we consider the cost of certification of the interruption of transmission and the cost-effectiveness of an eradication programme in the end game. There are no well documented examples of the cost and cost-effectiveness of an eradication programme in this phase, when the number of cases is low and much of the cost of the programme is for surveillance and certification; the objective is to understand from the GWD programme how certification will affect the cost and cost-effectiveness of the global yaws eradication strategy.

Part 3, the general discussion, consists of five chapters. After a short introduction to the discussion (Chapter 3.1), we summarize the main results, strengths and limitations of the published works (Chapter 3.2), address some cross-cutting questions, drawing comparisons when appropriate with other NTDs, and acknowledging recent developments in yaws research and financing (Chapter 3.3). In the last two chapters, we make recommendations for policy (Chapter 3.4) and future research (Chapter 3.5).
Chapter 1.4 A preview of economic theory and methods applied in the thesis

This chapter provides a preview of the economic theory and methods used in pursuit of the aims and objectives of the thesis. It is not meant as a comprehensive review of all methods used in economic evaluation. It is based on guidance contained in WHO’s Guide to Cost-Effectiveness Analysis and is consistent also with the reference case put forward by the Methods for Economic Evaluation Project.[54,55]

1.4.1 Cost analysis

The principle of cost analysis of health interventions is that decision-makers need to know the costs of the different options available to them, because more costly alternatives result in foregone consumption. A cost description estimates the resource use and unit costs or prices associated with the roll-out of health interventions. Cost minimization compares the costs of alternative interventions that are known, or assumed, to have an equivalent medical effect. [56]

In Paper 2.1.1, we perform a review and synthesis of all available cost descriptions of mass treatment for NTDs. In Paper 2.1.2, we use that synthesis to describe the cost of the yaws eradication strategy. In Paper 2.2.1, we compare the cost of two alternative testing strategies to minimize the cost of yaws diagnosis and surveillance. In Paper 2.3.1, using evidence from (ongoing) efforts to eradicate GWD, we describe the cost of certification of an eradication programme in the end game.

In cost analysis, relevant costs include: 1) the cost of providing health interventions such as outpatient visits, inpatient stays or population-based programmes, using resources such as labour, capital, consumables and overhead; and 2) the cost of accessing health interventions, including direct payments by patients and their families on things like transport. Costs are aggregated using an ingredients-based approach, in which the quantity of each input is multiplied by its price.

It is recommended to use as prices what are known as “economic costs”. Economic costs define the cost of a resource in terms of the value forgone by not using the same resource in its next best alternative use, also known as an opportunity cost. When the market price accurately represents a resource’s opportunity cost, it can generally be assumed to reflect its economic cost. When no market price is available or when it does not accurately reflect opportunity cost, such as for donated resources, a “shadow price” is needed.

In cost analyses of mass treatment for NTDs, estimating the shadow price of community health volunteers’ time is a particular challenge. Two approaches are possible: the opportunity cost approach and the replacement cost approach.

The most common method for using the opportunity cost approach to value volunteer time is applying a shadow wage corresponding to the average wage of the volunteer should he/she have chosen to work. The average wage of an agricultural worker is often used, as this is the most commonly reported occupation of community health volunteers in settings where NTDs are endemic. Volunteers are arguably giving up their leisure time, not the opportunity to work, but there is no consensus on how to value leisure time.

The replacement cost approach is also known as the proxy good method or the substitute method. The value of the volunteer’s unpaid time is based on what it would cost to hire a paid worker to perform the same tasks. An advantage of this approach is that it values volunteer time based on the value of their contribution to the health system, as opposed to their
alternative employment opportunities. A disadvantage is that it implicitly assumes that paid workers would require the same time to perform the tasks as the volunteers.

In Papers 2.1.1 and 2.1.2, we implicitly adopt a replacement cost approach, assuming that volunteer labor cannot be assumed to be available indefinitely, or on the scale or with the quality required for successful implementation of the global yaws eradication strategy.

1.4.1 Econometric modelling

Econometric models are statistical models used in economics, the most common of which is the linear regression model. “Health economics has a long tradition of estimating hospital cost functions econometrically.”[54] A cost function is a mathematical formula used to predict how total costs might change in response to changes in inputs, input prices, and, importantly, the scale and scope of operations.

In Paper 2.1.1, we apply an econometric model to published estimates of the cost of mass treatment campaigns for NTDs and then predict the cost per person treated in different settings. These predicted unit costs are then used to estimate the cost of the global yaws eradication strategy in Paper 2.1.2.

In mass treatment campaigns, the cost function will likely be heavily influenced by economies of scale and scope. In other words, the cost per person treated may depend upon the number of people treated and on the number of diseases for which they are treated. Average costs that fall (rise) with increasing scale and scope of delivery are called economies (diseconomies) of scale and scope. The magnitude of economies of scale and scope can be estimated through econometric modelling.

However, econometric models are not just used to estimate cost functions. In Paper 2.2.2, we develop an econometric model of case reporting and predict the probability that previously endemic countries would report cases if in fact transmission were currently ongoing.

1.4.3 Cohort modelling

A cohort model represents the experience of a simulated cohort of patients who receive (or do not receive) a health intervention. The experience of each individual cohort member is not considered in detail, only the proportion of the cohort who experience health events or health states over time. Events and their associated costs as well as the costs and utilities associated with health states can be multiplied by the relevant proportion of the cohort and aggregated to summarize the experience of the cohort.[57] The two most common cohort models in economic evaluation of health interventions are the Markov model and decision tree.

Markov models are built using disease states. “These are mutually exclusive and exhaustive and so each individual represented in the model can be in one and only one of these disease states at any given time. Individuals move (‘transition’) between disease states as their condition changes over time. Time itself is considered as discrete time periods called ‘cycles’ (typically a certain number of weeks or months), and movements from one disease state to another (in the subsequent time period) are represented as ‘transition probabilities’. Time spent in each disease state for a single model cycle (and transitions between states) is associated with a cost and a health outcome. Costs and health outcomes are aggregated for a modelled cohort of patients over successive cycles to provide a summary of the cohort experience.”[58]

In Paper 2.1.2, for example, we apply a Markov model to understand how the cohort of at-risk populations in currently endemic countries would progress through different states of
infection and morbidity under the global yaws eradication strategy. In Paper 2.3.1, we develop a similar model of (ongoing) efforts to eradicate GWD. Markov models are well-suited to the evaluation of disease elimination and eradication, as they allow longer time periods to be modelled, in continuous time. Strictly speaking, we implement population models, or models of multiple cohorts. Population models describe the health of the population over the lifetime of all the individuals in the initial cohort (i.e. alive during implementation of the eradication strategy) as well as future cohorts (i.e. alive when no further intervention is required).

An alternative to the Markov model is the decision tree, “in which distinct branches are used to represent a potential set of outcomes for a patient or patient cohort. A decision tree consists of a series of ‘nodes’ where branches meet: each node may take the form of a ‘choice’ (a decision about which alternative intervention to use) or a ‘probability’ (an event occurring or not occurring, governed by chance). Probabilities at any specific node must always add to 1. Costs and outcomes are assigned to each segment of each branch, including the end (‘leaf’) of each branch. Outcomes and costs for each branch are combined using branch possibilities and the tree is ‘rolled back’ to a decision node, at which the expected outcome and cost for each treatment alternative can be compared.”[59]

In Paper 2.2.1, we model the outcomes of two alternative testing strategies using treponemal and dual trep/non-trep RDTs for yaws diagnosis and surveillance. We use a decision tree model because the intervention in question (diagnosis) had distinct outcomes that could be measured at well-defined points over a short period of time.

1.4.4 Outcome measurement

Economic evaluation of health interventions requires a broadly defined measure of outcome that is relevant for all diseases affected by those interventions. “Using a non-disease specific health outcome measure (i.e. one that is generalisable across disease states) allows consideration of opportunity costs for the entire health sector, and facilitates comparisons across investment types.”[55]

Disability-adjusted life years (DALYs) were first used in the Global Burden of Disease and Injury study that was started in 1988 with the objective “to quantify the burden of disease and injury of human populations and define the main challenges at the global level using a measure that could also be used for cost-effectiveness analysis.”[54] Though the measure has since been refined, it continues to be routinely used by WHO, as well as major global health funders, for reporting on health and on cost-effectiveness, especially in low and middle income countries.[54,55]

One DALY can be thought of as one lost year of "healthy" life.[60] DALYs for a disease or health condition are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences. YLL is the number of deaths multiplied by the standard life expectancy at the age at which death occurs. In burden of disease studies, the same "ideal" life expectancy is used for all countries and population subgroups, based on an egalitarian logic.[60] In cost-effectiveness studies, however, it is much more common to use actual life expectancy. YLD is the number of prevalent cases multiplied by the disability weight. A disability weight is a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (equivalent to death).[60] These disability weights are now typically elicited in surveys of the general population, and come with uncertainty intervals.[61]

In Papers 2.1.2 and 3.1.1, our Markov models are set up to capture the cycle period prevalence of the different states associated with yaws and guinea worm disease, respectively. Neither yaws nor guinea worm disease cause much mortality. Therefore, outcome
measurement is mostly a matter of multiplying the period prevalences by associated disability weights and summing across states and periods. In the absence of disability weights specific to yaws or guinea worm disease, we use disability weights for comparable conditions (like “disfigurement level 1, with pain or itch” for primary yaws, or tertiary syphilis for tertiary yaws).

1.4.5 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) combines cost analysis, cohort modelling and outcome measurement to evaluate the effectiveness of two or more alternative interventions relative to their cost. The aim of the decision maker when evaluating an intervention is to maximize outcomes such as DALYs, while minimizing costs. Interventions that are both more effective at producing health benefits and are associated with net cost savings are said to be a “dominant” strategy.[62] In the event that an intervention is more effective and more costly, the decision-makers compare additional costs to additional DALYs.

Major methodological issues in the design of a CEA include defining the comparator, determining the time horizon, and choosing the discount rate.

Comparators usually include the interventions that are currently available to the population, as well as the null, zero-cost or “do nothing” alternative – i.e. comparing the new intervention to the situation that would exist if no interventions were implemented. WHO recommends including in all cost-effectiveness analyses the zero-cost alternative, to enhance generalizability across different settings.[54]

The time horizon is the period over which the costs and effects of the intervention and comparators are calculated. An economic evaluation should use a time horizon long enough to capture all costs and effects relevant to a decision problem.[55] However, in the interest of maintaining some comparability across studies, WHO recommends that interventions be evaluated under the assumption that they are implemented over a period of ten years; costs and health effects should be followed over the lifetime of the beneficiaries, or about 100 years.[54]

Given these long time horizons, the time preferences of the population need to be taken into account. Future costs and effects are discounted to reflect their value at the time that choices are being made between interventions. A discounting factor is applied to each value in the series of costs and effects and then the series is aggregated. There is not, however, global consensus on the appropriate discount rate to be used. WHO recommends that in the base case analysis a discount rate of 3% is applied to both health effects and costs, and that in sensitivity analysis, rates of 0% and 6% are applied to health effects and costs, respectively.[54]

The cost-effectiveness of an eradication programme with upfront costs for long-term benefits is highly dependent on the time horizon and discount rates chosen in the analysis – more so, in any case, than that of a control programme, for which both costs and benefits are ongoing. Furthermore, when evaluating a global strategy like that for yaws, there will be legitimate and often substantial differences in time preferences for health and wealth. In Papers 2.1.2 and 2.3.1, we are conservative with respect to the time horizon and perform sensitivity analysis on a full range of discount rates.

A key output of CEA is the incremental cost-effectiveness ratio (ICER) of an intervention relative to its comparator(s). “An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of ‘extra cost per extra unit of health effect’ – for the more expensive therapy vs the alternative.”[63] It is usually though not always expressed as
the cost per DALY averted. The average cost-effectiveness ratio (ACER), as used in this thesis, is defined as the ICER relative to the “do nothing” alternative.

The cost-effectiveness threshold is the value of the ICER below which an intervention is deemed to be cost-effective. One should distinguish here between supply-side and demand-side thresholds. With a supply-side threshold, “the underlying economic principle is that given a fixed budget a decision to reimburse a new healthcare intervention implies that funds will not be available to fund some other intervention which would deliver health benefits, and that these health benefits would be obtained at the ‘marginal’ rate represented by the threshold.”[64] A demand-side or willingness to pay (WTP) threshold “represents an estimate of what a consumer of health care might be prepared to pay for the health benefit – given other competing demands on that consumer’s resources.”[65]

In 2005, WHO’s Choosing Interventions that are Cost–Effective project suggested that WTP thresholds of 1-3 times GDP per capita per DALY averted could be used as generic global norms.[65] Owing to their (mis-) use in national priority-setting, the WHO thresholds have been criticized for being too inclusive, such that very few interventions are ever excluded. Recently, it has been argued that a lower threshold (such as 50% of GDP per capita) would be closer to a supply-side threshold, reflecting the reality of budget constraints in most low- and middle-income countries.[66] However, it is still good practice to complement CEA with information on affordability and feasibility.

In any case, such global norms should be replaced by national processes and a sectoral approach to CEA, involving league tables with country-specific ACERs and ICERs for all possible interventions.

1.4.5 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) is a technique that helps to quantify the level of certainty in the output of the analysis, in relation to uncertainty in the model inputs. It has broad applications not limited to health economics, but with particular usefulness in health economics due to considerable uncertainty around the outputs of econometric and cohort modelling, outcomes measurement, or, in the absence of data, around expert opinion. A probabilistic approach to uncertainty allows the decision-maker to consider multiple sources of uncertainty simultaneously.

PSA is a form of Monte-Carlo simulation where estimated variables are varied stochastically to estimate the distribution of the model output value. Most applications assume a specific distribution (e.g. normal, uniform, binomial) for each estimated variable. “Key elements of a Monte-Carlo simulation are to (a) define a domain of possible inputs (parameters); (b) generate input values randomly from probability distributions across the domain; (c) perform a deterministic computation of the model output based on the selected inputs; (d) repeat for a sufficient number of ‘draws’ of input values; (e) aggregate the results.”[67] A thousand or more draws is usually sufficient.

We use PSA in all of our models of cost-effectiveness, to put uncertainty intervals around the main results of interest, including costs, DALYs, ICERs and ACERs.
Part 2 Published papers
Chapter 2.1 The economics of mass treatment for yaws
Benchmarking the cost per person of mass treatment for selected neglected tropical diseases: an approach based on literature review and meta-regression with web-based software application.

Published paper
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Authors and Affiliations
Christopher Fitzpatrick a,b, Matthew Madin-Warburton a,c, Fiona M. Fleming d, Timm Schneider e, Filip Meheus f, Kingsley Asiedu g, Anthony Solomon a, Antonio Montresor a, Gautam Biswas a

a Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland
b fitzpatrickc@who.int
c University of York, United Kingdom
d Imperial College London, United Kingdom
e Universität Düsseldorf, Germany
f University of Capetown, South Africa

Abstract
Background: Advocacy around mass treatment for the elimination of selected Neglected Tropical Diseases (NTDs) has typically put the cost per person treated at less than US$ 0.50. Whilst useful for advocacy, the focus on a single number misrepresents the complexity of delivering “free” donated medicines to more than a billion people across the world. We perform a literature review and meta-regression of the cost per person per round of mass treatment against NTDs. We develop a web-based software application (https://healthy.shinyapps.io/benchmark) to calculate setting-specific unit costs against which programme budgets and expenditures or results-based pay-outs can be benchmarked.

Methods: We reviewed costing studies of mass treatment for the control, elimination or eradication of lymphatic filariasis, schistosomiasis, soil-transmitted helminthiasis, onchocerciasis, trachoma and yaws. These are the main 6 NTDs for which mass treatment is recommended. We extracted financial and economic unit costs, adjusted to a standard definition and base year. We regressed unit costs on the number of people treated and other explanatory variables. Regression results were used to “predict” country-specific unit cost benchmarks.
Results: We reviewed 56 costing studies and included in the meta-regression 34 studies from 23 countries and 91 sites. Unit costs were found to be very sensitive to economies of scale, and the decision of whether or not to use volunteers. Financial unit costs are expected to be less than 2015 US$ 0.50 in most countries for programmes that treat 100 thousand people or more. However, for smaller programmes, including those in the “last mile”, or those that cannot rely on volunteers, both economic and financial unit costs are expected to be higher.

Discussion: The available evidence confirms that mass treatment offers a low cost public health intervention on the path towards universal health coverage. However, more costing studies focused on elimination are needed. Unit cost benchmarks can help in monitoring value for money in programme plans, budgets and accounts, or in setting a reasonable pay-out for results-based financing mechanisms.

Author summary
Advocacy around mass treatment for the elimination of selected Neglected Tropical Diseases (NTDs) has typically put the cost per person treated at less than US$ 0.50. Whilst useful for advocacy, the focus on a single number misrepresents the complexity of delivering “free” donated medicines to more than a billion people across the world. Given the increasing focus of the NTD community on value for money and, in the context of universal health coverage, of the global health community on outreach beyond health facilities, there was a need for greater nuance. We performed the most comprehensive literature review and first regression analysis of differences between settings in the cost per person treated against six NTDs (excluding the cost of individual medicines). We considered more than ten possible drivers of cost. We found, for example, that the unit cost of treatment depends very much on the number of people treated (economies of scale). We then developed a web-based software application (https://healthy.shinyapps.io/benchmark) that can be used to predict setting-specific unit costs against which programme budgets and expenditures or results-based pay-outs can be benchmarked.

Introduction
Since the year 2006, more than 7 billion treatments against Neglected Tropical Diseases (NTDs) have been delivered to people in need. More than 850 million people were treated in 2014 alone for lymphatic filariasis (LF), schistosomiasis, soil-transmitted helminthiasis, onchocerciasis, trachoma and yaws. Up to 1.4 billion people are targeted for coverage, requiring an investment of an estimated US$ 2.8 billion in the period 2015-2020. [1]

The six abovementioned NTDs are caused by different pathogens (including bacteria and helminths). However, only four drugs (albendazole, azithromycin, ivermectin or diethylcarbamazine and praziquantel) are needed to treat them and the strategy for delivering those medicines to reduce morbidity and prevent transmission is similar. [1] Mass treatment is known formally as Preventive Chemotherapy (PC) or Mass Drug Administration (MDA) in the case of the five abovementioned NTDs, and Total Community Treatment (TCT) in the case of yaws. Mass treatment involves the single-dose administration of (largely donated) medicines to entire populations at risk, without the need for diagnosis.

In advocating for mass treatment against the five PC diseases, the NTD community has typically cited values of US$0.10 to US$0.50 as the delivery cost of per person per year. [1] These values exclude the cost of donated medicines. Whilst useful for advocacy, the focus on single numbers risks misrepresenting the complexity of delivering “free” medicines to more than a billion people across the world.
In this study we conducted a literature review of existing studies and extracted and standardized estimates of the unit cost of delivering mass treatment (excluding the cost of the individual medicines themselves). We considered the six non-zoonotic NTDs for which mass treatment is recommended by the World Health Organization (WHO). Mass treatment is also recommended for foodborne trematodiases, however, scale up for these diseases is more recent with no current data on the cost of delivery.

We developed a regression model of unit costs to better understand the drivers of variation between the studies. The aim of the study was to use this model to “predict” what unit cost one might expect in different settings, along the lines of what has been done by WHO-CHOICE for estimating unit costs of general health services [2]. We called these predictions benchmarks. Benchmarks are setting-specific unit costs against which programme budgets and expenditures might be compared or benchmarked. The regression results were then used to create a web-based software application for planners, funders and researchers. The benchmarks might also inform the design of payment-by-results type financing mechanisms whereby funders agree to pay for outputs (e.g. the number of people treated) rather than inputs (e.g. personnel and equipment).

**Methods**

This study was undertaken in four steps: 1. Literature search and review; 2. Data extraction; 3. Meta-regression; 4. Benchmarking.

**Literature Search and Review**

In June 2015, we conducted a search of the available literature on the cost of PC or MDA for the five PC diseases and TCT for yaws. The search was conducted in PubMed, in English; the terms are provided in Supplemental Information (Table S1). In order to maintain comparability in inputs, the search was limited to publications published since 1990. The initial literature search identified 182 studies.

Titles and abstracts were assessed for inclusion. Criteria for inclusion were that: 1) that the population targeted be either all children or all adults (not, for example, just pregnant women); 2) the intervention be mass treatment, rather than individual (diagnosis and) treatment; 3) that the reported outcome (cost) be based at least in part on primary data (some estimation was allowed) and that sufficient detail be provided to ascertain whether these costs were financial or economic and what portion of the costs could be attributed to medicines.

On this basis, 136 studies were excluded. We reviewed the references of the remaining 47 studies and identified another 7 studies. A list of 54 references was shared with disease-specific focal points within WHO and one further study was proposed from the grey literature.[3] Primary data collected by one of the authors (FF) was also considered for inclusion; this data is publicly available, as described under Data Extraction. A total of 56 full texts were assessed for inclusion in the meta-regression.

Upon reviewing the full texts, we excluded a total of 22 studies, listed in Supplemental Information (Table S2). Of those, 19 nineteen studies were based on the same cost data as an earlier study or another study reporting more detail. One study did not report the number of people treated. One study provided regional costs with no breakdown by country and one study provided costs for chemotherapy of detected cases only, not mass treatment.
This resulted in a final set of 34 studies being selected for inclusion in the meta-regression. These are listed in Supplemental Information (Table S2). In December 2015, searches undertaken in English, French and Spanish using Google Scholar produced no additional studies.

**Data Extraction**

Unit costs were defined as the cost per person per round, not per disease. We extracted unit costs or divided total costs by the number of people treated in a given year (across all rounds). We removed the medicines component (whether purchased or donated) and converted to base year prices (2015 US$) using the Gross Domestic Product (GDP) deflator.[4] Definitions of what constituted financial or economic costs varied across the studies. We applied a standard classification according to Table 1. One of the notable differences between financial and economic costs relates to the inclusion of Ministry of Health buildings and staff time. While many studies mentioned patient time and the use of volunteers, few reported their (economic) costs and they were therefore excluded from the analysis. We nonetheless recorded the use of volunteers as a dummy variable for use in the meta-regression.

**Table 1. Classification of financial and economic unit costs (excluding medicines\(^1\))**

<table>
<thead>
<tr>
<th>Cost</th>
<th>Financial</th>
<th>Economic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug delivery (i.e. shipment)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fuel and maintenance</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Office and other supplies</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Office utilities</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Planning and mapping</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Project staff salaries</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Per diems</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Training</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vehicles (rented)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vehicles (new)</td>
<td>Yes (annualized)</td>
<td>Yes (annualized)</td>
</tr>
<tr>
<td>Ministry of Health buildings</td>
<td>No</td>
<td>Yes (annualized)</td>
</tr>
<tr>
<td>Ministry of Health staff time</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Volunteer time</td>
<td>No</td>
<td>No(^2)</td>
</tr>
<tr>
<td>Treated person’s time or other costs</td>
<td>No</td>
<td>No(^3)</td>
</tr>
</tbody>
</table>

\(^1\) Excludes medicines used for mass treatment as well as for treatment of adverse events, if any, which were limited to early mass treatment with diethylcarbamazine.

\(^2\) Estimates of the economic cost of volunteer time were removed from the unit costs of the few studies that did report them.

\(^3\) Estimates of the economic cost of the treated person’s time or other direct or indirect costs associated with treatment or adverse reactions were removed from the unit costs of the few studies that took a societal perspective.
We extracted the number of people treated, the percentage of the target population that was treated, and other variables described in detail under *Meta-regression*. The coverage percentage was not always reported, nor the target population. For school-based programmes, we took the primary school net enrolment rate as a proxy for coverage. In the other cases, we estimated coverage using national data as reported to WHO.[5]

For study sites at the subnational level, we identified the geographical coordinates (administrative centers in the case of regions or districts) and nearest major cities (>100 000 inhabitants) and calculated the distance between them by road (in kilometers) using Google maps. We also recorded the travel time needed (in minutes by car), though this variable was later discarded as it performed no better than distance in predicting unit costs. In the absence of roads (e.g. in the islands of Papua New Guinea and Vanuatu) we used the flying distance to the nearest city.

Data were collated in a spreadsheet using Microsoft Excel. Data were then imported into R for data analysis and visualization.[6] All data are publicly available at https://healthy.shinyapps.io/benchmark, through the web-based application software described below.

**Meta-regression**

We employed meta-regression to examine whether differences in the average cost per person reported by included studies could be explained by moderator variables related to study methodologies or to the settings in which they were conducted.

Regression analysis was performed with the *plm* package for panel data.

We used the study reference as the cross-sectional unit, which allows us to account for the possible clustering of effects due to methodological differences between studies. We used the year, site and comparator as the longitudinal unit. By comparator we refer to the fact that in any given year and site, a study may report and compare multiple costs: economic versus financial costs, integrated versus standalone costs, school-age children versus total population, or one round versus two rounds of delivery.

Models were fit with both random and fixed (within) effects. However, for the purposes of benchmarking (outside of the sample), it would be problematic to select an appropriate fixed effect. We therefore focus in what follows on the random effects model. The results of the fixed effects model are provided in the Supplemental Information (S4 Table).

Model 1 is a random effects model on the full set of observations;

\[
(1) \log(ucb_{it}) = \alpha + eco_{it}\beta_1 + vol_{it}\beta_2 + \log(int_{it})\beta_3 + \log(rds_{it})\beta_4 + yrs_{it}\beta_5 + cov_{it}\beta_6 + sch_{it}\beta_7 + \log(pop_{it})\beta_8 + \log(den_{it})\beta_9 + nat_{it}\beta_{10} + \log(gdp_{it})\beta_{11} + u_{it} + \epsilon_{it}
\]

Model 2 is a random effects model on the subset of observations that are subnational (regional or district) sites, which allows for the inclusion of the distance variable *dis*;

\[
(2) \log(ucb_{it}) = \alpha + eco_{it}\beta_1 + vol_{it}\beta_2 + \log(int_{it})\beta_3 + \log(rds_{it})\beta_4 + yrs_{it}\beta_5 + cov_{it}\beta_6 + sch_{it}\beta_7 + \log(pop_{it})\beta_8 + \log(den_{it})\beta_9 + nat_{it}\beta_{10} + \log(gdp_{it})\beta_{11} + sqrt(dis_{it})\beta_{12} + u_{it} + \epsilon_{it}
\]

where
\( ucb \) is the unit cost (per person treated per round) in 2015 US$, excluding medicines and volunteer time; we consider with and without Purchasing Power Parity (PPP) conversion;

\[ i = 1, \ldots, I \] studies;

\[ t = 1, \ldots, T \] year-site-comparators;

\( a \) is an invariant intercept;

\( eco \) is a dummy indicating whether the unit cost is economic (1) or financial (0);

\( vol \) is the volunteer dummy for use of volunteers, the cost of which is not included in \( ucb \);

\( int \) is a variable with the number of diseases for which treatment is delivered within a given round;

\( rds \) is the average number of rounds per year;

\( yrs \) is the number of years during which the programme has been implemented;

\( cov \) is the percent coverage, or the number of people treated divided by the number of people targeted;

\( sch \) is a dummy indicating school-based treatment of school children only;

\( pop \) is the number of people treated per round;

\( den \) is the population density, defined as the total population divided by the land area, or people per km²;

\( nat \) is a dummy variable indicating a national programme rather than a subnational site;

\( gdp \) is GDP per capita in 2015 US$; with and without PPP conversion;[7]

\( dis \) is the distance in km from the study site to the nearest city of >100 000 inhabitants;

\( u_{it} \) is the between-study error; and

\( \epsilon_{it} \) is the within-study error.

We consider also the possibility of study- and country-specific dummy variables, as well as interactions between variables, as described in the Results.

**Benchmarking**

We used the resulting regression model coefficients to estimate or predict unit cost benchmarks across a variety of settings.

For the tables of this paper, we generated country-specific benchmarks for both economic and financial unit costs. We set population treated (\( pop \)) to 10 thousand, 100 thousand and 1 million people respectively; the school-based (\( sch \)) dummy to 0; the national programme (\( nat \)) dummy to 1; the integrated delivery (\( int \)), years (\( yrs \)) and rounds (\( rds \)) variables to 1; the coverage (\( cov \)) and population density (\( den \)) variables to the sample medians (85% and 134 respectively). We set GDP per capita in 2015 US$ (\( gdp \)) to country-specific values, but constrained it to the minimum and maximum of the sample (2015 US$ 466 and 3737 respectively) to avoid extrapolating too far outside of the available data. We set the volunteer (\( vol \)) dummy to 1 for financial benchmarks (resulting in lower cost) and to 0 for economic benchmarks (resulting in higher cost). To be clear, all unit cost benchmarks reported in this study exclude the cost of volunteer time. However, the economic unit cost benchmarks assume that volunteers are not used (ie. that all labor inputs are paid).

A web-based software application was developed using shiny (RStudio) to calculate setting-specific unit costs against which programme budgets and expenditures or results-based pay-outs can be benchmarked. In the software application, all of the above parameters can be chosen by the user.
The logarithmic transformation of the unit cost benchmark (ucb) was obtained with the vector of coefficients (B) and the matrix of new values for the explanatory variables (X) and

\[ \log(ucb) = BX' \]

The standard error of the (log) estimate was calculated using

\[ SEE = \sqrt{XVX'} \]

where V is the variance-covariance matrix.

With the mean and standard error, we randomly drew from a normal distribution and re-transformed (exponentiated) 10 000 values and extracted the mean, 2.5th and 97.5th centile values for the best estimates and 95% Confidence Intervals (CIs). A 95% CI means that if the data are resampled, best estimates are expected to fall within this interval in 95% of the samples.

In the software application, we also provide prediction intervals (PIs). The standard error of the (log) prediction becomes

\[ SEP = \sqrt{SSE/(n - 2) + XVX'} \]

where SSE is the sum of squared errors (residuals).

A 95% PI means that if a single observation is resampled, the unit cost is expected to fall within this interval in 95% of the samples.

**Results**

**Availability of studies**

These 34 studies included in the meta-regression cover 21 countries and 91 sites over 19 years for a total of 212 different observations of unit cost. The countries and sites from which the studies were taken are depicted, by disease, in Figure 1. A disproportionate number of observations are from Uganda (96).
Figure 1. Availability of costing studies among low- and middle-income countries, by disease. Most recent year refers to the most recent year of study, not the most recent year of publication.
There are 150 observations of financial cost from 29 studies and 130 observations of economic cost from 17 studies, with 12 studies reporting both (Table 2). Financial unit costs (excluding medicines) range from US$ 0.01 per treatment to US$ 8.50, with a median value of $0.20. Economic unit costs (excluding medicines and volunteer time) ranged from $0.02 to $2.90, with a median value of $0.40.

Table 2. Summary statistics for 34 studies of 23 countries and 91 sites over 19 years

<table>
<thead>
<tr>
<th>Statistic</th>
<th>N</th>
<th>Mean</th>
<th>St. Dev.</th>
<th>Min</th>
<th>Pctl(25)</th>
<th>Median</th>
<th>Pctl(75)</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>ucf</td>
<td>150</td>
<td>0.4</td>
<td>0.8</td>
<td>0.01</td>
<td>0.1</td>
<td>0.2</td>
<td>0.4</td>
<td>8.5</td>
</tr>
<tr>
<td>uce</td>
<td>130</td>
<td>0.7</td>
<td>0.6</td>
<td>0.02</td>
<td>0.3</td>
<td>0.4</td>
<td>1.0</td>
<td>2.9</td>
</tr>
<tr>
<td>vol</td>
<td>212</td>
<td>0.9</td>
<td>0.3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>int</td>
<td>212</td>
<td>2.0</td>
<td>1.5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>rds</td>
<td>212</td>
<td>1.2</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>yrs</td>
<td>212</td>
<td>4.0</td>
<td>2.9</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>cov</td>
<td>212</td>
<td>82.4</td>
<td>14.1</td>
<td>38</td>
<td>73.2</td>
<td>85</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>sch</td>
<td>212</td>
<td>0.2</td>
<td>0.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>pop</td>
<td>212</td>
<td>314,687.6</td>
<td>596,443.9</td>
<td>500</td>
<td>38,059</td>
<td>116,815.5</td>
<td>272,868</td>
<td>3,991,392</td>
</tr>
<tr>
<td>den</td>
<td>212</td>
<td>637.7</td>
<td>2,171.0</td>
<td>10.0</td>
<td>67.0</td>
<td>134.0</td>
<td>314.0</td>
<td>14,897.0</td>
</tr>
<tr>
<td>nat</td>
<td>212</td>
<td>0.2</td>
<td>0.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>gdp</td>
<td>212</td>
<td>739.4</td>
<td>624.8</td>
<td>138.5</td>
<td>359.6</td>
<td>466.4</td>
<td>810.0</td>
<td>3,737.7</td>
</tr>
<tr>
<td>dis</td>
<td>172</td>
<td>255.9</td>
<td>1,426.7</td>
<td>0</td>
<td>0</td>
<td>102</td>
<td>177.5</td>
<td>16,277</td>
</tr>
</tbody>
</table>

\(^{1}\) Where: ucf is financial unit cost in 2015 US$, not reported in all studies; uce is economic unit cost in 2015 US$, not reported in all studies; vol is the volunteer dummy for use of volunteers (not costed); int is the number of diseases for which delivery is integrated; rds is the number of rounds per year; yrs is the number of years of programme implementation; cov is the percentage coverage achieved; sch is the school-based dummy for treatment of school children only; pop is the total number of people treated; den is population density per km\(^2\); gdp is GDP per capita (2015 US$); den is population density (people per km\(^2\)); dis is the distance in km from the study site to the nearest city of >100 000 inhabitants, only for those studies that were not national.

Most studies are from low-income settings with 90% of observations from studies reporting the use of volunteers and 20% are from studies of school-based programmes. The average (median) observation is 116 816 people treated for 2 diseases over one round in the 3\(^{rd}\) year of programme implementation. Median coverage was 85% overall, which was the same for the school-based programmes subset. Median population density was 134 people per km\(^2\); among the subset of subnational sites, the average population density was slightly higher (142 people per km\(^2\)). Subnational sites were located an average (median) of 102 km from the nearest city of >100 000 inhabitants.

Figure 2 plots financial unit costs against populations treated, with each color representing a different study. The lines show the log-log within-study relationship between unit costs and population treated.
Similarly, Figure 3 shows the log-log within-study relationship between economic unit costs and population treated.
There are a number of clear outliers. Three studies stand out for their low estimates of cost, describing fewer cost categories than the others.[8][9][10] To the random effects regression model, we add dummy variables for these three studies. One study stands out for its high estimate of cost. In Tafea province (Vanuatu), the financial cost of TCT of 41 509 people distributed over five remote islands with very weak health and road infrastructure was about than 2015 US$ 8.47 per person.[11] To both the random and fixed effects regression models, we add a dummy variable for Vanuatu, a small island developing state (SIDS).

**Predictors of unit cost**

Regression model results for unit costs in 2015 US$ are presented in Table 3.
Table 3. Results from meta-regression of (log) unit costs in 2015 US$. Refer to Table 2 or Methods for a brief description of the variables. Additionally, VUT is a dummy for Vanuatu. Fri, Kri and Mon are dummies for three studies with incomplete cost categories. [8][9][10] Colons (:) indicate interaction terms.

<table>
<thead>
<tr>
<th>Dependent variable:</th>
<th>(1)</th>
<th>(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>log(ucb)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eco</td>
<td>0.157 (0.122)</td>
<td>0.178 (0.124)</td>
</tr>
<tr>
<td>vol</td>
<td>-1.348*** (0.288)</td>
<td>-0.830* (0.436)</td>
</tr>
<tr>
<td>log(int)</td>
<td>-0.170 (0.306)</td>
<td>-0.544 (0.630)</td>
</tr>
<tr>
<td>log(rds)</td>
<td>-0.260** (0.130)</td>
<td>-0.222* (0.125)</td>
</tr>
<tr>
<td>yrs</td>
<td>-0.007 (0.020)</td>
<td>-0.003 (0.022)</td>
</tr>
<tr>
<td>cov</td>
<td>-0.007** (0.003)</td>
<td>-0.008** (0.003)</td>
</tr>
<tr>
<td>nat</td>
<td>3.667* (2.097)</td>
<td></td>
</tr>
<tr>
<td>sch</td>
<td>2.266*** (0.563)</td>
<td>2.121*** (0.538)</td>
</tr>
<tr>
<td>log(pop)</td>
<td>-0.527*** (0.037)</td>
<td>-0.545*** (0.036)</td>
</tr>
<tr>
<td>log(den)</td>
<td>0.080** (0.041)</td>
<td>0.082* (0.042)</td>
</tr>
<tr>
<td>log(gdp)</td>
<td>0.738*** (0.162)</td>
<td>0.880*** (0.170)</td>
</tr>
<tr>
<td>VUT</td>
<td>1.787*** (0.612)</td>
<td>1.921*** (0.586)</td>
</tr>
<tr>
<td>Kri</td>
<td>-2.285** (1.038)</td>
<td>-1.641 (1.460)</td>
</tr>
<tr>
<td>Fri</td>
<td>-2.322** (1.076)</td>
<td>-2.174 (1.475)</td>
</tr>
<tr>
<td>Mon</td>
<td>-2.616** (1.115)</td>
<td>-2.860* (1.513)</td>
</tr>
<tr>
<td>sqrt(dis)</td>
<td></td>
<td>0.003 (0.005)</td>
</tr>
<tr>
<td>eco:log(int)</td>
<td>0.348*** (0.105)</td>
<td>0.339*** (0.103)</td>
</tr>
<tr>
<td>cov:nat</td>
<td>0.016 (0.014)</td>
<td></td>
</tr>
<tr>
<td>eco:sch</td>
<td>0.776*** (0.224)</td>
<td>0.765*** (0.237)</td>
</tr>
<tr>
<td>cov:sch</td>
<td>-0.025*** (0.007)</td>
<td>-0.019*** (0.007)</td>
</tr>
<tr>
<td>nat:log(pop)</td>
<td>0.041 (0.105)</td>
<td></td>
</tr>
<tr>
<td>nat:log(den)</td>
<td>-0.640*** (0.190)</td>
<td></td>
</tr>
<tr>
<td>nat:log(gdp)</td>
<td>-0.291 (0.247)</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>1.134 (1.179)</td>
<td>-0.140 (1.325)</td>
</tr>
</tbody>
</table>

| Observations         | 280 | 232 |
| R²                   | 0.665 | 0.677 |
| Adjusted R²          | 0.610 | 0.622 |
| F Statistic          | 23.127*** (df = 22; 257) | 24.760*** (df = 18; 213) |

Note: *p<0.1; **p<0.05; ***p<0.01

There is a significant and strongly negative association between unit costs and the number of people treated, confirming the expectation of important economies of scale. Similarly, an increase in the number of rounds per year is also associated with a significantly lower unit cost per person treated per round, suggesting that fixed (annual) costs can be shared across rounds too. Use of volunteers is associated with significantly lower unit costs, both financial and economic (including the cost of Ministry of Health staff time and assets but excluding the economic cost of volunteer time).
Population density (meant to capture logistical ease of access) is negatively associated with unit costs among national programmes, but positively associated with unit costs among subnational programmes. Among these subnational sites, distance from the nearest city (meant to capture logistical difficulty) does not turn out to be associated with unit costs. Integrated delivery of medicines is not associated with higher financial unit costs, but is associated with higher economic unit costs, suggesting that there may be some coordination costs related to integration.

Overall, unit costs are higher in national programmes, implying some diseconomies of scale as geographic coverage moves from subnational sites to national programmes covering more diverse settings. However, among subnational sites, the association between unit costs and programme coverage is negative, especially in the case of school-based programmes. School-based programmes are associated with higher unit costs after controlling for coverage and the use of volunteers; all school-based programmes benefited from high coverage (enrolment) and use of volunteers.

GDP per capita is positively associated with unit cost, capturing (at least in part) the quality and complexity of inputs. The number of years of programme implementation (meant to capture any learning-by-doing effects) is not significantly associated with unit cost, but the (negative) sign of the coefficient is as expected. Unit costs are very much higher in Vanuatu, possibly reflecting the higher cost of implementation in a SIDS, and very much lower in the three studies which we deemed to be incomplete in terms of cost categories.

Since the distance variable (subnational data) is not statistically significant, we proceed in what follows with random effects Model 1 (based on the full set of data). The $R^2$ statistic suggests that it explains about two thirds of the variation in unit costs reported in the literature. Transforming unit costs into PPP dollars does not much improve the explanatory power of the model. We therefore remained with the arguably more easily and widely understood estimates based on unit costs in US$. Results in PPP dollars are nonetheless presented with the fixed effects model results in the Supplemental Information (Table S4).

**Unit cost benchmarks**

Benchmarks for the financial unit cost in US$ are depicted in Figure 4 for all low and middle income countries, at three different scales of implementation. For programmes treating 100 000 people or more, the financial unit cost benchmark is less than US$ 0.50 for the vast majority of countries. However, the benchmark can exceed US$ 2.00 for programmes operating at a scale of about 10 000 people.
Figure 4. Financial unit cost benchmarks in low- and middle-income countries at different scales of implementation, using volunteers but excluding the (economic) cost of volunteer time. Excluding Vanuatu, which distorts the legend; see Table S5 in the Supplemental Information for results for Vanuatu.

Similarly, benchmarks for the economic unit cost in US$ are depicted in Figure 5. For programmes treating 100 000 people or more, the economic unit cost benchmark is less than US$ 1.00 for the vast majority of countries. However, the benchmark can exceed US$ 10.00 for programmes operating at a scale of about 10 000 people.
Figure 5. Economic unit cost benchmarks in low- and middle-income countries at different scales of implementation, not using volunteers. Excluding Vanuatu, which distorts the legend; see Table S5 in the Supplemental Information for results for Vanuatu.

Benchmarks for both financial and economic unit costs are presented in data tables with 95% confidence intervals in the Supplemental Information (Table S5). These regression results were used to create a web-based software application available at [https://healthy.shinyapps.io/benchmark](https://healthy.shinyapps.io/benchmark). Users can enter setting-specific parameter values to arrive at a benchmark unit cost for their setting. These benchmarks can be compared by researchers to individual unit cost estimates extracted from the studies. A guide to using the application can be found in Supplemental Information available within the application at the abovementioned link.
All unit cost benchmarks reported by the web-based application exclude the opportunity cost of volunteer time. However, one can choose to assume that volunteers are not used for the mass treatment campaigns, in which case the unit cost benchmarks are estimated as though all labor inputs are paid at their respective wages. This is true whether one chooses the random effects or the fixed effects model.

**Discussion**

This study provides the most up-to-date review of the literature on the cost of mass treatment for the control and elimination of six selected NTDs for which mass treatment is recommended by WHO. For the first time, the evidence has been standardized and synthesized in a meta-regression of the cost per person treated per round, controlling for differences between settings. We find that unit costs are very sensitive to economies of scale, and the decision of whether or not to use volunteers. Financial unit costs are expected to be less than 2015 US$ 0.50 in most countries with programmes that treat 100 thousand people or more. However, for smaller programmes, including those in the “last mile”, or those that cannot rely on volunteers, financial unit costs may be considerably higher.

Some of the regression results are surprising. Among subnational project sites, we do not find the expected significant positive association between unit cost and coverage nor between unit costs and population density or distance from the nearest city. These surprising results warrant further investigation; there may be better measures of logistical ease/difficulty of access.

This study then uses the meta-regression results to predict unit costs across a large number of different possible settings. One of the advantages of this approach over taking a simple arithmetic average across (subsets of) the available data is that it also gives robust confidence intervals. The confidence intervals can be used in economic evaluations, including cost-effectiveness analyses looking to generalize results across settings. Predicted values are not meant to be used as substitutes for detailed planning and budgeting. However, confidence intervals can be used to assess value for money in programme plans, budgets and accounts, or help set a reasonable pay-out for results-based financing mechanisms.

The approach can be used for other outreach interventions, beyond health care facilities, that may gain in importance in the context of universal health coverage. Indeed, our benchmarks may be relevant for intermittent preventive treatment (IPT) against malaria. IPT involves a full course of an anti-malarial treatment in areas of seasonal transmission, regardless of individual infection. In Ghana, the economic cost was at least US$ 2.35 (2008) per month of intervention for a group of 613 children that received IPT.[12]

In future, unit costs of mass treatment against NTDs could be benchmarked against the unit cost of other mass interventions. A review of the cost of vitamin A supplementation suggests that unit costs can vary by a factor of more than 1000 and are several-fold higher than has traditionally been maintained.[13] Our benchmarks are unlikely to be of relevance to mass immunization campaigns requiring a costly cold chain. However, they could give an indication of cost savings associated with the integration of mass treatment against NTDs within existing immunization campaigns.[14]

There are a few caveats. For one, confidence and prediction intervals are wide and even so do not fully reflect true uncertainty. While there are a good number of studies available, they do not cover as many countries. Most report only financial costs, excluding the cost of Ministry of Health resources (buildings and staff), for example, and therefore fail to estimate the full costs to the health system. Many appear to be from peri-urban areas rather than from
in which most of the population requiring treatment is found or indeed from the remotest areas where one would expect unit costs to be highest.

Another limitation is that while most programmes used volunteers, few studies considered the economic cost of their time. We controlled for the use of volunteers in the regression model and estimate that, all other things equal, the financial cost more than doubles in going from volunteers to paid health workers. Unfortunately, the use of unpaid volunteers may not be scalable: “fully-scaled NTD control programmes covering over a billion people cannot expect to recruit and retain sufficient numbers of volunteers if other major disease programmes are offering incentives.”[1]

Furthermore, while the focus continues to shift from control to elimination, most of the available costing studies are of control programmes. Of the 34 studies identified in our review, only 8 referred explicitly to eradication (yaws) or elimination (LF, onchocerciasis) as a programme objective.[1][15][16][17][18][19][20][21] Only one of those directly compared the costs of control and elimination strategies (for onchocerciasis), involving annual and biannual (twice yearly) mass treatment respectively; the difference is determined by the number of rounds rather than by so-called “last mile” costs .[21]

No study has been conducted in a country where eradication or elimination has actually been achieved. Egypt stopped PC and started post-PC surveillance for LF in 2014, but the available costs are from 2000-2001. Challenges to elimination posed by the parasite Loa loa, that can cause fatal side-effects upon treatment, have not been factored into any of the available costing studies of LF, and into only one country from one study of onchocerciasis.[3]

Finally, most of the available costing studies consider the early years of programme implementation. Some considered the cost of planning and mapping in these early years, but few considered longer-term monitoring and evaluation. A micro-costing study based on other sources (and therefore excluded from the meta-regression) estimates that the financial unit cost per treatment would increase two times towards the later phases of elimination of onchocerciasis in Africa.[22] This increase is driven by the reduction in the number of people in need of treatment and steady or increasing costs for surveillance.

Klepac et al (2015) provide a good summary of why the distinction between the “middle game” and the “endgame” matters.[23] First, the endgame is associated with higher unit costs; the last foci of infection or pockets of susceptibility will be those that are hardest to reach, either geographically or socially (e.g. treatment refusers). Second, the endgame may present fewer opportunities for cost-sharing across interventions; while elimination can and should continue to be delivered by strong health systems, frequency and timing become less flexible in the end-game.

The duration and total cost of the endgame is likely to be a function of: “ the underlying biology of the pathogen, the demography of the host(s), the connectedness of affected populations, the speed of roll out of control measures, their efficacy and the capacity for sustained effort, likely to be itself shaped by political agendas and financing.”[24] A prolonged and expensive endgame can lead to funder fatigue and motivate a (premature) switch in strategy from, for example, mass treatment to targeted treatment in remaining foci of infection or high-risk locations or populations.

While our review of the literature, published and grey, was thorough, more could be done to identify more studies, such as: looking at more databases and considering other languages spoken in a small number of endemic countries, namely Arabic, Chinese and Portuguese. In future, country and technical expert groups could be convened to reconsider the data and
approach used, similar to benchmarking work undertaken for the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Other refinements to this study might include benchmarks for the cost of post-mass treatment mop-up, known more formally in the trachoma and yaws literature as “enhanced coverage” and “total targeted treatment”, respectively, in which communities are visited a second time to treat only those not treated on the first visit.[11][25] More evidence is needed on the cost of post-mass treatment surveillance, including Transmission Assessment Surveys, and certification of eradication or elimination. Indeed, we are not aware of any studies of the cost of eradication or elimination of diseases (including guinea-worm disease or poliomyelitis) that explicitly included the cost of the certification process.

This comprehensive analysis confirms that mass treatment offers a low cost public health intervention on the path towards universal health coverage. However, more costing studies focused on elimination are needed. The novel web-based platform https://healthy.shinyapps.io/benchmark can be used to determine realistic unit cost benchmarks to assist monitoring value for money in NTD programme plans, budgets and accounts, or in setting a reasonable pay-out for results-based financing mechanisms by Ministries of Health and Finance in low- and middle-income countries.
References for this paper


Supporting Information

Selected Figures and Tables

S1 Table. Pubmed search terms

(filariasis>Title OR onchocerciasis>Title OR schistosomiasis>Title OR helminthiases>Title OR helminthiasis>Title OR helminth>Title OR trachoma>Title OR yaws>Title OR “neglected tropical diseases”>Title OR “neglected diseases”>Title OR “neglected infectious diseases”>Title OR ascariasis>Title OR hookworm>Title OR roundworm>Title OR trichuriasis>Title OR whipworm>Title OR bilharziasis>Title OR “snail fever”>Title OR “river blindness”>Title OR elephantiasis>Title OR “preventive chemotherapy”>Title OR “mass treatment”>Title OR “mass drug administration”>Title OR deworming>Title OR ivermectin>Title OR mectizan>Title OR albendazole>Title OR mebendazole>Title OR praziquantel>Title) AND (economic>Title OR economics>Title OR cost>Title OR costs>Title OR costing>Title OR resource>Title OR price>Title OR expenditure>Title OR spending>Title OR fund>Title OR funds>Title OR funding>Title) AND ("1990"[Date - Publication] : "3000"[Date - Publication])

S3 Table. Studies included in meta-regression


doi:10.1016/j.actatropica.2006.08.008


doi:10.1371/journal.pntd.0001362


### S4 Table. Results from meta-regression using fixed effects model or unit costs in 2015 IS (PPP)

**Dependent variable:**

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<th>log(ucb)</th>
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<td>-0.216* (0.129)</td>
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<td>cov</td>
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<tr>
<td>nat</td>
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<tr>
<td>log(gdp)</td>
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<td>Fri</td>
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<tr>
<td>Mon</td>
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<td>-2.762* (1.603)</td>
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<td>3.316** (1.365)</td>
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<td>-0.007** (0.003)</td>
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<td>2.279 (2.130)</td>
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<td>0.379** (0.168)</td>
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<td>1.635*** (0.609)</td>
<td>1.779*** (0.599)</td>
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<td>4.377*** (1.216)</td>
<td>3.316** (1.365)</td>
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</tbody>
</table>

Observations 280 232 280 232
\( R^2 \) 0.674 0.675 0.642 0.655
Adjusted \( R^2 \) 0.546 0.558 0.589 0.601
F Statistic 24.661*** (df = 19; 28.460*** (df = 14; 20.885*** (df = 22; 22.375*** (df = 18;

Note: *p<0.1; **p<0.05; ***p<0.01

Models 1 and 2 are fixed effects models of unit cost in 2015 US$. Models 3 and 4 are random effects models of unit cost in international dollars (IS), adjusted for purchasing power parity (PPP). Refer to Table 2 or Methods for a brief description of the variables. Additionally, \textit{VUT} is a dummy for Vanuatu. \textit{Fri}, \textit{Kri} and \textit{Mon} are dummies for three studies with incomplete cost categories. [8][9][10] Colons (:) indicated interaction terms.
All files

http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0005037#sec016
Paper 2.1.2 Where the road ends, yaws begins? The cost-effectiveness of eradication versus more roads

Published paper
Available at: http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003165

Authors and Affiliations
Christopher Fitzpatrick a,b, Kingsley Asiedu a, Jean Jannin a
a Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland
b fitzpatrickc@who.int

Abstract
Introduction: A disabling and disfiguring disease that “begins where the road ends”, yaws is targeted by WHO for eradication by the year 2020. The global campaign is not yet financed. To evaluate yaws eradication within the context of the post-2015 development agenda, we perform a somewhat allegorical cost-effectiveness analysis of eradication, comparing it to a counterfactual in which we simply wait for more roads (the end of poverty).
Methods: We use evidence from four yaws eradication pilot sites and other mass treatment campaigns to set benchmarks for the cost of eradication in 12 known endemic countries. We construct a compartmental model of long-term health effects to 2050. Conservatively, we attribute zero cost to the counterfactual and allow for gradual exit of the susceptible (at risk) population by road (poverty reduction). We report mean, 5th and 95th centile estimates to reflect uncertainty about costs and effects.
Results: Our benchmark for the economic cost of yaws eradication is uncertain but not high: US$ 362 (75-1073) million in 12 countries. Eradication would cost US$ 26 (4.2-78) for each year of life lived without disability or disfigurement due to yaws, or US$ 324 (47-936) per disability-adjusted life year (DALY). Excluding drugs, existing staff and assets, the financial cost benchmark is US$ 213 (74-522) million. The real cost of waiting for more roads (poverty reduction) would be 13 (7.3-20) million years of life affected by early-stage yaws and 2.3 (1.1-4.2) million years of life affected by late-stage yaws.
Discussion: Endemic countries need financing to begin implementing and adapting global strategy to local conditions. Donations of drugs and diagnostics could reduce cost to the public sector and catalyze financing. Resources may be harnessed from the extractive industries. Yaws eradication should be seen as complementary to universal health coverage and shared prosperity on the post-2015 development agenda.

Author Summary
A disabling and disfiguring disease that “begins where the road ends” (among poor and isolated communities), yaws is targeted by WHO for eradication by the year 2020. The global
campaign is not yet financed. We provide benchmarks for the cost and health effects of global yaws eradication, based on evidence from four yaws eradication pilot sites and other mass treatment campaigns. We suggest that a global yaws eradication campaign could be established with a relatively modest investment in the period 2015–2020; as little as US$ 100 million in the 12 known endemic countries. Eradication would cost about US$ 26 for each additional year of life lived without disability or disfigurement due to yaws between the years 2015 and 2050. The real cost of not doing anything but wait for more roads (the end of poverty) would be about 15 million years of life needlessly affected by disability and disfigurement. We expect that yaws eradication will be cost-effective. Importantly, from the perspective of universal health coverage, it will benefit some of the least well off citizens of the world. Yaws eradication should therefore be seen as complementary to universal health coverage and shared prosperity on the post-2015 development agenda.

Introduction

Yaws is one of two neglected tropical diseases (NTDs) targeted by the World Health Organization (WHO) for eradication. A 2013 World Health Assembly resolution calls for its eradication by the year 2020. A disabling and disfiguring disease that “begins where the road ends” it is found primarily among poor and isolated communities in warm, humid and tropical forest areas of Africa, South-East Asia and the Western Pacific. It is caused by a bacterium (*Treponema pallidum ssp pertenue*) related to syphilis but is not sexually-transmitted and mostly afflicts children. In its primary and secondary (early) stages it causes unsightly and often painful lesions of the skin (especially face and feet), cartilage and bones. About 10% of untreated cases suffer tertiary (late-stage) yaws, with permanent disability and disfigurement of the face, lower limbs and hands. In 1950, WHO estimated that 160 million people were infected with yaws. Between 2008 and 2012 more than 300 000 new cases were reported to WHO. Reporting yaws is not mandatory, however, and so the full burden of the disease is not currently known.

In the field, diagnosis is primarily based on epidemiology and clinical symptoms. Laboratory-based serological tests are widely used to confirm clinical cases. The same tests are used to confirm syphilis but cannot distinguish between the two diseases. Recently, a rapid syphilis test has been demonstrated to be effective in confirming yaws and can be used in the field. There is no vaccine for yaws. Prevention is based on the interruption of transmission through early diagnosis and treatment of individual cases and total (mass) or targeted treatment of affected populations. The epidemiology of the disease, the history of its control and the feasibility of eradication are described in detail elsewhere. WHO’s strategy for yaws eradication is based on single-dose oral treatment with azithromycin at 30 mg/kg (maximum 2 g). Because of the simplicity and convenience, it is now preferred to the traditional treatment with injectable benzathine penicillin.

Transmission has been shown to be interrupted with one or two rounds of treatment at high levels of population coverage and at intervals of up to 6 months. The approach is known as total community treatment (TCT) – treatment of an entire endemic community irrespective of the number of active clinical cases. Total targeted treatment (TTT) – treatment of all active clinical cases and their contacts – is carried out to “mop-up” any cases that were missed in the TCT round, after up to 6 months. The definition of contacts may vary between settings, but normally includes household members and, in the case of school-age children, classmates. Confirmation of clinical cases during TCT (for follow-up TTT) may be carried out using a rapid dual point-of-care treponemal and non-treponemal serological test. “Proof of
concept” pilot projects in Congo (Bétou and Enyellé districts), Papua New Guinea (Lihir island), Vanuatu (Tafea Province) and Ghana (West Akyem district) were successfully concluded in 2012 and 2013.

The tools exist for WHO and its partners to follow the global Guinea worm disease eradication campaign in eradicating another NTD. And yet, the effort is not financed, with no cash or in-kind donations yet received for a global yaws eradication campaign. As with other diseases of poverty, there is a tendency to hope that poverty reduction will resolve the problem. Unfortunately, the history of yaws suggests that a more concerted effort will be required. The dismantling of vertical yaws programs after 1964 led to a resurgence of yaws in the late 1970s, even as poverty rates declined.[1] To evaluate whether yaws eradication is a good investment within the broader post-2015 development agenda, we perform a cost and somewhat allegorical cost-effectiveness analysis of eradication, comparing it to a counterfactual in which we simply wait for more roads (the end of poverty).

**Methods**

In this section we describe the model and parameters for the cost-effectiveness analysis. We use evidence from four yaws eradication pilot sites and other mass treatment campaigns to set benchmarks for the cost of an eradication campaign in 12 known endemic countries in 2015-2020. Conservatively, we assign zero cost to the counterfactual of waiting for more roads (the end of poverty). We develop a compartmental (Markov) model of primary, secondary and tertiary stage infection for the period 2015-2050. We incorporate gradual exit of the susceptible (at risk) population by road (poverty reduction). Given considerable uncertainty about most of the model parameters, we perform probabilistic sensitivity analysis (Monte Carlo simulation) using RStudio version 0.98.507 for R version 3.0.2.[12][13]

The discount rate on costs is 3-6% per year (uniform distribution); the discount rate on health effects is 0-3% per year.[14] Best, low and high estimates correspond to the mean, 5th and 95th centile values from 1000 simulations.

**Population at risk**

A review of the literature from 1950 to 2013 indicates that at least 85 countries have reported yaws.[1] Ecuador and India reported interruption of transmission of the disease in 2003 and 2006 respectively. 12 countries currently reporting cases to WHO require technical assistance and financing: Benin, Cameroon, Central African Republic, Congo, Cote d'Ivoire, Democratic Republic of the Congo (DRC), Ghana, Indonesia, Papua New Guinea, Solomon Islands, Togo and Vanuatu. In 71 countries where no recent data are available, the absence of the disease needs to be verified.

Expert opinion puts the population at risk for yaws at a minimum of 5 percent of the populations of ten of the twelve known endemic countries.[15] The exceptions are the small island states of Solomon Islands and Vanuatu, where 100 percent of the population is assumed at risk.[16] For an upper bound on population at risk we employ data from the G-Econ 4.0 (May 2011) database.[17] G-Econ provides demographic and geophysical data for one-degree longitude by one-degree latitude cells – approximately 100 km by 100 km or the same size as most second administrative level boundaries. We summed the populations living in cells satisfying the following conditions favorable to the transmission of yaws: 1) average precipitation (mm per year) > 500; 2) average annual temperature (degrees Celsius) > 20; 3) tropical forest or woodland; and 4) population density per km² < 100.[18] We adjusted the reported 2005 populations to 2015 using rural population projections.[16]
In addition to demographic and geophysical data, G-Econ contains estimates of Gross Domestic Product (GDP) at the level of cells. We use Gross Cell Product (GCP) in the results section of this paper to assess the economic productivity of the lands on which populations at risk for yaws live and establish a threshold by which to assess cost-effectiveness.

**Cost of drugs and diagnostics**

To kick-start the pilot project, WHO procured limited quantities of generic azithromycin (Medopharm, India) at US$ 0.17 per 500 mg tablet. We used population data disaggregated by age to estimate dosage: 0-4 years (500 mg), 5-9 years (1000 mg), 10-14 years (1500 mg) and 15 years and older (2000 mg).[16] Based on experience from the pilot sites, TTT may be required. The number of index cases requiring mop-up is determined by the coverage, eligibility and cure rates in the model of health effects (described below). For the purposes of the cost benchmarks, we assumed based on experience in India that mop-up reaches the active index case plus 10-20 close contacts that include the secondary cases. For the purposes of detailed planning and budgeting, local evidence will be needed. We assume that a 10% buffer stock is required.

For the pilot, WHO also procured rapid dual non-treponemal and treponemal point-of-care serological tests (Chembio Diagnostic System Inc., New York, USA) at a negotiated price of US$ 2-2.50 per test. The number of clinical cases that may be serologically tested during TCT and TTT is determined by the model of health effects (below), with an allowance for clinical misdiagnosis of yaws-like lesions that increases the total number of tests by 10-30%. We have not estimated the cost of more expensive molecular tests (polymerase chain reaction) to monitor for drug resistance or to confirm eradication. We assume that surveillance (below) is clinical surveillance and we do not include costs for any additional tests.

**Cost of delivery**

Experience from the pilot sites suggests that the cost of delivery will vary considerably across endemic countries. In some pilot sites, the cost per person was relatively low. On the island of Lihir (Papua New Guinea), the financial cost of TCT of 16 941 people was about US$ 25 800 or US$ 1.52 per person. (personal communication with Oriol Mitja) This first round was completed in 40 days. Human resources included community and public health workers, a program coordinator, a nurse, a laboratory technician (half-time) and a driver. Six months later, the financial cost of TTT was US$ 11 400 or US$ 0.71 per person. Mop-up was completed in only 14 days because there was no serological testing and because fewer drugs were administered. In Ghana, the cost of TCT was even lower, but the program depended heavily on the contribution of volunteers.(personal communication with Abdul Aziz Abdulai)

In other sites, the cost per person treated was relatively high. In Tafea province (Vanuatu), the financial cost of TCT of 41 509 people distributed over five remote islands with very weak health and road infrastructure was about US$ 265 300 or US$ 6.39 per person.(personal communication with Jacob Kool) This amount included upfront investment in communication-for-behavioral-impact (COMBI). COMBI is thought to have improved acceptance rates and general hygiene and thereby reduced the need for a mop-up round. Likewise in the remote Bétou and Enyellé districts of the Congo, upfront equipment costs pushed unit costs into the high single digits. The team offered a mobile clinic and measles vaccination (requiring a costly cold-chain).(personal communication with Matthew Coldiron).

We did not assume that unit costs from the pilot sites were generalizable to other settings. In order to better understand the drivers of costs across settings, we reviewed the rather more expansive literature on the cost of mass drug administration (MDA) to control and eliminate
other NTDs: lymphatic filariasis (LF), schistosomiasis, soil-transmitted helminthiasis (STH), onchocerciasis and trachoma. The 25 identified studies are referenced in the Supporting Information (Table S1). We extracted both financial (F) and economic (E) costs: planning, mapping and training activities (F&E), drug shipment (F&E), vehicles that were rented (F&E) or borrowed from other programs (E), fuel and vehicle maintenance (F&E), per diems (F&E), project staff salaries (F&E), Ministry of Health staff time (E), office space (E), utilities (F&E) and supplies (F&E). We removed drugs from the cost of delivery. Capital cost annualization and overhead cost allocation were retained from the individual studies. We did not consider the cost of volunteer time because most studies did not report it. We extracted also the number of people treated and GDP per capita.

We converted unit costs to constant 2012 US$ and ran multivariate regressions on the number of people treated to capture economies of scale, on GDP per capita (constant 2012 US$) to capture differences in the quality and complexity of inputs, and on population density to capture differences in logistical difficulty. We opted for study/site fixed effects and a log-log specification. Regression results based on 103 observations from 57 study-countries are available in Supporting Information (Table S2). These results were used to generate country-specific benchmarks for the economic unit cost of TCT. With the mean and standard error of the log prediction, we simulated and re-transformed 1000 values and extracted the mean, 5th and 95th centile values for the best estimate and 90% credible interval (CI).

We used the same approach to generate benchmarks for the financial unit cost, using studies with financial cost estimates. In our review, financial costs were on average 66% (interquartile range 28-86%) of economic costs. Both economic and financial unit cost benchmarks are available in the Supporting Information (Table S3). All costs in this paper refer to economic costs, unless otherwise specified.

We assumed, based on experience from Lihir, that the cost of the TTT mop-up (if required) would be 30-50% of the cost of TCT. This assumption will be revisited as evidence comes in from other sites.

**Cost of surveillance**

We reviewed the literature from similar programs to estimate the cost of surveillance following TCT and TTT. The (economic) cost of prevalence surveys for trachoma was about US$ 1600-28 000 per district of 100 000-250 000 inhabitants in 2013 prices.[19] Only 6% of this cost was for supplies. In probabilistic sensitivity analysis, we assumed surveillance costs of US$ 2000-30 000 per 100 000 population at risk. We assumed clinical surveillance and did not include costs for any additional tests (see cost of diagnostics, above). Surveillance is one of the aspects of yaws eradication that may require the most adaptation to local conditions. Yaws elimination in India and Guinea worm disease elimination in most countries used rumor investigation, including cash rewards of between US$ 10-1000 for the reporting of (subsequently confirmed) cases. In India, the cost of rewards was small relative to that of serological surveys.

**Health effects**

Our compartmental (Markov) model is depicted in Figure 1. The population at risk moves to or through one of five possible states: primary, secondary, latent and tertiary yaws, or death (the terminal state). Ours is not the first compartmental model of yaws transmission.[20] But it is the first to distinguish between the stages of infection, and the first used in a cost-effectiveness analysis.
Figure 1. Compartmental (Markov) model of primary, secondary/latent and tertiary yaws. See Table 1 for sources and comments related to the epidemiological parameters E1-E8. The eradication scenario and counterfactual are differentiated by the programmatic parameters P1-P3, also in Table 1, which allow for cure and return by primary and secondary/latent cases to the susceptible (at risk) population.

Start values for the model are based on the maximum number of new cases reported in any given year 2008-2012.[21] We assumed conservatively that reported cases represented 30-90% of true incident cases. Based on experience with Buruli ulcer, another NTD affecting skin in poor and isolated populations, the number may be as low as 7% in the Democratic Republic of Congo and 18% in Cameroon.[22][23] Transition probabilities from one state to another are determined by epidemiological parameters, with distributions for probabilistic sensitivity analysis (Table 1). We converted rates and durations into probabilities. We converted all probabilities in half-year (6-month) cycle probabilities, based on the periodicity of TCT and TTT.
Table 1. Epidemiological and programmatic parameters for the compartmental model.
See Figure 1 for a graphical representation of the model.

<table>
<thead>
<tr>
<th>Min</th>
<th>Max</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic reproduction number ($R_0$)</td>
<td>0.9</td>
<td>0.999</td>
</tr>
<tr>
<td>Generation time (years)</td>
<td>0.08</td>
<td>5</td>
</tr>
<tr>
<td>Annual exit rate of the susceptible (at risk) population (annual reduction in $R_0$)</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Adult mortality of the susceptible and infected population, as a proportion of the adult mortality rate of the general population (probability of dying between 15 to 60 years)</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Duration of primary stage before onset of secondary/latent stage (years), without treatment</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Probability of progression from secondary to tertiary stage, without treatment</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Duration of primary and secondary yaws before onset of tertiary yaws (years), without treatment</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Ratio of latent to non-latent among secondary yaws cases</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

| Coverage (TCT round) | 90% | 99% | This is based on experience in the pilot sites.[15] Coverage in TTT rounds is assumed to be 100% of index cases and their close contacts. |
| Eligibility for treatment (TCT round) | 98% | 99% | This is based on age-disaggregated population data.[16] Infants under 6 months of age are ineligible for treatment with azithromycin. Eligibility in TTT rounds is assumed to be 100%. |
| Cure rate | Normal distribution; see Comment. | Mean=85.5% and standard deviation=0.031. Based on primary endpoint (cure at 6 months) of the intention-to-treat population from a randomized controlled trial in Papua New Guinea.[30] |

For both the eradication scenario and counterfactual, we made an optimistic assumption that the susceptible (at risk) population and, by extension, the basic reproduction number will decrease 2-7% per year, as a result of more roads (poverty reduction). These are the 50th and 75th centile values for the average annual rate of decline in the dollar-a-day poverty headcount of 98 developing countries over 1999-2013.[16][24] These correspond roughly to the values for India and China, respectively. This is an optimistic assumption resulting in a conservative estimate of cost-effectiveness.

The eradication scenario has additional, programmatic assumptions related to coverage, eligibility (for treatment) and cure rates (Table 1). Covered, eligible and cured individuals in the primary and secondary states return to the susceptible population. Tertiary yaws is
irreversible. The model assumes that TTT will treat all index cases and their contacts — this is a simplification but has no major effect on the model. The model has not been constructed to prove the feasibility of eradication, as this has already been done in the field. Future refinements of the model could, however, help identify the conditions under which it is more cost-effective to follow TCT with another round of TCT rather than TTT.

We allowed the model to burn in over a period of 10 years, the maximum duration of progression to tertiary disease. The model was run to the year 2050 to capture some of the longer-term benefits of eradication. In reality the benefits of eradication could extend well beyond 2050. We summed the number of (discounted) life-years spent in the primary and secondary (early-stage) and tertiary (late-stage) states, and compared the eradication scenario results to those of the counterfactual.

There are no specific disability weights for early or late-stage yaws. We calculated disability-adjusted life-years (DALYs) using weights for comparable conditions.[25] We used 0.029 (0.016–0.048) for early stage yaws based on disfigurement level 1 with itch or pain, described as: “a slight, visible physical deformity that is sometimes sore or itchy. Others notice the deformity, which causes some worry and discomfort.” This range contains an earlier point estimate of 0.048 for secondary syphilis.[26] We used 0.398 (95% CI 0.271–0.543) for late-stage yaws based on disfigurement level 3, described as: “an obvious physical deformity that makes others uncomfortable, which causes the person to avoid social contact, feel worried, sleep poorly, and think about suicide.” This range contains an earlier point estimate of 0.283 for tertiary syphilis.

Our analysis does not take into account the potential knock-on benefits of total community treatment with azithromycin for trachoma, chancroid, chlamydia, syphilis, gastrointestinal and respiratory tract infections or malaria, nor of any of the other health services delivered during the campaigns. Reductions in child-mortality have been associated with mass administration of azithromycin for trachoma, but awaits confirmation by a randomized controlled trial.[27] In Vanuatu, the pilot sites saw a dramatic decrease in the number of diarrheal cases and all-cause hospitalizations.(personal communication, Jacob Kool)

**Results**

**Population at risk**

Expert opinion puts the minimum population at risk for yaws in the 12 known endemic countries in 2015 at 21 million. Using G-Econ data, we calculate that as many as 74 million people live under conditions favorable to yaws infection, as mapped by Figure 2. The upper bound on the range of estimates produced for Indonesia comes close to that obtained in a recent, more detailed exercise by the national program.
Figure 2. Geographic distribution of the estimated population at risk in 12 known endemic countries. The legend gives the quintile values for the population at risk living within one-degree latitude by one-degree longitude cells (approximately 100 km by 100 km). Map credit: NASA Goddard Space Flight Center Image by Reto Stöckli (land surface, shallow water, clouds). Available at http://visibleearth.nasa.gov/view.php?id=57752.

Extending this analysis to the 71 countries where cases are known to have occurred historically, we estimate that the population in need of verification of the absence of the disease is 210 million. In what follows, we calculate only the cost of surveillance for this population.

**Costs**

Including buffer stock and mop-up, 75 (60–92) million grams of azithromycin are estimated to be required during 2015–2020. At US$ 0.17 per 500 mg tablet, the cost would be US$ 28 (22–34) million. The number of serology tests required for confirmation of clinical cases in the 12 endemic countries is estimated at 0.4 (0.2-0.5) million, at a cost of US$ 0.7 (0.4-1.1) million.

Best estimates from the regression models of the economic unit cost of delivery suggest a range, depending on the country, of US$ 0.20–10.41 per person. See Supporting Information for country-specific economic and financial unit cost benchmarks. The economic cost benchmarks imply that delivery would cost US$ 314 (31–1009) million. The financial cost would be lower. Both economic and financial cost benchmarks are reported in Table 2.
Table 2. Cost benchmarks for the 12 countries of known endemcity. Best estimates with 5th and 95th centiles, 2015 US$ millions; see Supporting Information for the studies and regression models used to estimate economic and financial unit costs; the difference between economic and financial costs is explained in the methods.

<table>
<thead>
<tr>
<th></th>
<th>Economic</th>
<th>Financial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Best</td>
<td>Low</td>
</tr>
<tr>
<td>Drugs</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>Diagnostics</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Delivery</td>
<td>314</td>
<td>31</td>
</tr>
<tr>
<td>Clinical surveillance</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>362</td>
<td>75</td>
</tr>
<tr>
<td>Total (excl. drugs)</td>
<td>334</td>
<td>48</td>
</tr>
</tbody>
</table>

Two to three years of clinical surveillance in the 12 known endemic countries adds about US$ 18 (11-29) million. The total economic cost benchmark is therefore US$ 362 (75-1073) million. Excluding drugs, the economic cost benchmark is US$ 334 (48-1038) million. The benchmark cost of clinical surveillance in the 71 countries requiring verification of the absence of the disease is about US$ 33 (7.5-59) million.

Health effects

In the absence of an eradication campaign in the 12 known endemic countries, the number of years of life lived with early-stage yaws would be 13 (7.5-21) million in the period 2015-2050. The credible intervals are large, reflecting our conservative choice of parameter distributions.

The number of years of life lived with late-stage yaws would be 3.0 (1.5-5.4) million. Early and late stages together amount to 16 (9.4-26) million years of life lived with yaws symptoms and 1.6 (0.8-2.9) million DALYs.

Given that tertiary yaws is irreversible, eradication would avert most but not all of this burden. It would leave 1.0 (0.6-1.7) million years of life lived with yaws symptoms and 0.3 (0.1-0.5) million DALYs.

Due to the eradication campaign, 13 (7.3-20) million years of life would be lived without early-stage yaws and 2.3 (1.1-4.2) million years of life without late-stage yaws. 1.3 (0.6-2.4) million DALYs would be averted.

Cost-effectiveness

The total economic cost per year of life lived without yaws symptoms is estimated at US$ 26 (4.2-78) for the 12 known endemic countries. There are no established thresholds for the acceptability of the cost per year of life lived without yaws symptoms, but Figure 5 shows that the probability of acceptability would exceed 50% at a threshold of US$ 11.35 and 90% at US$ 46.
Figure 5. Cost per year of life that could be lived without yaws symptoms: cost-effectiveness acceptability curve. Cost per year of life lived without yaws symptoms due to the eradication campaign. Symptoms include those of primary, secondary (excluding latent) or tertiary yaws. The x-axis gives a range of possible thresholds for the acceptability of the cost per year of life lived without yaws symptoms (in US$). The y-axis gives the probability that the model is consistent with yaws eradication being cost-effective at a given threshold.

The cost per DALY averted is US$ 324 (47-936). The interval is large, but well below WHO thresholds for cost-effectiveness of three times GDP per capita.[28] We estimate GCP per capita of US$ 733 (2005 US$) for the 74 million people living under conditions favorable to yaws infection, and GDP per capita of US$ 799 for the 12 known endemic countries as a whole. Even under the most conservative assumptions, yaws eradication is cost-effective.

Affordability

Populations at risk for yaws are poor, but the areas in which they live are economically productive. G-Econ data suggest a GCP of US$ 37 400 per square kilometer (2005 US$) and US$ 51 billion in total, or 17% of GDP in the 12 known endemic countries. The best estimate of the cost of eradication represents less than 0.5% of GCP and less than 0.1% of GDP. It would appear to be affordable from the perspective of the economy as a whole.

Recall also the difference between economic and financial costs. In practice, many costs will be covered by existing Ministry of Health staff and assets such as vehicles. Excluding drugs and Ministry of Health staff and assets, the financial cost of yaws eradication could be as little as US$ 213 (74-522) million in the 12 endemic countries.

Discussion

This paper provides the first economic evaluation of yaws eradication. It is largely prospective and, as a consequence, conclusions are limited by our uncertainty about many parameters, for both costs and effects. Most but not all of this uncertainty was reflected in a probabilistic sensitivity analysis. The number and distribution of people at risk for yaws needs
to be better mapped, to better model health effects, certainly, but also costs. Uncertainty around populations at risk is not fully reflected in the regression model estimates of the unit cost of delivery. In the case of DRC, for example, we may have overestimated economies of scale and underestimated logistical difficulty. The cost benchmarks presented in this study are certainly not a substitute for country plans and budgets. Recall that we have not included the cost of molecular tests to confirm eradication, though this may only need to start once clinical cases are no longer being found.

There is also uncertainty about the 71 countries of unknown endemicity. While we have included the cost of clinical surveillance in these countries, we have not included the cost of serological and molecular tests, much less the cost of TCT, which might be incurred if clinical yaws cases are identified in any one of them. Given that some of these countries share borders with the 12 countries of known endemicity, cross-border issues will incur, at the very least, some coordination costs. That said, we have also not included the health benefits that would accrue in these 71 countries, so the influence that their inclusion would have on the cost-effectiveness result is ambiguous.

The cost of the “end game” of any eradication effort is uncertain, with the emergence of complexities requiring some local adaptation of global strategies.[29] Much of the uncertainty will be resolved as endemic countries begin or, in the case of the pilot sites, continue to implement the program. Nonetheless, there are good reasons to believe that a global yaws eradication campaign could be established with a relatively modest investment in the period 2015-2020 – about US$ 100-500 million in the 12 endemic countries. The real cost of waiting for more roads (the end of poverty) would be millions of years of life lived with disability and disfigurement due to yaws. Yaws eradication appears to be very cost-effective under reasonable assumptions about its cost and effects, and even under optimistic scenarios of poverty reduction.

The main question that remains is how to finance the next phase of implementation. The governments of endemic countries are encouraged to take ownership of national elimination efforts. But the global public good of yaws eradication will likely require global financing. The cost to the public sector would be significantly reduced by drug donations from pharmaceutical companies, similar to those being made for other preventable NTDs. Donations of diagnostic tests would also help. At least as important is the catalytic effect that these in-kind donations could have. Financial and in-kind resources could be better harnessed from the extractive industries (e.g. mining, logging) and others (e.g. cocoa and coffee). These are industries with operations on or near the resource-rich lands where resource-poor populations still live with yaws. There is already some precedent for mining company support to yaws eradication implementation and research in Lihir.[30]

If endemic countries and their financing partners deliver within the range of costs and effects considered in this study, yaws eradication will be cost-effective relative to WHO thresholds. Of course, the case for investment in yaws eradication does not rest on cost-effectiveness alone. Policy-makers may be confronted with choices between public health interventions of similar cost-effectiveness relative to WHO thresholds. In the context of universal health coverage, priority-setting should consider also equity, with priority given to the worse off. There is no doubt that efforts to eradicate yaws will benefit some of the least well off citizens of the world. Yaws eradication should be seen as complementary to universal health coverage and shared prosperity on the post-2015 development agenda.
References for this paper


### Table S2. Regression models for the cost of mass drug administration (excluding drugs) per person treated

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(log) Population treated</td>
<td>-0.514****</td>
<td>-0.785****</td>
</tr>
<tr>
<td></td>
<td>[-0.68,-0.35]</td>
<td>[-0.97,-0.60]</td>
</tr>
<tr>
<td>(log) GDP per capita, 2012 US$</td>
<td>0.0405</td>
<td>0.654**</td>
</tr>
<tr>
<td></td>
<td>[-1.26,1.34]</td>
<td>[-0.09,1.40]</td>
</tr>
<tr>
<td>(log) Population density (per km2)</td>
<td>-1.809*</td>
<td>-4.546****</td>
</tr>
<tr>
<td></td>
<td>[-4.31,0.69]</td>
<td>[-6.54,-2.56]</td>
</tr>
<tr>
<td>Constant</td>
<td>14.36***</td>
<td>24.69****</td>
</tr>
<tr>
<td></td>
<td>[1.54,27.19]</td>
<td>[14.58,34.79]</td>
</tr>
</tbody>
</table>

| Observations | 103 | 97 |
| Groups       | 57  | 67 |
| $R^2$        | 0.578 | 0.862 |

Regression models fitted using data obtained from The 25 identified studies are referenced in Table S1. Financial (F) and economic (E) costs include: planning, mapping and training activities (F&E), drug shipment (F&E), vehicles that were rented (F&E) or borrowed from other programs (E), fuel and vehicle maintenance (F&E), per diems (F&E), project staff salaries (F&E), Ministry of Health staff time (E), office space (E), utilities (F&E) and supplies (F&E). Both costs exclude drugs and volunteer time. 95% confidence intervals for the regression coefficients are in square brackets. * p < 0.15, ** p < 0.10, *** p < 0.05, **** p < 0.01
<table>
<thead>
<tr>
<th>Country</th>
<th>Economic Best</th>
<th>Economic Low</th>
<th>Economic High</th>
<th>Financial Best</th>
<th>Financial Low</th>
<th>Financial High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin</td>
<td>3.69</td>
<td>0.21</td>
<td>14.02</td>
<td>2.39</td>
<td>0.71</td>
<td>5.70</td>
</tr>
<tr>
<td>Cameroon</td>
<td>1.25</td>
<td>0.14</td>
<td>3.67</td>
<td>0.69</td>
<td>0.28</td>
<td>1.35</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>2.70</td>
<td>0.22</td>
<td>9.67</td>
<td>1.36</td>
<td>0.37</td>
<td>3.13</td>
</tr>
<tr>
<td>Congo</td>
<td>10.41</td>
<td>0.10</td>
<td>38.65</td>
<td>5.51</td>
<td>0.86</td>
<td>15.82</td>
</tr>
<tr>
<td>Cote d'Ivoire</td>
<td>0.20</td>
<td>0.06</td>
<td>0.45</td>
<td>0.05</td>
<td>0.03</td>
<td>0.10</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>0.21</td>
<td>0.04</td>
<td>0.54</td>
<td>0.02</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Ghana</td>
<td>0.22</td>
<td>0.05</td>
<td>0.60</td>
<td>0.07</td>
<td>0.03</td>
<td>0.14</td>
</tr>
<tr>
<td>Indonesia</td>
<td>8.06</td>
<td>0.08</td>
<td>32.47</td>
<td>5.68</td>
<td>1.01</td>
<td>15.64</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>6.22</td>
<td>0.09</td>
<td>31.54</td>
<td>5.19</td>
<td>0.93</td>
<td>15.78</td>
</tr>
<tr>
<td>Solomon Islands</td>
<td>4.76</td>
<td>0.13</td>
<td>19.83</td>
<td>3.44</td>
<td>0.83</td>
<td>8.67</td>
</tr>
<tr>
<td>Togo</td>
<td>3.10</td>
<td>0.23</td>
<td>11.41</td>
<td>1.88</td>
<td>0.55</td>
<td>4.64</td>
</tr>
<tr>
<td>Vanuatu</td>
<td>9.01</td>
<td>0.11</td>
<td>33.20</td>
<td>6.34</td>
<td>1.09</td>
<td>17.66</td>
</tr>
</tbody>
</table>

Estimates of unit cost (2012 US$) obtained using the regression models reported in Table S2 and country-specific data on populations at risk of yaws, GDP per capita and population density. Financial (F) and economic (E) costs include: planning, mapping and training activities (F&E), drug shipment (F&E), vehicles that were rented (F&E) or borrowed from other programs (E), fuel and vehicle maintenance (F&E), per diems (F&E), project staff salaries (F&E), Ministry of Health staff time (E), office space (E), utilities (F&E) and supplies (F&E). Both costs exclude drugs and volunteer time. Best estimates are the mean, and low and high estimates are the 5th and 95th centile values, respectively.

All files

http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003165#s5
Chapter 2.2 The economics of yaws surveillance
Paper 2.2.1 The cost and cost-effectiveness of rapid testing strategies for yaws diagnosis and surveillance

Published paper

Available at: http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0005985

Authors and Affiliations

Christopher Fitzpatrick1*, Kingsley Asiedu1, Anita Sands1, Tita Gonzalez Pena1,2, Michael Marks3, Oriol Mitja4, Filip Meheus5,6, Patrick Van der Stuyft7,8

1 Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland
2 Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, United States of America
3 Clinical Research Department, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom
4 Barcelona Institute for Global Health, Hospital Clinic -University of Barcelona, Barcelona, Spain
5 Unit of Epidemiology and Control of Neglected Tropical Diseases, Institute of Tropical Medicine, Antwerp, Belgium
6 Prevention and Implementation Group, International Agency for Research on Cancer, Lyon, France
7 Unit of General Epidemiology and Disease Control, Institute of Tropical Medicine, Antwerp, Belgium
8 Department of Public Health, Ghent University, Ghent, Belgium

*Corresponding author: fitzpatrickc@who.int

Abstract

Background: Yaws is a non-venereal treponemal infection caused by Treponema pallidum subspecies pertenue. The disease is targeted by WHO for eradication by 2020. Rapid diagnostic tests (RDTs) are envisaged for confirmation of clinical cases during treatment campaigns and for certification of the interruption of transmission. Yaws testing requires both treponemal (trep) and non-treponemal (non-trep) assays for diagnosis of current infection. We evaluate a sequential testing strategy (using a treponemal RDT before a trep/non-trep RDT) in terms of cost and cost-effectiveness, relative to a single-assay combined testing strategy (using the trep/non-trep RDT alone), for two use cases: individual diagnosis and community surveillance.

Methods: We use cohort decision analysis to examine the diagnostic and cost outcomes. We estimate cost and cost-effectiveness of the alternative testing strategies at different levels of prevalence of past/current infection and current infection under each use case. We take the
perspective of the global yaws eradication programme. We calculate the total number of correct diagnoses for each strategy over a range of plausible prevalences. We employ probabilistic sensitivity analysis (PSA) to account for uncertainty and report 95% intervals.

**Results:** At current prices of the treponemal and trep/non-trep RDTs, the sequential strategy is cost-saving for individual diagnosis at prevalence of past/current infection less than 85% (81-90); it is cost-saving for surveillance at less than 100%. The threshold price of the trep/non-trep RDT (below which the sequential strategy would no longer be cost-saving) is US$ 1.08 (1.02-1.14) for individual diagnosis at high prevalence of past/current infection (51%) and US$ 0.54 (0.52-0.56) for community surveillance at low prevalence (15%).

**Discussion:** We find that the sequential strategy is cost-saving for both diagnosis and surveillance in most relevant settings. In the absence of evidence assessing relative performance (sensitivity and specificity), cost-effectiveness is uncertain. However, the conditions under which the combined test only strategy might be more cost-effective than the sequential strategy are limited. A cheaper trep/non-trep RDT is needed, costing no more than US$ 0.50 –1.00, depending on the use case. Our results will help enhance the cost-effectiveness of yaws programmes in the 13 countries known to be currently endemic. It will also inform efforts in the much larger group of 71 countries with a history of yaws, many of which will have to undertake surveillance to confirm the interruption of transmission.

**Author Summary**

Yaws is a non-venerereal treponemal infection. The disease is targeted by WHO for eradication by 2020. Testing is envisaged for diagnosis to confirm of clinical cases during treatment campaigns and for surveillance to certify the interruption of transmission. However resources available to the global eradication programme are severely limited and the cost of testing must be contained. Testing requires simultaneous detection of antibodies to both treponemal and non-treponemal antigens for diagnosis of active infection. Currently, there is one commercially available rapid diagnostic test for yaws that can do just that. However, it is considerably more expensive than the available syphilis tests detecting treponemal antibodies only. We evaluate the cost and cost-effectiveness of a sequential testing strategy (using the treponemal test first, before the combined test), relative to a combined testing strategy (using only the combined test). We consider the two use cases: individual diagnosis and community surveillance. We find that the sequential strategy is cost-saving for both diagnosis and surveillance in most relevant settings. Yaws eradication programme should consider adopting the sequential strategy. Still, a cheaper trep/non-trep RDT is needed, costing no more than US$ 0.50–1.00. Our results will help enhance the cost-effectiveness of yaws programmes in the 13 countries known to be currently endemic. It will also inform efforts in the much larger group of 71 countries with a history of yaws, many of which will have to undertake surveillance to confirm the interruption of transmission.

**Introduction**

Yaws is a non-venerereal treponemal infection caused by *Treponema pallidum* subspecies *pertenue* affecting primarily the skin in the early stages and the bone and cartilage in the late stages. In 1950, WHO estimated that 160 million people were infected with yaws. Between 2008 and 2012 more than 300 000 new cases were reported to the World Health Organization (WHO). The disease is now targeted by WHO for eradication by 2020. One or two rounds of mass treatment at high levels of population coverage have been shown to reduce prevalence of yaws near to elimination levels.[1] This approach is known as total community treatment
(TCT) – treatment of an entire endemic community irrespective of the number of active clinical cases. A second important element of the WHO strategy is 6 monthly Total Targeted Treatment (TTT) – treatment of all active clinical cases and their contacts – to mop-up cases missed in TCT rounds.

Confirmation of clinical cases during TTT programs may be carried out using a rapid diagnostic test (RDT) for the dual detection of treponemal and non-treponemal serological markers at or near to point-of-care. Serological testing is also envisaged for certification of the interruption of transmission of T. p pertenue.

Yaws and syphilis treponemes differ in less than 0.2% of the genome sequence.[2] Yaws is serologically indistinguishable from syphilis, caused by T. pallidum subspecies pallidum.[3] Serological tests developed for syphilis may therefore be used to diagnose yaws, especially among children, since its clinical manifestation and epidemiology differ from that of syphilis and may allow a differentiation of the two conditions. Serological diagnosis of clinically active yaws requires the detection of two distinct sets of antibodies: one against treponemal antigens and one against non-treponemal antigens. Treponemal in vitro diagnostics (IVDs), including T. pallidum particle agglutination assay (TPPA), T. pallidum hemagglutination assay (TPHA), and fluorescent treponemal antibody absorption test (FTA-ABS) are highly sensitive and specific but antibodies remain detectable for life following any treponemal infection even after successful treatment. A reactive treponemal test result can therefore indicate either current or past infection and may not be sufficient to indicate no new disease in people with clinical symptoms that look like yaws.

Non-treponemal IVDs, including Rapid Plasma Reagin (RPR) and Venereal Disease Research Laboratory (VDRL) assays, are less specific but the titers rise during active disease and fall following treatment, which can allow current and previous or treated infection to be distinguished. Titers refer to how many serial dilutions you can perform on the sample and still get a positive result. False positive results can occur when using non-treponemal assays alone due to acute viral infections, malaria, and connective tissue diseases which may also cause non-treponemal assays to be reactive. As a result, testing for yaws requires combined treponemal and non-treponemal assays to give accurate diagnosis of current yaws infection.

The most widely recommended yaws screening tool is the laboratory-based RPR followed by a treponemal test. RPR requires laboratory capacity, trained laboratory personnel, refrigeration for storage of reagents, and electricity to run equipment such as the refrigerator, centrifuge, and shaker. Because such facilities are generally not available in the remote areas where yaws is commonly endemic, diagnosis is often made on the basis of clinical findings only which may not be adequate for surveillance purposes. In places where laboratories are able to do the RPR, serum specimens have to be transported to centralized laboratories for testing and results are available in days or weeks. This delay may result in delayed treatment and continued transmission of the disease.

Rapid syphilis tests detecting treponemal antibodies (treponemal RDTs) are now commercially available, meeting minimum defined standards for quality, safety and performance for use at point-of-care. Treponemal RDTs have been introduced into national antenatal care programmes but these are not commonly used for yaws, as results of treponemal RDTs alone correlate poorly with presence of current infection, as explained earlier.

Currently, one commercially available RDT exists that is based on the simultaneous detection of antibodies to both treponemal and non-treponemal antigens. The DPP Yaws Trep & N.Trep Assay (Chembio, Medford, NY, USA) is designed for use in resource-limited settings where there is limited access to laboratory facilities. For brevity, we refer generically to the assay as a treponemal/non-treponemal RDT or “trep/non-trep RDT”. The dual
components of the assay allows clinicians to both screen and confirm the serological status within 15 minutes and allows for differentiation of current and past yaws.

In 2014, the use of trep/non-trep RDT for diagnosis of yaws infection was evaluated and compared with *T. pallidum* particle hemagglutination assay (TPHA) and RPR as reference standards for treponemal and non-treponemal antibodies detection, respectively.[4] In the low-resource setting of Papua New Guinea, the treponemal test line demonstrated a sensitivity of 88.4% and a specificity of 95.2%; the non-treponemal test line demonstrated a sensitivity of 87.9% and a specificity of 92.5%. A number of evaluations of a trep/non-trep RDT for the diagnosis of yaws infection have now been conducted, as synthesized in a recent meta-analysis.[5]

It is expected that the simpler trep/non-trep RDT should improve access to yaws diagnosis relative to the RPR test. However, use of the trep/non-trep RDT alone may not be the most economical option, especially in low treponemal test positive prevalence settings. In yaws elimination pilot projects, WHO had negotiated a price of US$ 2.50 per trep/non-trep RDT and US$0.45 per treponemal RDT. For surveys where large number of people are non-reactive to the treponemal test, such as in low endemicity settings, a combination of two rapid tests (treponemal RDT for screening, and trep/non-trep RDT for diagnosis) could be cost-saving.

Studies have reported that antenatal syphilis screening and treatment is highly cost-effective in low and middle income countries.[6] Some have modelled the cost-effectiveness of different screening strategies.[7][8][9][10] Terris-Prestholt et al. (2015) were the first to compare the full range of possible screening and treatment strategies for syphilis in multiple countries, including Peru, Tanzania and Zambia. This range included a sequential strategy using a treponemal RDT followed by a dual trep/non-trep RDT. They found that the dual-only strategy was significantly higher cost than the sequential strategy in all three countries, but resulted in more true cases being detected and treated, with the result that cost-effectiveness was about the same in two out of three countries, namely Tanzania and Zambia, where prevalence was highest.

No such economic evaluation of testing strategies has been done for yaws.

We therefore evaluate a two-assay sequential testing strategy in terms of both its cost and cost-effectiveness relative to a single-assay testing strategy. In the sequential strategy, a treponemal RDT is used as the screening assay of the testing strategy, followed by reflex testing with a trep/non-trep RDT for only the reactive treponemal specimens, as depicted in Figure 1. This strategy avoids unnecessary dual treponemal/non-treponemal testing of individuals with no past or current yaws infection (i.e. treponemal negative). The sequential testing strategy is compared to a single-assay testing strategy using the trep/non-trep RDT on the entire testing population.
Figure 1. Diagram of alternative testing strategies: combined (panel A) and sequential (panel B). Boxes represent tests and test results; diamonds represent diagnoses; dotted lines represent discordant treponemal and non-treponemal test results by the trep/non-trep RDT, excluded from Figure 2 for simplicity; in the case of discordant results between the treponemal RDT and the trep/non-trep RDT, the sequential testing strategy takes the result of the trep/non-trep RDT.

We aim to establish the conditions (namely, prevalence of past/current infection and relative prices of the treponemal and trep/non-trep tests) under which the sequential strategy would be cost-saving or cost-effective relative to the combined strategy, for the purposes of 1) individual diagnosis and 2) community surveillance. By diagnosis, we mean confirmation of clinically suspected cases in individuals before TCT or during TTT; by surveillance we mean screening of communities (mostly asymptomatic individuals) for the purpose of verification.
of the interruption of transmission in population after TCT and in countries of historic endemicity.

**Methods**

We use cohort decision analysis to examine the diagnostic and cost outcomes. We estimate cost and cost-effectiveness of the alternative testing strategies in a hypothetical testing population of 1000 people at different levels of past or current prevalence. We place these results in the context of treponemal positive and dually positive prevalences in Ghana, Papua New Guinea, Solomon Islands, and Vanuatu – four endemic countries in which population serosurveys were undertaken in the years 2013-2014. These surveys were administered both pre- and post-TCT.

In estimating costs, we take the perspective of the global yaws eradication programme and national health systems. We include the cost of commodities to be funded in large part by the global yaws eradication programme, and the cost of other inputs such as labor to be supplied by the national health system.

We apply a unit cost of US$ 2.50 for each trep/non-trep RDT. For the sequential strategy, we apply a unit cost of US$ 0.45 for each treponemal RDT, and US$ 2.50 for each trep/non-trep RDT. We also add the cost of alcohol swabs ($3 for 100), sterile lancets ($375 for 2000) and non-sterile gloves ($3 for 50 pairs). These prices are consistent with the UNICEF supply catalogue.[11] These ancillary costs increase the unit cost of each trep/non-trep RDT and treponemal RDT to US$ 2.78 and US$ 0.73 respectively.

We consider that every test requires 2–5 minutes of a district-level laboratory technician’s time (depending on experience, this is the time it takes to collect the sample, execute the test, read and report the result). It takes 10-15 minutes between execution of the test and reading of its results, but technicians can attend to other patients during that time. We asked national yaws eradication programmes to provide estimates of the wage of a district-level laboratory technician (in US$). It ranged from US$ 210–510 per month in 11 of the 13 endemic countries, and US$ 1500–1585 per month in two small island developing states (Solomon Islands and Vanuatu).

In the sequential strategy, the trep/non-trep RDT is applied only to treponemal test positives (true and false positives). Total costs (and savings) therefore depend not only on the unit costs described above, but on the sensitivity and specificity of the treponemal RDT for yaws testing. All else equal, a less sensitive (specific) treponemal RDT will result in a smaller (larger) number of trep/non-trep RDTs required in the sequential testing strategy. We use sensitivity and specificity of the treponemal RDT from the Jafari et al. (2013) metanalysis.[12] Sensitivities and specificities are reported in Table 1. In probabilistic sensitivity analysis (PSA), we use the 95% confidence intervals for the sensitivity and specificity results.

<table>
<thead>
<tr>
<th>Test Source</th>
<th>Disease</th>
<th>Sample subgroup</th>
<th>Line</th>
<th>Reference standard</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD BIOLINE Syphilis 3.0 (Standard Diagnostics, Inc.)</td>
<td>Syphilis</td>
<td>Sexually transmitted infection clinics</td>
<td>Trep</td>
<td>TPHA</td>
<td>88.7 (85.1–91.8)</td>
<td>99.2 (98.7–99.5)</td>
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<td></td>
<td></td>
<td>Ante natal care (ANC)</td>
<td>Trep</td>
<td>TPHA</td>
<td>82.2 (79.7–84.6)</td>
<td>97.9 (97.5–98.2)</td>
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<td>Hypothetical*</td>
<td>Yaws</td>
<td>Primary and secondary disease</td>
<td>Trep</td>
<td>TPHA</td>
<td>85.3 (80.9–89.3)</td>
<td>95.8 (93.8–97.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asymptomatic</td>
<td>Trep</td>
<td>TPHA</td>
<td>56.9 (49.5–65.6)</td>
<td>97.7 (95.3–99.1)</td>
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<tr>
<td>DPP Yaws Trep &amp; N.Trep Assay (Chembio Diagnostic Systems, Inc.)</td>
<td>Yaws</td>
<td>Primary and secondary disease</td>
<td>Trep</td>
<td>TPHA</td>
<td>88.3 (85.4–90.8)</td>
<td>95.8 (93.8–97.2)</td>
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<td></td>
<td></td>
<td>Non-trep</td>
<td>RPR</td>
<td>86.7 (83.3–89.6)</td>
<td>94.7 (92.8–96.3)</td>
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<tr>
<td></td>
<td></td>
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<td>Trep</td>
<td>TPHA/TPPA</td>
<td>60.2 (51.1–68.7)</td>
<td>97.7 (95.3–99.1)</td>
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<td>95.5 (92.6–97.5)</td>
<td></td>
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<td>Syphilis</td>
<td>Primary and secondary disease</td>
<td>Trep</td>
<td>TPHA/TPPA</td>
<td>95.1 (91.5–97.5)</td>
<td>85.7 (57.2–98.2)</td>
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<td></td>
<td></td>
<td>Non-trep</td>
<td>RPR</td>
<td>96.3 (92.9–98.4)</td>
<td>57.1 (34.0–78.2)</td>
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<tr>
<td></td>
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<td>Asymptomatic</td>
<td>Trep</td>
<td>TPHA/TPPA</td>
<td>91.2 (88.5–93.5)</td>
<td>95.6 (93.8–96.8)</td>
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<tr>
<td></td>
<td></td>
<td>Non-trep</td>
<td>RPR</td>
<td>94.7 (91.9–96.7)</td>
<td>67.1 (62.3–71.6)</td>
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</table>

* Sensitivity of the treponemal RDT for yaws is allowed to be lower than that of the trep/non-trep RDT and specificity is assumed to be equivalent.

Using the Jafari et al (2013) data, we calculate sensitivity and specificity of the treponemal RDT for two relevant subgroups: clinical syphilis cases to be confirmed at sexually transmitted infection clinics, and (asymptomatic) pregnant women to be screened at ante natal care (ANC) clinics. Unfortunately, the results from Jafari et al. (2013) relate to syphilis testing only—there is no evidence of the performance of the treponemal RDT for yaws testing. Marks et al. (2016) found that the sensitivities of both components of the trep/non-trep RDT were higher in patients with syphilis than in patients with yaws at low titers.[5] It is possible, if not probable, that the sensitivity of the treponemal RDT may therefore be worse for yaws than for syphilis.

We therefore adjust (downward) the sensitivity of the treponemal RDT by the ratio of the sensitivity of the trep/non-trep RDT for yaws to the sensitivity of the trep/non-trep RDT for syphilis. This adjustment, while crude, allows for the possibility that the sensitivity of the treponemal RDT could be inferior to that of the treponemal line of the trep/non-trep RDT. In PSA, we allow the sensitivity of the treponemal RDT to vary between this adjusted number and that of the treponemal line of the trep/non-trep RDT. We assume that the specificity of the treponemal RDT for yaws is the same as that of the treponemal line of the trep/non-trep RDT. The hypothetical performance of the treponemal RDT for yaws is reported in Table 1.
We multiply unit costs by the total number of each test required. From total costs, we calculate the cost savings associated with sequential testing strategy. We then calculate the so-called threshold unit cost of the trep/non-trep RDT at which the sequential strategy would no longer be cost-saving, assuming a fixed price for the treponemal RDT. That is, we calculate the unit cost of the trep/non-trep RDT such that:

\[
C_d \times P < C_t \times P + C_d \times P \times \left\{ T_p \times \text{Se}_t + (1 - T_p) \times (1 - \text{Sp}_t) \right\}
\]

And where:
- \( C_d \) is the unit cost of the dual trep/non-trep RDT, including the price of the assay as well as ancillary costs;
- \( P \) is the population to be tested;
- \( C_t \) is the unit cost of the treponemal RDT, including the price of the assay as well as ancillary costs;
- \( T_p \) is the prevalence of past/current infection in the testing population;
- \( \text{Se}_t \) is the sensitivity of the treponemal RDT; and
- \( \text{Sp}_t \) is the specificity of the treponemal RDT.

Simplifying and re-arranging, the sequential strategy is no longer cost-saving when:

\[
\frac{C_d}{1 - \{ T_p \times \text{Se}_t + (1 - T_p) \times (1 - \text{Sp}_t) \}} < C_t
\]

Or:

\[
\frac{(C_d - C_t)}{C_d} < T_p \times \text{Se}_t + (1 - T_p) \times (1 - \text{Sp}_t)
\]

That is, when the percentage difference in unit cost of the treponemal RDT relative to the trep/non-trep RDT is less than the percentage of cases that will test positive using the treponemal RDT, which includes both true and false positives. This reactivity rate is determined by the treponemal positive prevalence (\( T_p \)) and sensitivity (\( \text{Se}_t \)) and specificity (\( \text{Sp}_t \)) of the treponemal RDT. At current prices of the trep/non-trep and treponemal RDTs, the reactivity rate would have to be more than about 74%. Of course, a low reactivity rate of the treponemal RDT, while leading to cost-savings, may not be cost-effective if it results in fewer correct diagnoses.

We calculate the total number of correct diagnoses for each strategy over the full range of prevalences. Decision trees depicting the possible pathways to correct diagnosis are depicted for both strategies in Figures 2 and 3.
Figure 2. Decision model of diagnosis of current infection under the combined testing strategy. The decision to be made is whether an individual has current infection or not (box); the individual’s combined test result (circles) can be either: dually positive (suggesting current infection), treponemal positive only (past infection), or dually negative (never any infection); this depends on the Sensitivity (Se) and Specificity (Sp) of the treponemal line (Se2a and Sp2a, respectively) and of the non-treponemal line (Se2b and Sp2b), as well as on the prevalence of past/current infection in the total population (Pr1) and the prevalence of current infection in the population of past/current infections (Pr2); the treponemal line provides either a true or false diagnosis of past/current infection; this depends on Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of the treponemal line (PPV2a and NPV2a, respectively); PPV is calculated as \((Se \times Pr1)/(Se \times Pr1 + (1–Sp) \times (1–Pr1))\); NPV is calculated as \(Sp \times (1–Pr1)/(1–Se) \times Pr1 + Sp \times (1–Pr1)\); the non-treponemal line provides either a true or false diagnosis of current infection; this depends on PPV and NPV of the non-treponemal line (PPV2b and NPV2b), using the prevalence of current infection in the population of past/current infections (Pr2); red lines indicate pathways to false diagnoses of current infection; note, the treponemal line can give a false positive diagnosis of past/current infection and yet the non-treponemal line can still give a correct overall diagnosis of no current infection.

\[ a = (Se2a \times Pr1 + (1–Sp2a) \times (1–Pr1)) \times (Se2b \times Pr2 + (1–Sp2b) \times (1–Pr2)) \]

\[ b = (Se2a \times Pr1 + (1–Sp2a) \times (1–Pr1)) \times (Sp2b \times (1–Pr2) + (1–Se2b) \times Pr2) \]
Figure 3. Decision model of diagnosis of current infection under the sequential testing strategy. In the sequential strategy, the individual’s first test result (circles) can be either: treponemal positive (suggesting past/current infection), or treponemal negative (never any infection); this depends on the Sensitivity (Se) and Specificity (Sp) of the treponemal RDT (Se1 and Sp1, respectively), as well as on the prevalence of past/current infection in the total population (Pr1); the treponemal line provides either a true or false diagnosis of past/current infection; this depends on Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of the treponemal RDT (PPV1 and NPV1, respectively); PPV is calculated as \( \frac{Se \times Pr1}{Se \times Pr1 + (1 - Sp) \times (1 - Pr1)} \); NPV is calculated as \( \frac{Sp \times (1 - Pr1)}{(1 - Se) \times Pr1 + Sp \times (1 - Pr1)} \); those with a true negative result for past/current infection are logically also truly negative for current infection; among those with a false negative result for past/current infection, we assume that the prevalence of current infection among false past/current infection negatives is the prevalence of current infection in the population of past/current infections (Pr2); those with either true or false positive results for past/current infection receive a second test; their second test result can be either: dually positive (suggesting current infection), treponemal positive only (past infection), or dually negative (never any infection); for simplicity, we assume that we use only the non-treponemal line; the non-treponemal line provides either a true or false diagnosis of current infection; this depends on PPV and NPV of the non-treponemal line (PPV2b and NPV2b), using the prevalence of current infection in the population of past/current infections (Pr2); red lines indicate pathways to false diagnoses of current infection.
We assume that the percentage of past/current infections that are current is the same in the subset of true past/current infection positives identified by the treponemal RDT as it is in the total population of past/current infections (Figure 3). This assumption is thought to be reasonable; in Marks et al (2016), 74% of TPHA positive people had positive RPR; 75% of people with a positive treponemal RDT had a positive RPR, and 77% had a positive non-trep RDT. We also assume that the prevalence of current infection among false past/current infection negatives is (at most) equal to the prevalence of current infection among past/current infections; in any case, in an eradication programme, the number of false negatives will tend towards zero.

We use sensitivity and specificity of the trep/non-trep RDT from the Marks et al. (2016) meta-analysis. Performance characteristics depend on the use case of the trep/non-trep RDT: yaws diagnosis or yaws surveillance. In confirmation of clinical cases, more people will have high titres (where the test performs better) while in confirmation of the interruption of transmission more people will have low titers (where the test performs less well). We therefore consider performance characteristics for primary and secondary disease, or asymptomatic cases (Table 1). The former is applied to populations with clinical symptoms requiring diagnosis, while the latter is applied to populations requiring surveillance.

We calculate the cost per correct diagnosis (true current infection positive or negative) under each strategy (sequential or combined strategy) and use case (diagnosis or surveillance). However, we also report the cost per true positive diagnosis, considering that true positive and negative diagnoses may not be equivalent in their benefits. In the context of individual diagnosis for eradication, for example, true positive diagnosis may be more important than a true negative diagnosis, at least from the perspective of the health system. The incremental cost of treating a false positive is relatively trivial, even considering the cost attributed to any side effects. There are very few and minor side effects associated with azithromycin and indeed, many collateral benefits for diarrheal and other diseases. From the perspective of patients, however, there may be psychosocial costs associated with false positive results.

We then calculate the incremental cost-effectiveness ratio (ICER) of the higher cost combined strategy, for the range of treponemal and dually positive prevalences over which it is not dominated by the sequential strategy. By not dominated, we mean that while the cost is higher, the number of correct diagnoses is also higher. We present cost savings and cost-effectiveness of the alternative testing strategies in the context of survey population prevalences obtained in four countries: Ghana, Papua New Guinea (PNG), Solomon Islands, and Vanuatu.[13–15]

Pre-TCT survey population prevalences obtained using trep/non-trep RDTs are provided in Supporting Information S1 Table. Treponemal positive prevalence varied from 22% in Vanuatu to 51% in Papua New Guinea. Among those testing treponemal positive, non-treponemal positives were between 21% in Solomon Islands and 71% in Vanuatu. Out of the total population tested, dually positive prevalences were between 7% in Solomon Islands and 18% in Papua New Guinea.

Post-TCT survey population prevalences obtained using trep/non-trep RDTs are presented for four countries in Supporting Information S2 Table. The treponemal positive prevalence decreased to between 15% in Ghana and 42% in Solomon Islands. Among those testing treponemal positive, non-treponemal positives were between 5% in Solomon Islands and 49% in Vanuatu. The dually positive prevalence decreased, as a percentage of the population tested, to between 1% in Solomon Islands and 8% in Vanuatu.

We are not in this paper attributing these reductions in prevalence to TCT. We are simply using pre- and post-TCT prevalence as a proxy for the prevalence that one might encounter in community surveillance and individual diagnosis settings, respectively.
Use cases and prevalences of the testing population are not independent. In particular, prevalences will be higher when doing individual diagnosis than when doing community surveillance. We therefore focus on the following plausible ranges of prevalence: for individual diagnosis, current/past infection prevalence of 20-55%, of which 20-75% is currently infected; for community screening, current/past infection prevalence of 15-45%, of which 5-50% are currently infected.

We report best estimates using the median of 1000 simulations and the 95% confidence intervals using the 2.5th and 97.5th centiles. All data analysis and visualization were done using R (Foundation for Statistical Computing, Vienna, Austria).[16] All the necessary code is provided as Supporting Information.

Results

We present results separately for the two use cases: individual diagnosis and community surveillance. The differences in results between use cases are driven by different values of sensitivity and specificity in populations with different clinical presentations (stages of disease).

We visualize results over the full range of possible prevalences of past and/or current infection of the testing populations but focus on the plausible ranges determined by treponemal and dually trep/non-trep positive prevalences in Ghana, Papua New Guinea, Solomon Islands, and Vanuatu.

Individual diagnosis

At the current price of the treponemal RDT and a high prevalence of past/current infection of 51% (the treponemal positive prevalence in pre-TCT Papua New Guinea), we obtain a threshold unit cost for the trep/non-trep RDT of US$ 1.38 (1.31-1.46), including ancillary costs (i.e. swabs, lancets and gloves) and laboratory technician time, or US$ 1.08 (1.02-1.14) for the price of the assay alone. This is the unit cost below which the sequential strategy would no longer be cost-saving for individual diagnosis in a testing population where about one in two are or have been infected.

More generally, costs savings of the sequential strategy in diagnosing 1000 individuals are presented in Figure 4 (top row) across all scenarios of prevalence. At current prices of the treponemal and trep/non-trep RDTs, the sequential strategy is cost-saving if the prevalence of past/current infection of the testing population is less than 85% (81-90). Within the plausible range of prevalence (20-55%), the savings are US$ 1079 (703-1448) per 1000 people tested. Above 85%, it is the combined strategy that is cost-saving.
Figure 4. Cost savings of the sequential testing strategy across different scenarios of prevalence, per 1000 people tested, by use case. Best – best estimate (median); Low – low estimate (2.5th centile); High – high estimate (97.5th centile); cost savings are expressed per 1000 people tested.

The number of correct diagnoses of current infection (true positives and true negatives) is presented in Supporting Information S1 Figure (top two rows). Based on our assumptions about the relative performance of the treponemal RDT for yaws, the number of correct diagnoses is somewhat higher under the combined strategy than under the sequential strategy. However, in the plausible range of prevalences, more than 900 correct diagnoses are made for every 1000 people tested under both strategies. It is only at higher prevalences that differences between the strategies become non-trivial. The number of true current infection positives is presented in Supporting Information S2 Figure.

Given our assumptions about the relative performance of the treponemal RDT, there is a range of prevalences over which a higher cost and (hypothetically) more sensitive combined strategy could be more cost-effective than the sequential strategy. Incremental cost-effectiveness ratios (ICERs; ratio of incremental costs over incremental benefits or incremental cost per correct diagnosis gained) are presented in Figure 5 (top row), across different scenarios of prevalence. At prevalence of past/current infection of 51% and current infection of 18% (again, the trep/non-trep RDT positive prevalences in pre-TCT Papua New Guinea), the ICER is US$ 58 (42-103) per correct diagnosis gained.
Figure 5. Incremental cost-effectiveness (cost per correct diagnosis gained) of the combined testing strategy across different scenarios of prevalence, by use case. Best – best estimate (median); Low – low estimate (2.5th centile); High – high estimate (97.5th centile); ICER – Incremental Cost Effectiveness Ratio (cost per correct diagnosis); black rectangles indicate where the sequential strategy may be more costly and more effective; grey areas without an ICER value indicate negative ICERs, where the combined testing strategy is less effective and more costly or more effective and less costly.

At very high prevalence of past/current infection, where it becomes cost-saving, a more sensitive combined strategy may dominate the sequential strategy. At very low prevalence of either past/current infection or current infection, it is specificity that matters more for the number of correct diagnoses, and even a more sensitive combined strategy may be dominated by the sequential strategy. In theory, there is a combination of prevalences (very high prevalence of past/current infection and very low prevalence of current infection) where a more sensitive combined strategy could produce fewer correct diagnoses of current infection (this is the area depicted by a black rectangle in Figure 5). In practice, however, this combination is unlikely.

In Supporting Information S3 Figure (top row), we present the same figure, but using only true positive diagnoses in the denominator of the ICER. Here, the ICER is US$ 38 (32-48) at prevalence of past/current infection of 51% and current infection of 18%. Given our assumptions about the relative performance of the treponemal RDT, the combined strategy is nowhere dominated by the sequential strategy when considering only true positive diagnoses; the combined strategy dominates the sequential strategy wherever it is cost-saving.

The cost-effectiveness plane is presented in Supporting Information S4 Figure (top row), at the lower and upper limits of the plausible range of prevalence: for individual diagnosis, the current/past infection prevalence ranges from 20% (lower limit) to 55% (upper limit), of which 20% (lower limit) or 75% (upper limit) are currently infected. It shows that at the lower limit, the combined testing strategy is less effective in spite of being more costly; at the upper limit it results in somewhere between 20–60 additional correct diagnoses (per 1000 tested) for somewhere between US$ 500–600.
Community surveillance

At the current cost of the treponemal RDT and a low prevalence of past/current infection of 15% of the testing population (similar to Ghana post-TCT), we obtain a threshold unit cost for the trep/non-trep RDT of US$ 0.84 (0.81-0.88), including ancillary costs and laboratory technician time, or US$ 0.54 (0.52-0.56) for the price of the assay alone.

At current prices of the treponemal and trep/non-trep RDTs, the sequential strategy is cost-saving in surveillance at all levels of prevalence of past/current infection – see Figure 4 (bottom row). Within the plausible range of prevalence (15-45%), the savings are US$ 1527 (1279-1748) per 1000 population.

The number of correct diagnoses of current infection (true positives and true negatives) is presented in Supporting Information S1 Figure (bottom two rows). Again, based on our assumptions about the relative performance of the treponemal RDT for yaws, the number of correct diagnoses is somewhat higher under the combined strategy than under the sequential strategy. Again, under both strategies, in the plausible range of prevalences, more than 900 correct diagnoses are made for every 1000 people tested.

ICERs are presented in Figure 5 (bottom row). At a prevalence of past/current infection of 42% and prevalence of current infection of 6% (similar to post-TCT Papua New Guinea), the best estimate is US$ 355 per correct diagnosis gained by the combined strategy. However, the low estimate is in an area of the plot where the combined strategy is dominated by the sequential strategy. Again, at very low prevalence of either past/current infection or current infection, it is specificity that matters more for the number of correct diagnoses.

In Supporting Information S3 Figure (bottom row), we present the same figure, but using only true positive diagnoses in the denominator of the ICER. Here, the ICER is US$ 117 (90-155) at a prevalence of past/current infection of 42% and prevalence of current infection of 6%. Given our assumptions about the relative performance of the treponemal RDT, the combined strategy is nowhere dominated by the sequential strategy when considering only true positive diagnoses; but, unlike in the diagnosis use case, the combined strategy is never cost-saving and nowhere dominates the sequential strategy.

The cost-effectiveness plane is presented in In Supporting Information S4 Figure (bottom row), again at the lower and upper limits of the plausible range of prevalences: for community screening, current/past infection prevalence ranges from 15% (lower) to 45% (upper), of which 5% (lower) to 50% (upper) are currently infected.

Discussion

In summary, this study finds that, at current prices, a sequential strategy is cost-saving relative to use of a combined strategy for individual diagnosis, at a prevalence of past/current infection less than 85% (81-90); it is cost-saving for community surveillance at a prevalence of less than 100% (i.e. always). The threshold prevalence for community surveillance is so high because when titres are low, the reactivity rate of the treponemal RDT is so low and so few people will need a non-treponemal result.

It turns out that the sequential strategy is no longer cost-saving for individual diagnosis in testing populations with high prevalence of past/current infection (i.e. 51%) when the price of the trep/non-trep RDT is less than US$ 1.08 (1.02-1.14). Likewise, the sequential strategy is no longer cost-saving for community surveillance in populations with low prevalence of past/current infection (i.e. 15%) when the price of the trep/non-trep RDT is less than US$ 0.54 (0.52-0.56).
In the absence of evidence assessing relative performance (sensitivity and specificity), the cost-effectiveness of a hypothetically more sensitive combined strategy is uncertain. However, the conditions under which it might be cost-effective are fairly limited. This finding is true even under fairly pessimistic assumptions about the performance of the treponemal RDT for yaws.

In addition to its relatively high cost, a major limitation of the current trep/non-trep RDT is its reduced sensitivity for low titer yaws, at least in the Solomon Islands where it was tested. Further research is required to determine whether available treponemal RDTs (for syphilis) perform any better for low titer yaws. Reduced sensitivity is likely to be a greater problem when using the test as part of yaws surveillance; a higher sensitivity assay will be needed to confirm interruption of transmission, such as RPR or even polymerase chain reaction (PCR) as PCR positive trep/non-trep RDT cases have been observed. Criteria for eradication of yaws in the Morges strategy of 2012 are: 1) absence of new indigenous cases for 3 consecutive years; 2) absence of evidence of transmission for 3 continuous years measured with sero-surveys among children aged 1–5 years (for example, no young children with RPR sero-reactivity); and 3) Negative PCR for *Treponema pallidum subspecies pertenue* in suspected lesions.[17]

There are several limitations to this study.

Serology does not result in identification of all cases of current yaws where early infection may be seronegative, and seropositive patients could have persisting antibodies after successful treatment. Therefore PCR is now considered the gold standard for the diagnosis of active yaws. The sensitivity and specificity of both the treponemal RDT and trep/non-trep RDT have not been assessed relative to PCR. However, there is no reason to believe that the bias favors the sequential testing strategy, as both the treponemal and trep/non-trep RDTs have been assessed against the same standard.

As described in the methods, treponemal RDTs have not been assessed for yaws, and we have therefore had to infer sensitivity and specificity from test performance for syphilis, as reported by Jafari et al (2013). Performance in syphilis is likely to be better than it is in yaws, as the trep/non-trep RDT also performs better in syphilis than in yaws. Although titres are often higher in syphilis compared with yaws (especially asymptomatic disease), it is unclear why Marks et al (2016) found that trep/non-trep performance was worse for yaws even when controlling for titre. Again, yaws and syphilis treponemes differ in less than 0.2% of the genome sequence.[2] Notwithstanding, that the specificity for yaws will be equal to or lower than that reported for syphilis should possibly be further assessed.

More generally, it should be noted that reported sensitivities and specificities can depend upon contextual factors, at least partially, and therefore the results of the meta-analyses of both Jafari et al (2013) and Marks et al (2016) may not fully reflect test performance in all settings, which underscores the need of interpreting our results in the light of the sensitivity analysis we performed.

Our probabilistic sensitivity analysis was focused on uncertainty around the relative performance of the tests, and to a lesser extent on costs. We assumed that the cost of traded commodities, procured by the global yaws eradication programme from international markets, was deterministic. Furthermore, we had only one estimate per country for the wage of laboratory technicians at the district level. In settings where either the commodity or labor costs are highly uncertain and/or their distribution highly skewed, a more sophisticated analysis of costs could be warranted.

We have not considered the time and other indirect costs incurred by the tested populations. The treponemal RDT produces results after 10 minutes; the trep/non-trep RDT
requires 15 min. Under the sequential strategy, therefore, treponemal negatives wait 5 fewer minutes and treponemal positives wait 10 more minutes. Had we taken these costs into account, the results might have been less favorable to the sequential testing strategy in higher treponemal positive settings. Therefore, from a patient’s perspective too, there is a case to be made for negotiating lower prices for the trep/non-trep RDT in settings with a high prevalence of past/current infection.

A cheaper trep/non-trep RDT is needed, costing no more than US$0.50 –1.00, depending on the use case.

However, other strategies are theoretically possible. RPR is already available and the centralized execution and availability of results may not be a major problem in some settings. Furthermore, a non-trep point of care RDT (alone, without the treponemal RDT) is technically feasible but has not yet been developed. An alternative strategy could involve the treponemal RDT followed by either RPR or the non-trep RDT. A reverse sequential strategy (non-trep test followed by the trep test) could also be possible.

Of course, these alternative sequential strategies not considered in our analysis would only be cost-saving relative to our original sequential strategy as long as the price of the RPR or non-trep RDT did not exceed the cost of the trep/non-trep RDT. Unfortunately, the cost of RPR, including transport to centralized or even international laboratories, will be prohibitively high in most of the settings in question, and we know of no plans to manufacture a non-trep point of care RDT.

Diagnosis and surveillance are essential to the yaws eradication effort. However, the yaws eradication effort is yet to be funded.[18] There are two situations of particular relevance in which savings could be substantial if the sequential testing strategy was implemented: first, during mass screening campaigns, before and after TCT; second, during final screening campaigns, including verification of the interruption of transmission. Cost savings from the sequential strategy could be reallocated to other essential interventions, such as sensitization to increase treatment coverage.

Our results will help enhance the cost-effectiveness of yaws programmes in the 13 countries known to be currently endemic. It will also inform efforts in the much larger group of 71 countries with a history of yaws, many of which will have to undertake surveillance to confirm the interruption of transmission.
References for this paper


89
**Supporting Information**

Selected Figures and Tables

**S1 Table. Pre-TCT treponemal and dually positive survey population prevalence.**

<table>
<thead>
<tr>
<th></th>
<th>GHA</th>
<th>PNG</th>
<th>SOL</th>
<th>VAN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>95% CI</td>
<td>N</td>
</tr>
<tr>
<td>Total tested</td>
<td>975</td>
<td>1.00</td>
<td>–</td>
<td>991</td>
</tr>
<tr>
<td>Trep positive</td>
<td>322</td>
<td>0.33</td>
<td>(0.3-0.36)</td>
<td>508</td>
</tr>
<tr>
<td>Trep negative</td>
<td>653</td>
<td>0.67</td>
<td>(0.64-0.7)</td>
<td>483</td>
</tr>
<tr>
<td>Trep/non-trep dually positive</td>
<td>108</td>
<td>0.11</td>
<td>(0.09-0.13)</td>
<td>181</td>
</tr>
</tbody>
</table>

GHA—Ghana; PNG—Papua New Guinea; SOL—Solomon Islands; VAN—Vanuatu; in Solomon Islands, post-TCT prevalence was assessed 6 months after TCT, whereas in other sites it was assessed 12 months after TCT; Ghana and Vanuatu used the trep/non-trep RDT, whereas Papua New Guinea and Vanuatu used the RPR with titre > 1:8; prevalences are therefore not directly comparable.

**S2 Table. Post-TCT treponemal and dually positive survey population prevalence.**

<table>
<thead>
<tr>
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<th>SOL</th>
<th>VAN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>95% CI</td>
<td>N</td>
</tr>
<tr>
<td>Total tested</td>
<td>1342</td>
<td>1.00</td>
<td>–</td>
<td>910</td>
</tr>
<tr>
<td>Trep positive</td>
<td>199</td>
<td>0.15</td>
<td>(0.13-0.17)</td>
<td>386</td>
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<tr>
<td>Trep negative</td>
<td>1143</td>
<td>0.85</td>
<td>(0.83-0.87)</td>
<td>524</td>
</tr>
<tr>
<td>Trep/non-trep dually positive</td>
<td>41</td>
<td>0.03</td>
<td>(0.02-0.04)</td>
<td>59</td>
</tr>
</tbody>
</table>

GHA—Ghana; PNG—Papua New Guinea; SOL—Solomon Islands; VAN—Vanuatu; in Solomon Islands, post-TCT prevalence was assessed 6 months after TCT, whereas in other sites it was assessed 12 months after TCT; Ghana and Vanuatu used the trep/non-trep RDT, whereas Papua New Guinea and Vanuatu used the RPR with titre > 1:8; prevalences are therefore not directly comparable.
S1 Fig. Number of true diagnoses of current infection across different scenarios of prevalence, by use case and strategy.

Best—best estimate (median); Low—low estimate (2.5th centile); High—high estimate (97.5th centile).
S2 Fig. Number of true current infection positives across different scenarios of prevalence, by use case and strategy.

Best—best estimate (median); Low—low estimate (2.5th centile); High—high estimate (97.5th centile).
S3 Fig. Incremental cost-effectiveness (cost per true positive gained) of combined testing strategy across different scenarios of prevalence, by use case.

Best—best estimate (median); Low—low estimate (2.5th centile); High—high estimate (97.5th centile); ICER—Incremental Cost Effectiveness Ratio (cost per correct diagnosis); grey areas without an ICER value indicate negative ICERs, where the combined testing strategy is less effective and more costly or more effective and less costly.
S4 Fig. Incremental costs and effects (correct diagnoses gained) of the combined testing strategy at the lower and upper limits of the plausible range of prevalence, by use case.

Dots represent the 1000 simulated values from the probabilistic sensitivity analysis; for individual diagnosis, the current/past infection prevalence ranges from 20% (lower limit) to 55% (upper limit), of which 20% (lower limit) or 75% (upper limit) are currently infected; for community screening, current/past infection prevalence is 15–45%, of which 5–50% are currently infected; cost and effects are expressed per 1000 people tested.

All files

http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0005985#sec011
Abstract

Background: The World Health Organization (WHO) has targeted yaws for global eradication. Eradication requires certification that all countries are yaws-free. While only 14 Member States currently report cases to WHO, many more are known to have a history of yaws and some of them may have ongoing transmission. We reviewed the literature and developed a model of case reports to identify countries in which passive surveillance is likely to find and report cases if transmission is still occurring, with the goal of reducing the number of countries in which more costly active surveillance will be required.

Methods: We reviewed published and unpublished documents to extract data on the number of yaws cases reported to WHO or appearing in other literature in any year between 1945 and 2015. We classified countries as: a) having interrupted transmission; b) being currently endemic; c) being previously endemic (current status unknown); or d) having no history of yaws. We constructed a panel dataset for the years 1945-2015 and ran a regression model to identify factors associated with some countries not reporting cases during periods when there was ongoing (and documented) transmission. For previously endemic countries whose current status is unknown, we then estimated the probability that countries would have reported cases if there had in fact been transmission in the last three years (2013-2015).

Results: Yaws has been reported in 103 of the 237 countries and areas considered. 14 Member States and 1 territory (Wallis and Futuna Islands) are currently endemic. 2 countries are believed to have interrupted transmission. 86 countries and areas are previously endemic (current status unknown). Reported cases peaked in the 1950s, with 55 countries reporting at least one case in 1950 and a total of 2.35 million cases reported in 1954. Our regression model suggests that case reporting during periods of ongoing transmission is positively associated with socioeconomic development and, in the short-term, negatively associated with
independence. We estimated that for 66 out of the 86 previously endemic countries whose current status is unknown, the probability of reporting cases in the absence of active surveillance is less than 50%.

**Discussion:** Countries with a history of yaws need to be prioritized so that international resources for global yaws eradication may be deployed efficiently. Heretofore, the focus has been on mass treatment in countries currently reporting cases. It is also important to undertake surveillance in the 86 previously endemic countries for which the current status is unknown. Within this large and diverse group, we have identified a group of 20 countries with more than a 50% probability of reporting cases in the absence of active surveillance. For the other 66 countries, international support for active surveillance will likely be required.

**Author Summary**

Yaws is a disabling and disfiguring disease. When the World Health Organization (WHO) was established in 1948, yaws was among the major public health problems that the new health agency chose to prioritize. In 2013, it formally targeted yaws for global eradication. While only 14 Member States currently report cases to WHO, many more are known to have a history of yaws and some of them may have ongoing transmission. Eradication requires certification that all countries are free of yaws. Certification, in turn, requires surveillance – and in some settings this may require population surveys or purposive case search. We reviewed the historical literature and developed a statistical model to better understand what factors were associated with some countries not reporting cases despite (likely) ongoing transmission. There are at least 86 countries or areas that stopped reporting cases but where yaws may still be present. Our model identified socioeconomic development and independence as factors associated with case reporting. Within the large and diverse group of countries with a history of yaws, we have identified a group of 20 countries with more than a 50% probability of reporting cases in the absence of active surveillance. For the other 66 countries, international support for active surveillance will likely be required.
Introduction

The endemic treponematoses are a group of chronic bacterial infections. This group is made up of: yaws, caused by Treponema pallidum subsp. pertenue; endemic syphilis (also known as bejel), caused by T. pallidum subsp. endemicum; and pinta, caused by T. carateum. Of these, yaws produces the highest burden of disease globally. It is transmitted through direct skin-to-skin contact. In its primary and secondary (early) stages it causes lesions of the skin (especially on the face and feet), cartilage and bones, resulting in pain as well as social stigma. About 10% of untreated cases suffer tertiary (late-stage) yaws, with permanent disability and disfigurement of the face, lower limbs and hands [1].

In 1948, when the World Health Organization (WHO) was established, endemic treponematoses were among the major public health problems that the new health agency chose to prioritize. The second (1949) World Health Assembly (WHA) adopted resolution 2.36 to address endemic treponematoses. The extensive geographical range of these infections and the high morbidity and disability they caused justified this urgency. In 1950, WHO estimated that 160 million people were infected with yaws [2].

WHO- and UNICEF-led initiatives of 1948–1953 targeted yaws in Bechuanaland (Botswana), Ecuador, Haiti, India, Indonesia, Lao People’s Democratic Republic, Liberia, Paraguay, Philippines and Thailand [3]. Success in those initial pilot projects supported the planning of mass treatment campaigns using injectable penicillin in 46 countries from 1953–1963. These campaigns reduced the estimated global prevalence of infection from 50 million to 2.5 million by 1964 [4].

At the time, no formal certification process to confirm local elimination had been developed. Vertical yaws programmes were progressively integrated into national primary health care systems. By 1995 WHO estimated the global prevalence at 460,000 infectious cases. Over 300,000 new cases were reported by 13 countries during 2008 to 2012 [2]. It is difficult to ascertain whether the countries that stopped reporting yaws cases did so due to the interruption of transmission or simply the interruption of reporting.

The endemic treponematoses are so-called “diseases of poverty”, and human development, including economic growth, poverty reduction, improved access to health care and education, and improvements in access to water and sanitation naturally help to eliminate them by eliminating conditions which favour ongoing transmission. Interruption of transmission of endemic syphilis in Bosnia-Herzegovina, for example, was achieved by mass treatment campaigns “against a background of rapid socioeconomic change in the affected population, along with the creation of modern health services to cover the entire population” [5]. Among the factors to which are attributed the recession of yaws in Sri Lanka are: use of soap, improved water, and extended roads [6].

In 2013, the sixty-sixth WHA adopted resolution 66.12, targeting the eradication of yaws by 2020. Eradication is the “permanent reduction to zero of the worldwide incidence of an infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed” [7]. A global eradication programme therefore requires certifying that all countries are free of the disease. To achieve global certification of guinea worm disease (dracunculiasis) eradication, for example, WHO has been formally certifying every individual country, even if no indigenous case has ever been recorded there [8]. However, different countries will require different levels of intensity in the surveillance activities undertaken to proceed through the stages of certification.

A country reporting zero new indigenous yaws cases over a complete calendar year is considered to be in the first, pre-certification stage. In some countries, active community-based surveillance and periodic case searches, including cash rewards, may be required to
detect new cases. In others, passive surveillance through Integrated Disease Surveillance and Response or other existing systems, plus ad hoc case searches, may suffice.

It is currently recommended that a country will enter into certification only if: 1) it has reported 0 new indigenous cases for 3 or more consecutive calendar years; 2) it shows no evidence of recent transmission (no children aged 1–5 years with rapid plasma reagin seroreactivity); and 3) it documents negative polymerase chain reaction (PCR) for *Treponema pallidum* subspecies *pertenue* in suspected lesions [9]. Certification activities include a visit by an international team to assess the adequacy of the surveillance system, review records of rumour cases and interview health workers and affected populations.

After certification, a country will automatically enter into post-certification. Some surveillance will need to be maintained until global eradication is achieved. In countries with strong health systems, this may again be passive surveillance; in others, relatively active but localised surveillance may be required, particularly if there is transmission of yaws in a neighbouring country.

The cost of global certification of guinea worm disease eradication has not been trivial. Pre-certification and certification/post-certification have cost millions of US$ a year [10]. Lessons from that programme suggest that “It is important to reduce the cost of certification and at the same time to ensure that interruption of the disease transmission has really taken place. It is also important not to overload a country’s health system with work when the disease is no longer a public health problem and interest in it has waned” [11].

In the case of yaws eradication, the group of countries that will have to undertake surveillance is larger and more diverse, and the cost could be higher. In this study, we reviewed the literature for reports of active yaws cases and developed a descriptive model to identify countries in which passive surveillance is likely to find cases if transmission is still occurring, and thereby provide evidence to inform a reduction in the number of countries in which augmented efforts and more costly active surveillance will be required.

**Methods**

A literature search was conducted on 21 September 2016 for articles published between 1 January 1945 and 21 September 2016. We updated the search on 21 December 2017.

We searched for articles on yaws (frambesia). We considered other variations on the name, based on the languages of the major colonial empires of the post-World War II era: Dutch (framboesia), French (pian), Spanish (buba) and Portuguese (bouba). Given the post-colonial alignment of many African states with the Union of Soviet Socialist Republics (USSR), we confirmed that search engines were capturing transliterated results for фрамбезия OR frambeziya. We checked also for “pathek” (specific to Indonesia), “parangi” (specific to Sri Lanka), “gangosa” and “goundou” (referring to particular clinical manifestations).

In PubMed, our search included the following terms: yaws[MeSH] OR yaws[Title] OR treponematoses[Title] OR “Treponema pertenue”[Title] OR framboesi*[Title] OR framboesia*[Title] OR pian[Title] OR buba[Title] OR bouba[Title]. In Global Health – CABI, we applied the same search terms but using “yaws” as a subject term rather than a MeSH term.

The search terms yaws OR treponematoses OR “Treponema pertenue” OR frambesia OR framboesia OR pian OR buba OR bouba were applied (without limit to field) in the WHO Institutional Repository for Information Sharing (WHO IRIS), containing all the published information produced by WHO, including proceedings of the WHA and WHO Executive
Board, monographs, periodicals, unpublished technical documents, press releases, fact sheets and administrative documents of the governing bodies. From the Pan American Health Organization Institutional Repository for Information Sharing (PAHO IRIS) we extracted all “Health in the Americas” reports containing any of the above search terms, as not all of these regional reports were available through WHO IRIS.

For citations from developing countries and regions and articles published in journals that are less frequently indexed in PubMed and Global Health – CABI, we performed the same search within Global Index Medicus, and the regional indexes for Africa (AIM), Latin America and the Caribbean (LILACS), South-East Asia (IMSEAR), Eastern Mediterranean (IMEMR), and Western Pacific (WPRIM).

We also searched for the same terms in the WHO Archives, containing mainly textual paper documents, such as correspondence and mission reports. For reasons of confidentiality, these records can be consulted only 20 years after their production, so this search was limited to documents dated 7 April 1948 (the date WHO was established) to 21 December 1997.

We complemented these sources with those in the Global Infectious Disease Epidemiology Network review, which extracted reported case numbers from health ministry publications and ProMED, an internet-based reporting system on infectious disease outbreaks [12].

We included documents reporting active primary/secondary cases with clinical manifestations, regardless of whether these were laboratory-confirmed or not. Active cases include both infectious yaws (i.e., presenting with skin lesions) and non-infectious yaws (i.e., presenting with cartilage and bone but no skin lesions). Reports of latent cases (i.e., infections without any lesions, detectable only by serology) or late / tertiary cases with permanent clinical manifestations (e.g., gangosa, goundou) but no active disease were also included, but classified as reports of zero new cases.

Case reports of imported cases only were not included. However, if the country of origin was reported, we checked to ensure that the country of origin was nonetheless listed in our database as a country with a history of yaws.

We reviewed all titles and available abstracts. If available abstracts were relevant but did not contain the number of reported cases or the countries in which those cases occurred, we attempted to retrieve the full text. If full texts did not contain both the number and year(s) of cases, but instead only a general statement about past endemicity, we marked the country as previously endemic but did not further consider the reference for analysis. If the full text was not available, we classified the reference as “full text not available”. If no abstract or full text was available, we classified the reference as “abstract and full text not available” and it was not further considered in the present study.

One author extracted from each document (abstract and, if available, full text) the country and year of case reports and number of cases reported and entered data into an Excel spreadsheet. Separately, the same author extracted information on the mass treatment campaigns of 1946–1963, both national and subnational, as summarized in two WHO documents [3,13]. After 1963, programs were implemented only sporadically [14].

When cases were reported for periods of multiple years, we recorded the average number of cases per year for each year (assuming that case reporting occurred in each year of the period). In the case of inconsistencies between sources reporting on the same country and year, we took the higher number, assuming that lower numbers represented partial reports (i.e., less than 12 months’ reporting or less than national coverage).
We classified all countries and areas for the year 2015, the latest year for which WHO had received case reports at the time of writing (Table 1).

Table 1. Grouping of countries according to yaws endemicity status in 2015

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Description</th>
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<tr>
<td>A.1</td>
<td>Interrupted transmission</td>
</tr>
<tr>
<td>A.2</td>
<td>Currently endemic</td>
</tr>
<tr>
<td>B.1</td>
<td>Previously endemic</td>
</tr>
<tr>
<td>B.2</td>
<td>No history of case reports</td>
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</tbody>
</table>

We described the distribution of endemicity by WHO region and World Bank income group. Income groups are based on Gross National Income (GNI) per capita (Atlas method) of 2013 [15].

We constructed a panel dataset based on all $N$ countries with a history of case reports (A.1, A.2 and B.1), over a maximum $T=71$ years (1945-2015), as determined by the availability of data (see below). We calculated the frequency of case reporting and total number of cases reported over time. We then performed a multivariable regression of the case reporting variable on other variables with which it might be associated.

Case reporting was represented by a binary variable. It was coded as 1 in years in which a positive and specific number of cases were reported and 0 in years in which there was no positive report (0 cases or no report) or in which the specific number of cases and years were not reported. It was coded as not available (i.e. missing) in the years after the last case report for a given country. In other words, we limited ourselves to data before the last reported case, to focus on the absence/presence of case reports due to the absence/presence of adequate surveillance, rather than due to the absence/presence of new cases.

We considered a generalized linear model with random effects. With random effects we could include time-invariant variables and make predictions beyond the countries used in the model (i.e., for those countries without case reports). The problem of omitted variable bias was not a major concern insofar as we were not trying to get estimates of the true regression coefficients, but to make predictions that were the best that the available data would allow.

In particular, we considered the following model specification:

\[
REP_{it} = \text{REP}_{i,t-3}\beta_{1} + \log(gdp_{it})\beta_{2} + IND_{it}\beta_{3} + IND_{it-3}\beta_{4} + IND_{it-9}\beta_{5} + IND_{it-9}\beta_{6} + IND_{it-1}\beta_{7} + CON_{it}\beta_{9} + CON_{it-3}\beta_{10} + \sqrt{\text{AIDS}_{it}}\beta_{12} + CAM_{it}\beta_{13} + ARA_{i}\beta_{14} + u_{i} + \epsilon_{t}
\]

for $i=1,\ldots,N$ countries and $t=1,\ldots,T_{i}*$ years, where:

$REP_{it}$ is a dummy variable indicating if there was a case report in any of the last three calendar years up to and including year $t$ in country $i$, from 1947 (based on years 1945–1947)
until the year of the last case report, available through this study; the choice of three years is determined by one of the criteria for yaws certification (see Introduction);

$REP_{it-3}$ is a lagged dependent variable to model the dynamics (persistence) in case reporting, the idea being that a country is more likely to report in the current period if they reported in the previous period, in part because of recent experience with detecting the disease; a three-year lag was chosen to avoid any overlap in years between the dependent and lagged dependent variables;

$gdp_{it}$ is a three-year moving average (mean) of expenditure-side real GDP per capita at chained PPPs, for a comparison of relative living standards across countries, available from the Penn World Tables (version 9.0) from 1950, but not for all countries [18,19]; this variable is meant to capture the overall quality and reach of surveillance systems;

$IND_{it}$ is a dummy variable indicating whether a country gained independence from any colonial powers in any of the last three calendar years up to and including year $t$; colonial history data are available from the Correlates of War since 1945 [20]; this variable is meant to capture any political disruption to surveillance systems;

$IND_{it-3}$, $IND_{it-6}$, $IND_{it-9}$, and $IND_{it-12}$ are 3-, 6-, 9- and 12-year lags of the $IND_{it}$ variable, allowing for some persistence in political disruption to surveillance systems;

$CON_{it}$ is a dummy variable indicating whether there was armed conflict in any of the last three calendar years up to and including year $t$, defined by at least 25 battle-related deaths; data are available from Uppsala Conflict Data Program since 1946 [21]; again, this variable is meant to capture disruptions to surveillance systems;

$CON_{it-3}$ is a 3-year lag of the $CON_{it}$ variable, allowing for some persistence in disruption to surveillance systems due to armed conflict;

$aids_{it}$ is a three-year moving average (mean) of the estimated number of AIDS-related deaths per 10,000 population, available from UNAIDS since 1990, and assumed equal to 0 in the period 1945-1989 and for all countries not reporting data to UNAIDS; this variable is meant to serve as a proxy for reorientation of yaws surveillance systems toward other public health priorities in the 1990s [22];

$CAM_{it}$ is a dummy variable indicating whether a mass campaign (national or subnational) was undertaken in any of the last three calendar years up to and including year $t$; data are based on campaigns led by WHO or UNICEF in 1948–1963 [3,13]; during years of mass campaigns, the probability of detecting and reporting cases is higher than with passive surveillance alone;

$ARA_{it}$ is a time-invariant dummy variable for countries where Arabic is an official language; this variable is meant to correct for the fact that our literature review did not include Arabic language search terms, and that many Arabic language journals are not indexed by PubMed;

$\alpha$ is the intercept;

$u_{it}$ is the country-specific random effect;

$\varepsilon_{i}$ is the year-specific random effect; and

$T_{i}^*$ is the year of the last case report for country $i$.

Logarithmic ($\log$) and square root ($\sqrt{\cdot}$) transformations were done to improve fit of the linear model by minimizing Akaike Information Criterion values.
The lagged dependent variable \((REP_{t-3})\) will be correlated with the error term. The regression coefficient for the lagged dependent variable \((\beta_1)\) will be upwardly biased and the coefficients for other variables will be downwardly biased, in absolute terms. We therefore also ran Model (2), replacing the lagged dependent variable with two new variables:

\[
(2) \quad REP_{it} = \sqrt{\text{yrs}_{it-3})} \beta_0 + \log(\text{num}_{it-3}) \beta_1 + \log(\text{gdppc}_{it}) \beta_2 + IND_{it} \beta_3 + IND_{it-3} \beta_4 + IND_{it-6} \beta_5 + IND_{it-9} \beta_6 + IND_{it-12} \beta_7 + CON_{it} \beta_8 + CON_{it-3} \beta_9 + \sqrt{\text{aid}_{it}} \beta_{10} + \text{CAM}_{it} \beta_{11} + \text{ARA}_{it} \beta_{12} + \alpha + u_i + \epsilon_t
\]

where:

- \text{yrs}_{it-3} is the number of years since the most recent case report (previous to \(t-3\)); a three-year lag was chosen to avoid any overlap in years with the dependent variable; and
- \text{num}_{it-3} is the number of cases reported in the most recent case report, per 10 000 population; again, a three-year lag was chosen to avoid any overlap in years with the dependent variable.

Given that GDP data were available for a limited number of countries (and that GDP data are more likely to be missing for poorer countries), we also considered as a proxy for the quality and reach of surveillance systems, the logistic transformation of urban population share \((urb_{it})\), with complete data since 1950 [23]:

\[
(3) \quad REP_{it} = \sqrt{\text{yrs}_{it-3})} \beta_0 + \log(\text{num}_{it-3}) \beta_1 + \logit(urb_{it}) \beta_2 + IND_{it} \beta_3 + IND_{it-3} \beta_4 + IND_{it-6} \beta_5 + IND_{it-9} \beta_6 + IND_{it-12} \beta_7 + CON_{it} \beta_8 + CON_{it-3} \beta_9 + \sqrt{\text{aid}_{it}} \beta_{10} + \text{CAM}_{it} \beta_{11} + \text{ARA}_{it} \beta_{12} + \alpha + u_i + \epsilon_t
\]

Using the resulting regression coefficients from Model (3), and setting the Arabic language variable to 0, we predicted the probability of case reporting in the years after the last reported case. Since the regression model was run on data from years of (presumed) ongoing transmission, the predicted probabilities for (later) years of unknown transmission should be interpreted as the probability that a given country would report cases in a given three-year period if there were in fact new cases to report.

The predicted value for the year 2015, \(REP_{2015}\), is constrained to values between 0 and 1. In the absence of mass treatment campaigns \((CAM_{2015} = 0)\), we interpreted \(REP_{2015}\) as the probability that a given country would “report” cases through routine, generally passive surveillance, if transmission were ongoing. We therefore used \(REP_{2015}\) to identify countries in which passive surveillance might be sufficient. For the sake of illustration, we set the minimum cut-off for the probability of reporting at 50%.

All data were analysed using the open-access software R [16]. The data and code are available with this paper as Supporting Information.

### Results

#### Literature search

The PubMed, Global Health – CABI and Global Index Medicus searches identified 2434 items to be assessed. WHO IRIS yielded 5450 results. Given the volume of results and low yield (2 relevant documents) from the first 100 results, we limited our WHO IRIS search to the following titles: “Weekly epidemiological record” yielded 73 references; “Report on the world health situation”, 20; “Reported cases of notifiable diseases”, 12; “Country health information profiles”, 8; and “Socioeconomic and health indicators”, 12. PAHO IRIS yielded
9 reports on “Health conditions in the Americas”. WHOLIS provided 58 documents. WHO Archives yielded another 18 correspondences and mission reports.

Altogether, after removing duplicates, we identified 2392 documents. 162 of these did not have an available abstract or full-text. The remaining 2230 documents were assessed for inclusion. Full-texts were assessed for inclusion only when the year and number of case reports was not reported in the abstract. 73 full-texts were not available. Another 1744 documents were found to not contain case reports of non-imported active clinical yaws cases.

A total of 413 abstracts or full-texts had relevant data that could be extracted. The flow diagram and list of included studies, after removal of duplicates, is provided in Supporting Information S1 Figure and S2 Table.

**Status of endemicity**

We describe here the status of yaws endemicity for the 194 Member States of WHO, as well as for 9 areas for which we found separate case reports in the literature: British Virgin Islands, French Guiana, Guadeloupe, Guam, Martinique, Montserrat, New Caledonia, Puerto Rico, and Wallis and Futuna Islands.

Of the 203 countries and areas considered, 96 have reported active clinical non-imported yaws cases since 1945. Figure 1 displays the endemicity status for the 96 countries with some history of yaws case reports, as defined in this study. References to yaws were found for another 7 Member States, not displayed here because no specific case reports could be extracted from the available references. These 7 Member States are: Bangladesh (Chittagong Hills), El Salvador, Honduras, Marshall Islands, Myanmar (“Northern and Southern Burma”), Nauru and Nicaragua [12,24–27].
Figure 1. Yaws endemicity status, 2015. A.1: Interrupted transmission; A.2: Currently endemic; B.1: Previously endemic (current status unknown); B.2: No history of case reports. References to yaws were found for another 7 Member States, displayed here as not available (NA) because of non-specific case reports: Bangladesh, El Salvador, Honduras, Marshall Islands, Myanmar, Nauru and Nicaragua. In addition to Member States, there are 9 countries or areas with a history of yaws for which categorization is not displayed on this map: British Virgin Islands, French Guiana, Guadeloupe, Guam, Martinique, Montserrat, New Caledonia, Puerto Rico, and Wallis and Futuna Islands. Created using R and World Health Organization shapefiles under Creative Commons license (CC-BY).

Two of the 96 countries (Ecuador and India) report having interrupted transmission, although one (Ecuador) has not yet been certified by WHO. 14 WHO Member States and one non-Member State (Wallis and Futuna Islands) are currently reporting yaws cases. These are all located within the African, South-East Asian and Western Pacific Regions (Table 2).
### Table 2. Yaws endemicity status by WHO region, 2015

<table>
<thead>
<tr>
<th>Region</th>
<th>A: Current status known</th>
<th>B: Current status unknown</th>
<th>Total countries and areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A.1: A.2:</td>
<td>B.1: B.2: No history</td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>0 8</td>
<td>28 11</td>
<td>47</td>
</tr>
<tr>
<td>Americas</td>
<td>1 0</td>
<td>24 10</td>
<td>35</td>
</tr>
<tr>
<td>Eastern</td>
<td>0 0</td>
<td>2 19</td>
<td>21</td>
</tr>
<tr>
<td>Europe</td>
<td>0 0</td>
<td>0 53</td>
<td>53</td>
</tr>
<tr>
<td>South East Asia</td>
<td>1 2</td>
<td>2 6</td>
<td>11</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>0 4</td>
<td>15 8</td>
<td>27</td>
</tr>
<tr>
<td>Non Member</td>
<td>0 1^a</td>
<td>8^b 0</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>2 15</td>
<td>79^c 107</td>
<td>203</td>
</tr>
</tbody>
</table>

^a Wallis and Futuna

^b British Virgin Islands, French Guiana, Guadeloupe, Guam, Martinique, Montserrat, New Caledonia, Puerto Rico, and Wallis and Futuna Islands.

^c References to yaws were found for another 7 Member States, not included here because of non-specific case reports: Bangladesh, El Salvador, Honduras, Marshall Islands, Myanmar, Nauru and Nicaragua.

The current status of another 79 countries and areas with a history of yaws case reports remains unknown. These previously endemic countries are widely distributed: 28 of 47 Member States in Africa, 24 of 35 in the Americas, and 15 of 27 in the Western Pacific. Europe is the only WHO Region with no history of yaws since 1945.

The 14 currently endemic WHO Member States are all low- and lower-middle income countries (Table 3). Of the 79 previously endemic countries, 23 are low income and 16 are lower-middle income; at least 35 are today upper-middle income or high income.

### Table 3. Yaws endemicity status by World Bank income group, 2015

<table>
<thead>
<tr>
<th>Income group</th>
<th>A: Current status known</th>
<th>B: Current status unknown</th>
<th>Total countries and areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A.1: Interrupted</td>
<td>A.2: Currently</td>
<td>B.1: Previously</td>
</tr>
<tr>
<td></td>
<td>transmission</td>
<td>endemic</td>
<td>endemic</td>
</tr>
<tr>
<td>Low</td>
<td>0 4</td>
<td>23 7</td>
<td>34</td>
</tr>
<tr>
<td>Lower-middle</td>
<td>1 10</td>
<td>16 21</td>
<td>48</td>
</tr>
<tr>
<td>Upper-middle</td>
<td>1 0</td>
<td>24 32</td>
<td>57</td>
</tr>
<tr>
<td>High</td>
<td>0 0</td>
<td>11 47</td>
<td>58</td>
</tr>
<tr>
<td>Not categorized by the</td>
<td>0 1^a</td>
<td>5^b 0</td>
<td>6</td>
</tr>
<tr>
<td>World Bank</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2 15</td>
<td>79^c 107</td>
<td>203</td>
</tr>
</tbody>
</table>

^a Wallis and Futuna

^b British Virgin Islands, French Guiana, Guadeloupe, Guam, Martinique, Montserrat, New Caledonia, Puerto Rico, and Wallis and Futuna Islands.

^c References to yaws were found for another 7 Member States, not included here because of non-specific case reports: Bangladesh, El Salvador, Honduras, Marshall Islands, Myanmar, Nauru and Nicaragua.
Counting the 79 countries with specific case reports as well as the 7 countries with non-specific case reports, there are 86 previously endemic countries (current status unknown) that could, in principle, enter into pre-certification on the basis of a single report of zero cases to WHO. This large and diverse group of countries therefore requires further sub-categorization to inform the prioritization of active surveillance towards subsequent certification by WHO.

**Frequency of case reports**

Figure 2 depicts the number of countries reporting cases and cases reported, over the years 1945–2015. 54 countries reported yaws cases in 1950. The greatest number of cases reported in a given year was 2.35 million in 1954, in the midst of mass treatment campaigns by WHO and UNICEF. When displayed against a logarithmic scale, a large but temporary drop in the number of cases reported is visible in the second half of the 1990s, when high burden countries Cote d’Ivoire and the Solomon Islands both temporarily stopped reporting cases.

**Figure 2. Number of yaws cases reported, and countries and areas reporting cases and undertaking mass treatment campaigns, 1945-2015.** The number of countries and areas undertaking national or subnational campaigns refers to the period 1948-1963 only.
Figure 3 identifies the 96 countries and areas with some history of yaws case reports (A.1, A.2 and B.1 countries) with the year of the most recently reported case. Puerto Rico last reported a case in 1945. Most countries have not reported a case since the mid-1980s. The 14 Member States considered by WHO as currently endemic have all reported at least one case since 2004. Furthermore, Wallis and Futuna Islands last reported cases in 2010. Ecuador and India last reported cases in 2005 and 2003, respectively.

Figure 3. Year of most recently reported yaws case in currently or previously endemic countries/areas, 2015. In addition to Member States, there are 9 countries or areas with a history of yaws for which data are not included in this map: British Virgin Islands, Guadeloupe, French Guiana, Guam, Montserrat, Martinique, New Caledonia, Puerto Rico, and Wallis and Futuna; for Bangladesh, El Salvador, Honduras, Marshall Islands, Myanmar, Nauru, and Nicaragua we found only general references to yaws endemicity (but no case reports). Created using R and World Health Organization shapefiles under Creative Commons license (CC-BY).

The percentage of countries reporting cases before the (country-specific) most recent case report (i.e., in years of known transmission) varied from a low of 17% (3 out of 18) in 1998 to a high of 86% (12 out of 14) in 2010. 60 countries reported in fewer than 50% of years of known transmission; 24 countries, including Australia, reported in fewer than 20% of such years; 14 countries, including China (with only one report, in 1957) [28], reported in fewer than 10% of such years.

Profound change has occurred in many previously endemic countries since their most recent case reports. Most have experienced real economic growth of 100–200%. A large number of countries gained their independence from colonial powers in the 1960s. By the year 1990, 50 countries had experienced at least one year of more than 25 battle-related deaths in armed conflict. By the year 2000, 50 were reporting AIDS-related deaths of more than 1 per 10 000 population.

In the next section, we report on factors associated with case reporting in the years before the most recent case report.
Variables associated with case reporting

The results of the regression model are presented in Table 4.

Table 4. Association between yaws case reporting and selected variables in the years before the most recent case report, all countries with a history of yaws. In the leftmost column, short variable descriptions are provided with the variable names as they appear in equations 1-3 – please refer to the Methods for a detailed description of each variable; the next three columns give the regression coefficients for each of the three model specifications corresponding to equations 1-3; the standard error of the estimate is reported in parentheses below the coefficient.

<table>
<thead>
<tr>
<th>Variable Description</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-2.96***</td>
<td>-2.42***</td>
<td>1.68***</td>
</tr>
<tr>
<td>Case reported in previous period, REP&lt;sub&gt;t-3&lt;/sub&gt;</td>
<td>0.99***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average GDP per capita in current period, log(gdp&lt;sub&gt;t&lt;/sub&gt;)</td>
<td>0.38***</td>
<td>0.46***</td>
<td></td>
</tr>
<tr>
<td>Independence obtained in current period, IND&lt;sub&gt;t&lt;/sub&gt;</td>
<td>-0.75***</td>
<td>-0.78***</td>
<td>-0.15</td>
</tr>
<tr>
<td>Independence obtained in previous period, IND&lt;sub&gt;t-3&lt;/sub&gt;</td>
<td>-1.36***</td>
<td>-1.28***</td>
<td>-0.49**</td>
</tr>
<tr>
<td>Independence obtained in previous period, IND&lt;sub&gt;t-6&lt;/sub&gt;</td>
<td>-1.41***</td>
<td>-1.42***</td>
<td>-0.70***</td>
</tr>
<tr>
<td>Independence obtained in previous period, IND&lt;sub&gt;t-9&lt;/sub&gt;</td>
<td>-1.21***</td>
<td>-1.20***</td>
<td>-0.66***</td>
</tr>
<tr>
<td>Independence obtained in previous period, IND&lt;sub&gt;t-12&lt;/sub&gt;</td>
<td>0.30</td>
<td>0.39*</td>
<td>0.59***</td>
</tr>
<tr>
<td>Armed conflict in current period, CON&lt;sub&gt;t&lt;/sub&gt;</td>
<td>0.33**</td>
<td>0.39**</td>
<td>0.36**</td>
</tr>
<tr>
<td>Armed conflict in previous period, CON&lt;sub&gt;t-3&lt;/sub&gt;</td>
<td>-0.02</td>
<td>0.02</td>
<td>0.00</td>
</tr>
<tr>
<td>Average AIDS deaths in current period, per 10 000 population, sqrt(aids&lt;sub&gt;t&lt;/sub&gt;)</td>
<td>-0.19***</td>
<td>-0.15**</td>
<td>-0.21***</td>
</tr>
<tr>
<td>Mass treatment campaign undertaken in current period, CAM&lt;sub&gt;t&lt;/sub&gt;</td>
<td>0.47**</td>
<td>0.29</td>
<td>0.04</td>
</tr>
<tr>
<td>Arabic language is an official language, ARA</td>
<td>0.17</td>
<td>-0.00</td>
<td>0.28</td>
</tr>
<tr>
<td>Number of years since most recent case report, sqrt(yrs&lt;sub&gt;t-3&lt;/sub&gt;)</td>
<td>-0.36***</td>
<td>-0.31***</td>
<td></td>
</tr>
<tr>
<td>Number of cases reported in most recent case report, per 10 000</td>
<td>0.07***</td>
<td>0.08**</td>
<td></td>
</tr>
<tr>
<td>Average urban population share in current period, logit(urb&lt;sub&gt;t&lt;/sub&gt;)</td>
<td>0.64***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Log-Likelihood: -835.67, -788.15, -1091.27
Num. obs.: 1773, 1681, 2232
Model (1) is applied to an unbalanced panel of 63 out of 96 countries, with a total of 1773 observations. Model (2) replaces the lagged dependent variable from Model (1). Persistence in case reporting is captured instead by the number of years since the most recent case report, and by the number of cases reported in that year.

Replacing GDP per capita with the urban population share, Model (3) is applied to an unbalanced panel of 77 out of 96 countries, with a total of 2232 observations. 19 of 96 countries and areas with some history of yaws last reported cases before 1960 and did not have sufficient observations for the specified lagged variables.

In all three models, most of the regression coefficients have the expected signs. Negatively associated with yaws case reporting are: independence (becoming less negatively associated the greater the number of years since independence), AIDS deaths per 10 000 population, and number of years since the most recent case report. Positively associated with yaws case reporting are: case reporting in the previous period or the number of cases reported in the most recent case report, mass treatment campaigns and GDP per capita or the urban population share.

It is worth noting that the coefficients on the armed conflict variable are not of the expected sign, being positively associated with case reporting. This unexpected result could be due to imprecise estimation, with armed conflict following independence in many countries. In any case, as these are meant to be predictive not explanatory models, we do not go into any detail here on the statistical significance of any individual coefficient.

**Predicted probability of case reporting**

Using Model (3), we predicted the probability that a given country would report cases in the three year period ending in 2015, through passive surveillance alone, if there were in fact new cases (i.e., conditional on there being ongoing transmission). The predicted probabilities $REP_{i20}$ are displayed in Figure 4 for 86 previously endemic countries (current status unknown). Since we used a random effects model, we were able to predict probabilities also for the 7 Member States with only non-specific case reports (Bangladesh, El Salvador, Honduras, Marshall Islands, Myanmar, Nauru and Nicaragua), with the conservative assumption that a single case was reported in 1945.
Predicted probabilities and their 95% confidence intervals are presented, by country, in Supporting Information S2 Table.

There are 66 countries and areas with less than a 50% probability of reporting cases in the three year period ending 2015, even if there had in fact been ongoing transmission. That leaves only 20 countries and areas with a more than 50% probability of reporting cases in the absence of active surveillance. If we consider uncertainty and take the lower bound of the 95% confidence interval, only 8 countries and areas had a better than 50:50 chance of reporting cases. Only four of these countries/areas have a probability (best estimate) of 80% or higher: Puerto Rico, Guadeloupe, Nauru and Singapore.

The median predicted probability for currently endemic countries and areas is 73%, ranging from 6% in Wallis and Futuna Islands to 89% in Congo. Excluding Wallis and Futuna, which is an outlier (with a 100% rural population), the range is 60-89%. The prediction that the probability of reporting is significantly less than 100% even for currently endemic countries is given credence by the fact that WHO has not received reports from these countries in all years since formal adoption of the yaws eradication target.

**Discussion**

There is a need to prioritize countries with a history of yaws so that international resources for global eradication can be deployed efficiently.

So far the focus has been on mass treatment in the Member States that are currently reporting cases to WHO. A strategy for roll-out of mass treatment for yaws has been
articulated [9]. WHO continues to focus on mobilizing the necessary resources, including donations of medicines and rapid diagnostic tests, for “total community treatment” of endemic villages. Based on our review of the literature, there is a territory (Wallis and Fortuna Islands) belonging to a Member State (France) that can also be considered currently endemic, but from which WHO is not currently receiving reports.

It is also important to develop a strategy for surveillance in the 86 previously endemic countries whose current status is unknown. Within this large and diverse group, we have identified a group of 20 countries more than a 50% probability of reporting cases in the absence of active surveillance. These countries could, in principle, begin to prepare a dossier for certification. The dossier would have to include, based on current requirements, no evidence of clinical yaws among children aged 0–15 years and evidence of the absence of rapid plasma reagin sero-reactivity among children aged 1–5 years [9].

For subsequent certification, as in the case of guinea worm disease eradication [11], countries should be required to provide WHO a signed declaration confirming the absence of local transmission and also to complete an assessment of whether they indeed have satisfactory surveillance which could detect yaws cases if they occurred. Quality standards for “satisfactory surveillance” need to be formalized and documented, based on the experience of the expert group led by WHO that certified the eradication of yaws in India in 2016.

The remaining 66 previously endemic countries will likely need international support for active surveillance. The ones with a high probability of transmission should undertake population surveys (they will require mapping for eventual intervention); others, with a low probability of transmission, should consider purposive case search (to provide evidence of the absence of cases). In this study, we cannot distinguish between these two groups of countries because we have only estimated the probability of reporting conditional on transmission, not the probability of transmission itself. The latter is hardly possible with the available data, but a Delphi approach could perhaps permit meaningful grouping of these countries.

There are several other limitations to this study.

First, the literature identified 235 studies for which the abstract or full-text could not be retrieved. However, when the title or abstract referred to yaws in a specific country, we confirmed that case reports had been extracted from other references. Most (141 of 235) of the studies in this category were published in 1960 or earlier – during a time when reporting to WHO was still quite complete – so it is likely that relevant data were available to us from other sources.

Second, more troublingly, is the inconsistent definition of cases in the literature – sometimes referring to clinically suspected, sometimes lab-confirmed clinical cases; sometimes officially notified, sometimes independently reported cases; sometimes infectious cases only, sometimes both infectious and non-infectious cases. On the other hand, we have used a measure of case reporting that should be relatively insensitive to inconsistencies in case definitions: we used not the number of cases reported, but simply a binary variable indicating that there was at least one case reported.

Third, the descriptive model was limited by the availability of historical data from 1945. For example, we could not include poverty or income inequality measures because data were available only from 1980, and then only somewhat inconsistently until 1990. In high income countries where economic wealth is unequally distributed over geographic areas, there may remain neglected communities with inadequate surveillance.

Fourth, we limited our regression analysis to modelling presence/absence of case reporting conditional on ongoing transmission in the years before the last reported case. A
model of disease transmission in the years after the last reported case was beyond the scope of this paper.

Fifth, the 50% cut-off was chosen arbitrarily. Our recommendations are therefore based primarily on the relative ranking of countries, not on their predicted probabilities, which are low overall. Threshold probabilities can be made more evidence-based as active surveillance is undertaken. One might wish to sample some of the countries with a high probability of reporting but no reports and do active surveillance regardless; if cases are found, there is reason to question the robustness of the model and/or cut-off.

In spite of these limitations, our work will facilitate discussions with countries to assess their interest in and readiness for either certification (based on passive surveillance) or active surveillance. Integration of active surveillance with other large scale prevalence surveys for trachoma and other neglected tropical diseases could be considered [31–33].
References for this study


Supporting Information

Selected Figures and Tables

Supporting Information S1 Figure. Flow diagram of literature review.

Records identified through Pubmed, Global Health – CABI and Global Index Medicus (n = 2434)

Additional records identified through other sources (n = 210)

Records after duplicates removed (n = 2392)

Abstracts assessed (n = 2230)

Full-texts assessed if necessary (n = 2157)

Abstracts or full-texts from which data were extracted (n = 413)

Abstracts and full-texts not available (n = 162)

Full-texts not available when necessary (n = 73)

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**All files**

All other files will be available with the published paper.
Chapter 2.3 The economics of certification
Paper 2.3.1 The cost-effectiveness of an eradication programme in the end game: evidence from guinea worm disease

Published paper
Available at: http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0005922

Authors and Affiliations
Christopher Fitzpatricka*, Dieudonné P. Sankaraa, Junerlyn Farah Aguaa, Lakshmi Jonnalageddaa, Filippo Rumiia, Adam Weissa, Matthew Bradenb, Ernesto Ruiz-Tibenb, Nicole Krusec, Kate Brabandc, Gautam Biswasb
a Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland
b Guinea Worm Eradication Program, The Carter Center, Atlanta, Georgia, United States of America
c Development Office, The Carter Center, Atlanta, Georgia, United States of America
* fitzpatrickc@who.int

Abstract
Background: Of the three diseases targeted for eradication by WHO, two are so-called Neglected Tropical Diseases (NTDs) – guinea worm disease (GWD) and yaws. The Guinea Worm Eradication Programme (GWEP) is in its final stages, with only 25 reported in 2016. However, global eradication still requires certification by WHO of the absence of transmission in all countries. We analyze the cost-effectiveness of the GWEP in the end game, when the number of cases is lower and the cost per case is higher than at any other time. Ours is the first economic evaluation of the GWEP since a World Bank study in 1997.

Methods: Using data from the GWEP, we estimate the cost of the implementation, pre-certification and certification stages. We model cost-effectiveness in the period 1986-2030. We compare the GWEP to two alternative scenarios: doing nothing (no intervention since 1986) and control (only surveillance and outbreak response during 2016-2030). We report the cost per case averted, cost per disability adjusted life year (DALY) averted and cost per at-risk life year averted. We assess cost-effectiveness against a threshold of about one half GDP per capita (less than US$ 500 in low income countries). All costs are expressed in US$ of 2015.

Results: The GWEP cost an estimated US$ 11 (95% uncertainty interval, 4.70-12.49) per case averted in the period 1986-2030. The pre-certification and certification phases can cost about US$ 0.0041 and US$ 0.0015 per capita per year, respectively, plus up to US$ 4-6 million per year in global and regional costs. The cost per DALY averted by the GWEP relative to doing nothing is estimated at US$ 222 (118–372) in 1986-2030. The GWEP is probably more cost-effective than control by the year 2030. The cost of the GWEP is certainly
more cost-effective than control if willingness to pay for one year of life lived without the risk of GWD exceeds US$ 0.10.

**Discussion:** Even if economic costs are two times as high as the financial costs estimated for the period to 2020, the GWEP will still be cost-effective relative to doing nothing. Whether the GWEP turns out to be the most cost-effective alternative in the period beyond 2015 depends on the time horizon. When framed in terms of the number of years of life lived without the risk of GWD, a case can be made more easily for finishing the end game, including certification of the absence of transmission.

**Author Summary**

Of the three diseases targeted for eradication by WHO, two are Neglected Tropical Diseases (NTDs) – guinea worm disease and yaws. The decision to pursue eradication of these diseases was based, in part, on economic arguments made at a time when case numbers were high. There is, in fact, little published evidence of the cost and cost-effectiveness of an eradication programme in the end game, when the number of cases is lower and the cost per case is higher than at any other time. The Guinea Worm Eradication Programme (GWEP) is in its final stages, with only 25 cases reported in 2016. Ours is the first economic evaluation of the GWEP since a World Bank study in 1997. For the first time for any eradication programme, we document the full cost of certifying the absence of transmission in all countries with a history of the disease. We analyze the cost-effectiveness of the GWEP to find that it remains highly cost-effective in spite of high costs in the end game. These results will be of interest to funders of guinea worm disease and yaws eradication, but also to policymakers considering eradication of other NTDs.

**Introduction**

Eradication is the “permanent reduction to zero of the worldwide incidence of an infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed”.[1] Only one human disease has ever been eradicated. The eradication of smallpox (formally declared in 1980) is estimated to have avoided 1.5 million deaths per year in developing countries and led to a benefit of about US$ 1070 million per year globally. The economic benefit to industrialized countries of avoided vaccination costs alone amounts to about US$ 350 million per year.[2]

Of the three diseases currently targeted for eradication by the World Health Organization (WHO), two are so-called Neglected Tropical Diseases (NTDs) – guinea worm disease (GWD) and yaws. The economic benefit of GWD eradication will be smaller in absolute terms than that of smallpox, because GWD does not affect the developed world. Nonetheless, GWD eradication will be a major victory for public health. It will be the first parasitic disease to be eradicated (smallpox is a virus) and the first disease to be eradicated without the use of a vaccine or medicine.[3] Progress towards eradication has already been a major victory for the “forgotten people of forgotten places” who no longer suffer from GWD and its effects on such communities, despite the fact that their standards of living have not improved very much, if at all, since the eradication campaign began.

The Guinea Worm Eradication Programme (GWEP) is in its final stages, with only 22 cases reported in 2015 and 25 cases in 2016. However, the target date for eradication has been pushed back a number of times (first 1995, then 2009, then 2015). The inability of the campaign to meet the first two arguably over-ambitious target dates set by the World Health Assembly was due to a lack of funding to support national eradication efforts. Failure to meet
the 2015 target is attributed primarily to insecurity (especially armed conflict) in some of the remaining endemic countries, as well as unexpected new modalities of transmission (through dogs) in Chad.[4]

Eradication requires formal certification by WHO of the absence of transmission in all countries including those with a history of endemicity. WHO established the International Commission for Certification of Dracunculiasis Eradication (ICCDE) in 1995, “to evaluate the status of countries applying for certification of dracunculiasis eradication and to recommend whether a particular country should be certified as free of transmission.”[5] A country endemic for GWD “reporting zero indigenous cases over a complete calendar year is deemed to have prevented transmission of guinea-worm disease and is classified in a precertification stage”.

To be declared free of GWD, “a country that has stopped transmission of the disease must have reported zero indigenous cases through active surveillance for at least three calendar years.”[6] Prerequisites are that:

1. Surveillance activities of an adequate standard have been undertaken for at least three years since the last reported indigenous case.
2. In the event of an imported case, a full investigation has been performed to confirm the endemic area of origin; full case containment activities have been undertaken.
3. A register of suspected cases has been maintained; their movements and activities have been documented and all sources of potentially contaminated drinking water have been identified.

A national report documents “all actions taken from the beginning of the programme, including the three-year pre-certification period, to interrupt transmission and confirm zero occurrences of guinea-worm disease cases.” An International Certification Team (ICT) then visits the country to verify the information in the national report: “During its visit, ICT assesses the adequacy of the surveillance system and reviews records of investigations for rumored cases and subsequent actions taken.”[6]

The last formal economic evaluation of the GWEP was undertaken in 1997 by the World Bank (WB), when the number of cases was estimated at about 330,000 cases (with 152,185 cases being reported).[7] At that time, the cost of the programme (1987-1998) was estimated at US$ 87.46 million (nominal prices, unadjusted for purchasing power) or 1987 US$ 68.46 million (constant prices, adjusted for purchasing power). That study assumed that in the absence of the GWEP, the incidence of cases would have remained at the level of 1986 (prior to initiation of activities) or 2.25 million cases per year. It estimated that by 1998, 13 million cases would have been prevented by the GWEP, at a cost of about US$ 5 per case averted (at 1987 prices) and an economic rate of return (ERR) of 29%.

The case for investment in 2016, when there were 25 cases, is not the same as in 1997, when there were still tens of thousands of cases of GWD. The WB study considered a project horizon up to the year 1998 only, while recognizing that “the longer it takes for eradication efforts to be successful, the lower are the projected economic returns”. [7] By 2004, about US$ 125 million had been spent and another US$ 53.5 million committed through to 2010.[8] Costs have therefore increased to at least double the WB estimate.

In this paper, we update the investment case for the GWEP. We analyze the cost-effectiveness of the GWEP in the end game, when cases are low, the cost per case is high, and much of the cost is for pre-certification and certification rather than implementation. We compare the GWEP to two alternative scenarios: doing nothing (no intervention since 1986) and control (surveillance and outbreak response only in 2016-2030, without certification of global eradication).
Guinea Worm Disease (GWD)

GWD is caused by the parasitic worm Dracunculus medinensis, which infects people who drink water from stagnant sources containing tiny copepods (“water fleas”) harboring microscopic infective larvae. Approximately one year after infection, adult female worms measuring up to one meter emerge painfully through a person’s skin. When the wound is cooled in water, the worm releases hundreds of thousands of larvae, contaminating the source and continuing the cycle of the disease. The emerging worm makes it difficult for hosts to walk, care for themselves, grow food, work or attend school.[9–11] Secondary bacterial infections usually ensue and exacerbate pain and prolong recovery time, and may lead to permanent disability. Although rare today, death as a result of tetanus was not an unusual event during the early years of the GWEP.

Endemic transmission of GWD is a consequence of extreme poverty in remote and marginalized communities of sub-Saharan Africa. Standards of living in these communities have not changed much or at all since the 1980s, when the GWEP began. Hospitals and clinics are often absent or kilometers away, hindering access to modern medical care. The absence of a known cure is another barrier to seeking modern medical care. There is no drug to cure GWD or vaccine to prevent it, and humans do not develop immunity to the disease. However, disease transmission can be prevented.

The Guinea Worm Eradication Programme (GWEP)

GWD eradication efforts started in the 1980s, just after the successful eradication of smallpox in 1979. In 1986, the first World Health Assembly (WHA) resolution on GWD called on affected Member States to “establish as quickly as possible, within the context of primary health care, plans of action for eliminating dracunculiasis, giving high priority to endemic areas in providing safe sources of drinking water.”[12] WHO, The Carter Center (TCC), the United Nations International Children's Emergency Fund (UNICEF), and United States Centers for Disease Control and Prevention (CDC) became the lead organizations of a global programme to eradicate GWD. Working together with the ministries of health in endemic countries and a coalition of partner organizations, GWD has been reduced more than 99.9 percent. Figure 1 shows the dramatic drop from an estimated 3.5 million cases occurring annually in 21 countries in 1986 to 25 cases reported in four countries in 2016.
As there is no medical treatment for GWD, the strategy for eradication relies on the identification of all villages with endemic transmission of GWD and interrupting transmission in each. National GWEPs, with support from partners, interrupt transmission of GWD by creating and sustaining networks that permit: 1) community-based education of residents about the disease and what they can do to prevent infected residents from contaminating sources of drinking water via prompt detection and containment of cases; 2) filtration of all drinking water through cloth filters and pipe filters; and 3) treatment of contaminated stagnant water sources with ABATE larvicide. In addition, since its inception, national GWEP programs have advocated with water sector organizations for the provision of safe sources of drinking water to affected communities.

The current role of the ICCDE and WHO within the GWEP includes verification of the absence of transmission via assessment of the surveillance quality during the three year pre-certification period. Since its establishment in 1995 to the end of 2016, the ICCDE has met eleven times.[13] It has certified 198 countries, territories and areas (belonging to 186 WHO Member States) as free of GWD. The latest country to attain this status in January 2015 was Ghana. The population living in endemic countries has been halved since 2013, with certification of these countries (Figure 1).

An additional eight countries await certification: four endemic countries (Chad, Ethiopia, Mali and South Sudan); two countries in the pre-certification phase (Kenya and Sudan); and two which have not reported any recent history of the disease (Angola and the Democratic
Republic of Congo). To achieve global certification of GWD eradication, “WHO must formally certify every individual country even if no transmission has ever been recorded in that particular country.”[5]

WHO is providing financial and technical assistance in all eight countries yet to be certified, including for surveillance at cross border areas and in refugee camps in the four endemic countries. It has full responsibility in supporting pre-certification activities in Kenya and Sudan, as well as in supporting full verification of Angola and the Democratic Republic of Congo for certification. In addition, it provides assistance for surveillance in at least ten certified countries at risk of disease re-introduction.

TCC has responsibility for assisting national GWEPs to interrupt transmission. From mid-2015, TCC has also been responsible for supporting the four remaining endemic countries to prepare for certification up to 36 months after interruption of transmission. Activities include providing financial and technical assistance for the surveillance system, investigating rumours of possible cases, responding to outbreaks, establishing a reward system for reporting cases, developing capacity for rigorous investigation and reporting of cases, and providing monthly reports about these investigations.

Other partners, namely UNICEF and Water Aid, have focused on provision of safe, clean water (in particular, by providing boreholes).

**Methods**

**Data collection**

For the years 1986-1996, financial costs were retained from the WB study.[7] For the period after 1996, we extracted financial costs from the records of TCC and WHO, including the ICCDE.

TCC’s financial costs were extracted for the years 2008-2015, including the cost of implementation activities per country per year. Data were available from the 10 countries in which activities were still ongoing in the period 2008-2015, namely: Burkina Faso, Chad, Ethiopia, Ghana, South Sudan, Mali, Nigeria, Niger, Sudan, and Uganda.

TCC costs include the financial cost of in-kind donations, as reported to TCC by their donors. These include the production cost of cloth for filters from E.I. DuPont Corporation and chemical larvicide (ABATE) from BASF (formerly American Home Products).[8]

WHO’s financial costs in the years 2000-2007 and 2009-2014 were available by year and categorized by type (staff and other personnel costs; contractual services; property and equipment; general operating expenses; supplies, commodities, materials; transfers and grants to counterparts and travel). Whatever assets Ministries of Health deployed for the project were largely purchased by WHO during this timeframe and are included here. Data included disbursements to 30 countries and 27 organizations.

We also extracted demographic and epidemiological data from WHO and other United Nations sources. These include the total population (since 1986, with projections to 2030), and the number of cases (1986-2015). These data are publicly available for all countries endemic for GWD.

**Cost description**

We included all available financial costs from the perspective of providers (TCC, WHO and national GWEP programmes) as well as in-kind donors. All costs were converted to US$ of 2015 (2015 US$) using the GDP deflator for the United States.[14]
We combined both TCC and WHO sources to obtain total financial costs by country and year in the period 2008-2015, and projections of the cost of completing the GWEP in 2016-2020. We analyzed unit costs by phase (implementation, pre-certification and certification) and year within each phase. We calculated the following unit costs: cost per case and cost per capita for the intervention phase; cost per capita for the pre-certification and certification phases. We extracted the median, 2.5th and 97.5th centile values of cost per capita across all available countries and years within a phase.

Using these phase-specific unit costs, we imputed missing costs in the years 1997-2007. Given uncertainty around these imputations, we employed probabilistic sensitivity analysis (PSA). We assumed triangular distributions, using the median and centiles as the mode and min and max, respectively. We ran 1000 iterations of all calculations and extracted the mean as well as 2.5th and 97.5th centile values for the uncertainty intervals.

We compared financial costs of the GWEP to the null scenario of having done nothing since 1986; the null scenario is also referred to as the zero cost scenario.

We considered also a control scenario in which in the period 2016-2030, rather than pursuing eradication, surveillance and outbreak response activities alone are maintained indefinitely at pre-certification and certification levels (i.e. at the same unit cost per capita) in endemic/pre-certified and certified countries, respectively. The assumption is that surveillance during pre-certification is the minimum required to detect recrudescence and respond to an outbreak; surveillance during certification phase is the minimum required to detect case importation and respond.

Activities undertaken to interrupt transmission (during the implementation phase) and certify countries (during the certification phase) have been described in the introduction, under “The Guinea Worm Eradication Programme (GWEP)”. District-level, risk-based surveillance activities are detailed in Supporting Information S1 Table, for endemic districts (typical of the implementation phase), high risk districts (pre-certification phase) and normal risk districts (certification phase).

Markov modelling

We developed a compartmental (Markov) model, depicted in Supporting Information S2 Figure. Transition probabilities from one state to another are determined by epidemiological parameters, with distributions for PSA (Supporting Information S3 Table). We converted rates and durations into probabilities. We converted all probabilities in weekly cycle probabilities.

The population at risk moves to or through one of the following possible states: asymptomatic infections, symptomatic but uncomplicated cases, complicated cases, cases with permanent disability, and death (the terminal state). Uncomplicated cases experience disfigurement, with pain and itch, for at least 2–4 weeks, as the worm emerges. About half become complicated cases, with secondary bacterial infections, abscesses, arthritis, contracture of joints and severe disability lasting up to another 16 weeks. In fact, pain can persist as much as 12–18 months after the emergence of worms in about a quarter of cases. The case fatality rate is about 0.1%. Permanent disability (e.g. “locked” knees or other joints) occurs in about 0.5% of all cases.

In order to keep the model tractable, we conservatively assume that individuals in the permanent disability state are not re-infected or at least that there is no additional disability weight associated with symptomatic infection when the individual is already in a state of permanent disability.
Start values for the number of new (incident) cases are based on, as a minimum, the highest number of reported cases since 1986 (1.3 million cases) and, as a maximum, the 2.25 million cases cited in the WB study. We allowed the model to run over a period of 100 years or 5200 weeks to populate the states of the model; the observations of this “burn in” period were discarded. The model was then run for a period of 45 years or 2340 weeks, coinciding with the period 1986-2030. In reality the benefits of eradication would extend well beyond 2030.

The model was run twice, to estimate health effects 1) under the GWEP, and 2) under the null scenario (no intervention). The epidemiological parameters that differ between the two are: 1) the reproduction number, described below; and 2) the probability of complications (which indirectly impacts also on the probability of permanent disability). Complications are reduced from 50–76% of cases under the null, to 25-50% of cases under the GWEP.

Health effects under the control scenario are the same as under the GWEP until 2015; given the lack of data on what would happen in the absence of implementation activities after 2015, we assumed that surveillance and outbreak response activities succeed in maintaining incidence at 2015 levels, but never achieving eradication.

For the null scenario, we conservatively assumed no increase in the number of cases over time (an average of 0.985–0.999 secondary cases generated by an index case over the course of the infectious period). For the GWEP, we took monthly data on the number of cases, available from 1999 to 2015 (a period of roughly exponential decrease). We performed a panel linear model (with fixed country effects) of the logarithm of cases on the month number to obtain an average monthly rate of decrease, with 95% confidence interval. The estimated effective (or actual) reproduction number ($R_n$) reflects the control efforts in place in that period. The formula is:

$$R_n = \Lambda^2 \times (L \times D) + \Lambda \times (L + D) + 1$$

where $L$ and $D$ are the average durations of the latent and infectious periods, respectively and $\Lambda$ is the rate of decrease.[15] The above equation holds when the latent and infectious periods are assumed to follow the negative exponential distribution.[16] The combined average durations of the latent and infectious periods ($L+D$) is known as the serial interval or generation time – that is, the time interval between successive cases in a chain of transmission. In the case of GWD, we assume an infectious period ($D$) of 1-2 weeks and a generation time of 45-65 weeks. We used the 95% confidence interval on $\Lambda$ and ranges for $L$ and $D$ to calculate a range of plausible values for $R_n$.

After running the two models, we weighted calculated disability-adjusted life years (DALYs). There are no disability weights specific to GWD; we therefore referred to generic health states from the Global Burden of Disease Study 2010 [17]. For GWD without complications, we used 0.188 (95% CI 0.125–0.267) based on disfigurement level 2 with itch or pain, described as: “a visible physical deformity that is sore and itchy. Other people stare and comment, which causes the person to worry. The person has trouble sleeping and concentrating.”[17] For GWD with complications, we used 0.295 (95% CI 0.196–0.409) based on gout: acute, described as: “severe pain and swelling in the leg, making it very difficult to get up and down, stand, walk, lift, and carry heavy things. The person has trouble sleeping because of the pain.” Conservatively, these disability weights were applied only to a maximum of 20 weeks, not the 12-18 months reported elsewhere.[18]

For permanent disability, the disability weight is provided in Supporting Information S3 Table.

In the absence of detailed information on the percentage of cases with infection by multiple worms (in particular, how this percentage has changed under the GWEP), we have
conservatively assumed that the uncertainty intervals on the duration of disease and on the
disability weight capture also infection by multiple worms.

Again, we ran 1000 iterations of all calculations and extracted the mean as well as 2.5\textsuperscript{th} and 97.5\textsuperscript{th} centile values for the uncertainty intervals.

**Cost-effectiveness analysis**

We estimated the cost per life year at risk averted, cost per case averted, and cost per DALY averted in the periods 1986-1996, 1986-2020 and 1986-2030. We applied willingness-to-pay (WTP) thresholds of about one half of GDP per capita to the cost per DALY averted, or less than US$ 500 in low-income countries. One half of GDP per capita is conservative compared to traditional WTP thresholds of one to three times GDP per capita.[19,20]

Life years at risk are defined as the number of years of life lived in GWD endemic countries. The entire population of a country is assumed to remain at risk until that country is certified as free of GWD. As described above, we consider also a control scenario in which in the period 2015-2030, rather than pursuing eradication, surveillance and outbreak response activities are maintained indefinitely at pre-certification and certification levels in endemic/pre-certified and certified countries, respectively. In the control scenario, therefore, the populations of countries not yet certified in 2015 are never removed from risk.

Average cost-effectiveness ratios (ACERs) were calculated relative to the null scenario of having done nothing since 1986. There is some inconsistency in the literature about the definition of the ACER; however, the alternative of dividing total cost by total effect is not considered informative. Instead we compared the costs and effects of each scenario (eradication or control) with a single option, "do nothing".

We discounted all costs and effects by between 0 and 3\% per annum, applying the same rate to both costs and effects. Using the 1000 iterations of costs and effects, we calculated the cost-effectiveness, and extracted the mean as well as 2.5\textsuperscript{th} and 97.5\textsuperscript{th} centile values for the uncertainty intervals.

It is worth noting here the ways in which our methods differ from that of the 1997 WB study.

The WB study calculated the cost per case averted, but not the cost per DALY averted. It relied on a human capital approach to generate cost-benefit ratios. The human capital approach places monetary weights on healthy time using market wage rates. The WB study used agricultural value-added and the assumption that a 1\% increase in labor input increases agricultural output by 0.66\% (output elasticity of labor); it assumed that on average 5 weeks of production time (12.5\% of annual work time) is lost per case of GWD.

The human capital approach is based on a strong assumption of full employment. To be fair, the WB study addressed this issue head-on, arguing that "unemployment is not a major factor in the analysis. … The rural labor [sic] sector (on which this study exclusively focuses) primarily comprises unskilled workers (with relatively low levels of education) as well as subsistence farmers. Therefore increases in productive labor [sic] time are expected to result in the augmentation of agricultural output."[7]

Nonetheless, the approach is problematic in informal settings where agricultural value-added is hard to measure. Moreover, it ignores the suffering of children and the elderly (those not part of the “productive age group” referred to in the WB study). More pragmatically, the approach results in measures such as ERR that cannot be readily compared across diseases priorities for which cost per DALY averted is the standard measure.
In summary, we update the cost per case averted, but do not update the ERR and focus instead on the cost per DALY averted as the primary measure of cost-effectiveness.

Results

Cost description
In Figure 2, annual financial costs of the GWEP are presented, by country phase, for the period 2009-2014. Most of the cost has been for implementation. However, many costs are not country-specific. These “general costs” refer to costs incurred by global and regional organizations for multi-country activities and can therefore not be assigned to any one phase. There are also significant costs associated with the pre-certification phase. Annual pre-certification costs range from about US$ 343 000 in Côte d’Ivoire to more than US$ 1.6 million in Nigeria. Total spending is influenced by population size and land mass.

Figure 2. Annual financial costs of the GWEP, by country phase and general, 2009-2014. General costs refer to costs incurred by global and regional organizations for multi-country activities; costs are expressed in nominal prices (unadjusted for purchasing power).

Figure 3 shows these annual financial costs by country, on a per capita basis (divided by the total population of that country). Note that the y-axis is on a logarithmic scale. It reveals considerable cross-country variation. Implementation costs are particularly high in South Sudan relative to other countries. Ongoing civil unrest has “periodically delayed programme implementation due to restricted access for health-care workers; programme staff undertaking active surveillance, case detection, and case containment activities; and population displacement between areas where dracunculiasis is endemic and those where it is not present.”[21] Steadily increasing costs in Chad reflect the occurrence of dog infections from 2013.[4]
Countries that moved from implementation to pre-certification (Ghana and Sudan) saw little change in costs. During pre-certification, unit costs tend to increase over time. An exception is Kenya, which has been in pre-certification for over 15 years and has had relatively low spending per capita throughout the period 2009-2014.

Countries that moved from pre-certification to certification (Burkina Faso and Togo) saw little change or a small increase in costs. Countries that have been certified do need to undertake some surveillance activities to prevent outbreaks from imported cases. Civil unrest and displacement within neighboring endemic countries requires certified countries to heighten surveillance. However, resource requirements are less than those required in countries that are endemic or undergoing pre-certification.

Table 1 summarizes per capita costs in all phases, proving the median and 2.5th and 97.5th centile values used in our imputation of costs. The average cost of implementation is US$
The average costs of pre-certification and certification are US$ 0.0041 per capita per year and US$ 0.0015 per capita per year, respectively. These costs are in addition to the US$ 4-6 million per year in general, multi-country costs (Figure 2). Certified countries on average spend 22 times and 5 times less compared to endemic countries and countries undergoing pre-certification respectively. For the implementation phase, we can compare cost per capita to the cost per case (Table 1). The range on the cost per case per year is wide, extending from US$ 533 to US$ 166,951.

Table 1. Unit cost per year by phase, 2015 US$, median (2.5th and 97.5th centiles), 2009-2014

<table>
<thead>
<tr>
<th></th>
<th>Implementation</th>
<th>Pre-certification</th>
<th>Certification</th>
<th>General(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per case</td>
<td>31224</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(533-166,951)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per capita</td>
<td>0.0225</td>
<td>0.0008</td>
<td>0.008</td>
<td>0.0132</td>
</tr>
<tr>
<td></td>
<td>(0.0000-0.4163)</td>
<td>(0.0000-0.0138)</td>
<td>(0.0000-0.0054)</td>
<td>(0.0061-0.0416)</td>
</tr>
<tr>
<td>Excluding South Sudan</td>
<td>0.0128</td>
<td>same</td>
<td>same</td>
<td>same</td>
</tr>
<tr>
<td></td>
<td>(0.0000-0.0709)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excluding South Sudan</td>
<td>0.0176</td>
<td>0.0041</td>
<td>0.0015</td>
<td>same</td>
</tr>
<tr>
<td>and zeros(^2)</td>
<td>(0.0004-0.0717)</td>
<td>(0.0004-0.0139)</td>
<td>(0.0002-0.0066)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) General costs are costs incurred by global and regional organizations for multi-country activities.

\(^2\) Zeros refer to countries that did not undertake any activities in a given year.

Figure 4 gives annual financial costs of the GWEP and control scenarios in the years 1986-2020, with reported costs in the years 1986-1996 and 2008-2015 and best estimates and 95% uncertainty intervals (grey area) in the years 1997-2007 and 2016-2020. The GWEP and control scenarios differ only in the period 2016-2020. The control scenario assumes surveillance and outbreak response activities at the level of pre-certification and certification unit costs in endemic/pre-certified and certified countries, respectively, including general, multi-country activities. A high degree of uncertainty about the costs of both the GWEP and control scenarios means that these estimates overlap.
Figure 4. Annual financial costs of the GWEP and control scenarios, 1986-2020, best estimate and 95% uncertainty intervals. The control scenario assumes surveillance and outbreak response activities at the level of pre-certification and certification unit costs in endemic/pre-certified and certified countries, respectively, including multi-country activities; costs are expressed in nominal prices (unadjusted for purchasing power).

Our estimate of the cost of the GWEP in the period 1986-2020 is, in undiscounted nominal dollars, US$ 432 million (95% uncertainty interval, US$ 351-553 million). Our estimate for the period 1986-2004 is US$ 182 million (US$ 117-280 million), higher than but not inconsistent with the US$ 125 million reported elsewhere.[8]

Markov model

In Figure 5 we present the results of two runs of the Markov model over a period of 2340 weeks (1986-2030): estimated weekly number of new cases, prevalent infections and disabilities and excess deaths under the GWEP and null scenarios. With 0.985–0.999 secondary cases per index case, the number of new cases decreases slowly under the null scenario. With an effective reproduction number of 0.59–0.74, the number of new cases drops rapidly under the GWEP, driving the decrease in the prevalence of asymptomatic infections, uncomplicated cases, complicated cases and permanent disabilities. The number of excess deaths is also lower under the GWEP, but the effect is small and uncertain.
Figure 5. Estimated weekly number of infections, cases and deaths – GWEP and null scenarios, 1986-2030. The null scenario assumes no intervention since 1986.
Figure 6 shows the estimated weekly number of at-risk life years, cases and DALYs averted by the GWEP relative to the null scenario, again over the period of 2340 weeks (1986-2030). The vast majority of cases are averted early on in the GWEP. About 25-30 thousand cases are averted each week, or 1.3–1.6 million cases per year. The total number of DALYs averted increases more gradually over the period 1986-2030. In terms of at-risk life years averted, impact is much more recent, with large numbers of people removed from risk of GWD in 2013 and after 2015.

Figure 6. Estimated weekly number of at-risk life years, cases and DALYs averted by the GWEP relative to the null scenario, 1986-2030.
**Cost-effectiveness**

Table 2 gives the average cost-effectiveness ratios, with best estimates and 95% uncertainty intervals, for the GWEP compared to the null scenario. In its first decade (1986-1996), the GWEP is estimated to have cost about US$ 34 per case averted. By 2020, it cost about US$ 11 per case averted. This result is more conservative than that obtained by the WB study, which put the cost per case averted at about US$ 10 (or US$ 5 at 1987 prices) in 1986-1998; their reported result did not include time discounting of cases averted or allow for a decreasing number of cases in the absence of the GWEP. In the period 1986-2030, the cost per DALY averted by the GWEP relative to doing nothing is estimated at US$ 222 (118–372), much less than US$ 500 or one half of GDP per capita in most low-income countries. The cost per at-risk life year averted is much lower, at about US$ 0.06.

Table 2. Average cost-effectiveness ratio, 2015 US$, best estimate and 95% uncertainty intervals

<table>
<thead>
<tr>
<th>Period 1986-</th>
<th>Cost per at-risk life year averted</th>
<th>Cost per case averted</th>
<th>Cost per DALY averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996 NA²</td>
<td>33.83 (21.06–50.61)</td>
<td>1081 (557–1891)</td>
<td></td>
</tr>
<tr>
<td>2020 0.17 (0.12–0.25)</td>
<td>10.94 (6.62–16.80)</td>
<td>280 (150-475)</td>
<td></td>
</tr>
<tr>
<td>2030 0.06 (0.04–0.09)</td>
<td>9.18 (5.42–14.45)</td>
<td>222 (118–372)</td>
<td></td>
</tr>
</tbody>
</table>

¹ The null is the do nothing scenario, with zero costs and a natural history of disease since 1986.
² No at-risk life years averted, since the first GWD endemic country was certified in 2005.

Figure 7 shows cost-effectiveness acceptability curves (CEACs) for the comparison of the GWEP to both the null (do nothing) and control scenarios. The CEAC represents the probability that an intervention is cost-effective across a range of possible thresholds of willingness-to-pay. Values of the CEAC closer to 1 indicate that uncertainty in the cost-effectiveness of the reference intervention is very low.[22] Figure 7 (solid line) shows that the probability that the GWEP is more cost-effective than doing nothing exceeds 90% at a willingness-to-pay threshold of about US$ 300 per DALY averted.
Figure 7. Probability of being cost-effective, by willingness-to-pay (US$) for a DALY averted, in the period 1986-2030. The control scenario assumes surveillance and outbreak response activities at the level of pre-certification and certification unit costs in endemic/pre-certified and certified countries, respectively, including multi-country activities; it further assumes that these surveillance and outbreak response activities succeed in maintaining incidence at 2015 levels.

Whether the GWEP is more cost-effective than the control scenario is less clear in terms of the cost per DALY averted, given uncertainty about the costs of both scenarios (Figure 7, dashed line). Recall that we have assumed that surveillance and outbreak response activities at the level of pre-certification and certification unit costs in endemic/pre-certified and certified countries, respectively, succeed in maintaining incidence at 2015 levels. This assumption puts the probability of cost-effectiveness of GWEP compared to control at nearly 50% (a coin toss), at a willingness to pay threshold of about US$ 500 per DALY averted.

Figure 8 is another CEAC, similar to Figure 7, but in which the willingness-to-pay thresholds are expressed per at-risk life year averted. It shows that the GWEP is certainly more cost-effective than both the do nothing and control scenarios, if willingness to pay for one year of life lived without the risk of GWD exceeds US$ 0.10.
**Figure 8. Probability of being cost-effective, by willingness-to-pay (US$) for an at-risk life year averted, in the period 1986-2030.** The control scenario assumes surveillance and outbreak response activities at the level of pre-certification and certification unit costs in endemic/pre-certified and certified countries, respectively, including multi-country activities; it further assumes that these surveillance and outbreak response activities succeed in maintaining incidence at 2015 levels.

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**Discussion**

The GWEP continues to be highly cost-effective in the period 1986-2030. Even if economic costs are two times as high as the financial costs estimated for the period to 2020, the GWEP will still be cost-effective relative to doing nothing.

Whether the GWEP turns out to more cost-effective than a simple control strategy in the period beyond 2015 will depend much on the time horizon. The longer the time horizon, the greater the cost of control relative to the GWEP (assuming eradication is indeed achieved by 2020).

The benefits of eradication may not be fully captured by standard metrics such as cost per DALY averted. When framed in terms of the number of years of life lived without the risk of GWD, a case can be made more easily for finishing the end game, including certification of the absence of transmission. We refer the reader to an extensive review of all the health and economic benefits that can be attributed to a “year of life lived without the risk of GWD”.[23]

To the best of our knowledge, ours is one of the first analyses of the cost-effectiveness of an eradication programme in the end game. Most economic evaluations of eradication and elimination programmes do not explicitly break down the costs over time. Among the few studies that provide costs over time, the vast majority do not break it down by category or phase. Only one study (of polio eradication) considered the cost of certification, estimated at US$ 492 million in the post-elimination period.[24]
Another study examined the difference in costs between control and eradication of polio.[25] They found that although control has a lower initial annual cost, the cumulative costs of the two strategies will become equal after 6 years and thereafter the control strategy will cost more. Moreover after 20 years, the control strategy will cost US$ 800 million more than the eradication strategy.

In addition to more up-to-date and comprehensive data, this study has several strengths relative to a 1997 evaluation of the GWEP by the WB. We have developed a Markov model to estimate the number of DALYs averted. We have performed probabilistic sensitivity analysis on the most uncertain parameters.

Our study does have limitations. First, we have not considered all possible alternatives to the GWEP as it was implemented.

In theory, accelerated scale up might have involved higher annual costs over lower number of years for some of the endemic countries. In practice, however, the end point of global eradication is unlikely to have come much sooner. The primary constraint to scale up has been security concerns preventing full access to endemic areas – sometimes for months or years. As a matter of fact, all the four remaining endemic countries have experienced serious security concerns. Sudan and South Sudan have experienced uninterrupted conflict since the start of the GWEP.

Also in theory, scale up might have been faster or cheaper if some of the cost of global and regional level activities had been shifted to the country level. In practice, however, without global and regional coordination, the GWEP would not have been successful in mobilizing the necessary resources, including financial, human as well as political capital. Without independent verification that countries had met all the criteria for being certified free of the disease, global eradication would not be possible.

A less theoretical limitation is that not all costs have been included. We have not included, for example, the cost to UNICEF of providing boreholes. Note, that we have also not included the collateral benefits of these public health goods on other diseases. Some smaller donors have supplemented intervention costs (for example, the Japan International Cooperation Agency in Ghana).

The GWEP has benefitted from volunteers and general staff of national Ministries of Health and local non-governmental organizations. In some countries, small rewards have been paid by Ministries of Health directly. We were unable to survey national GWEPs to obtain data on ministry of health staff time used for the purposes of implementing programmes. To our knowledge, the WB study also did not include these domestic contributions.

Furthermore, projected costs in 2016-2020 might be too low. The budget envisaged in this analysis is for US$ 111 million. TCC originally developed a proposal for $210 million, with the last case in 2016 and global certification by 2020.

On the other hand, we have certainly omitted some of the benefits, including DALYs averted. A study in Sudan found that “children were three times more likely to be malnourished if more than half the adult members had suffered from the GWD in the previous year.”[26] In countries with ongoing activities, the national GWEP maintains surveillance for both GWD and acute flaccid paralysis (for polio surveillance).

Some of the financial costs included are not incremental costs, but rather costs shifted from the national health system and patients to the GWEP. In South Sudan, Ethiopia and Mali the vast majority if not all patients are hospitalized at GWEP case containment centers. Only in Chad have patients, so far, been hospitalized at health units or district hospitals serving the affected areas. Included in the TCC costs is between $100 and $200 per patient for first aid
treatment costs associated with GWD, including occlusive bandages, topical antibiotic, a bed mat, bed sheets, a mosquito net and three meals a day.

Like the WB study, we have ignored “the benefits in terms of reduced infection-related expenditures among cases as well as positive effects on savings and income in the long run”. [7] The GWEP is thought to help keep children in school by stopping children getting the disease and preventing their parents becoming unwell, requiring their children to work in their place. [27]

Nor have we amortized the financial cost of assets over their useful lives, including the case containment centers built in South Sudan, Ethiopia and Mali. The legacy of GWEP’s established health infrastructure and networks will include community-based surveillance and health education delivery systems that are poised to deliver other essential interventions. The system of trained village volunteers undertaking health promotion and surveillance are already used for other health activities.

All these limitations considered, even if the true economic cost of eradication were as much as two times higher than the costs we have estimated for the period 1986-2030, the GWEP would still be cost-effective relative to the alternative that was decisively rejected by TCC, WHO and their partners in 1986 – doing nothing. Having re-asserted the cost-effectiveness of the GWEP as a whole, future research could help identify which of its individual components have driven that cost-effectiveness, and whether benefits could have been delivered earlier, or at lower cost.
References for this paper


### Supporting Information

#### Selected Figures and Tables

**S2 Table. Epidemiological parameters for the Markov model of guinea worm disease.**

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Parameters</th>
<th>Sources</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1 Reproduction</td>
<td>Uniform</td>
<td>Countertactual Min=0.985 Max=0.999 GWEP Min=0.59 Max=0.74</td>
<td>This study. Conservative assumption of no increase in numbers; on the low end, we allow for 1.5% decline over the generation time. For the GWEP, we estimated the effective reproduction number using monthly data on the number of cases.</td>
</tr>
<tr>
<td>E2 Generation</td>
<td>Uniform Min=45 Max=65 including 43-61 weeks of asymptomatic infection.</td>
<td>Cairncross, S., Muller, R., and Zagaria, N. (2002). Dracunculiasis (Guinea Worm Disease) and the Eradication Initiative. Clinical Microbiology Reviews 15, 223–246.</td>
<td>From the time infection occurs, it takes between 10–14 months (43–61 weeks) for the transmission cycle to complete until a mature female worm emerges from the body. When submerged in water, the female worm releases larvae. Consumed by copepods, larvae develop to the infective third stage in 14 days (2 weeks); infected copepods live up to 4 weeks.</td>
</tr>
<tr>
<td>E4 Disability</td>
<td>Beta  $\alpha = 22.07927$ $\beta = 94.23169$</td>
<td>Disfigurement: level 2, with itch or pain; a visible physical deformity that is sore and itchy. Other people stare and comment, which causes the person to worry. The person has trouble sleeping and concentrating. Mean: 0.188 95% CI: 0.125–0.267</td>
<td></td>
</tr>
<tr>
<td>E5 Probability of</td>
<td>Uniform Min=0.50 Max=0.76 Min=0.25 Max=0.50</td>
<td>Cairncross, S., Muller, R., and Zagaria, N. (2002). Dracunculiasis (Guinea Worm Disease) and the Eradication Initiative. Clinical Microbiology Reviews 15, 223–246. Severe incapacitation is associated with secondary infection of the lesion; this occurs in roughly half of cases; early studies from Nigeria (1989-1991) suggest 58-76% of patients were unable to leave their beds. For the GWEP, we assumed that complications were as much as halved.</td>
<td></td>
</tr>
<tr>
<td>E6 Duration of</td>
<td>Triangular Min=2 Mode=8</td>
<td>Aehyung Kim, Ajay Tandon and Erenesto Ruiz-Tiben A review of twelve studies suggests an</td>
<td></td>
</tr>
<tr>
<td>E8</td>
<td>Probability of permanent disability from GWD complications</td>
<td>Beta</td>
<td>$\alpha = 12.60608$</td>
</tr>
<tr>
<td>E9</td>
<td>Disability weight for permanent disability</td>
<td>Beta</td>
<td>$\alpha = 28.44683$</td>
</tr>
<tr>
<td>E11</td>
<td>Case fatality rate from GWD complications</td>
<td>Triangular</td>
<td>Min=natural mortality*1.01</td>
</tr>
</tbody>
</table>
S1 Fig. Markov model of guinea worm disease.

Epidemiological parameters (E1-E11) are described in S2 Table.

All files

http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0005922#sec018
Part 3 General discussion
Chapter 3.1 Introduction to the discussion

This thesis aimed to inform the strategy for yaws eradication focusing on health economic aspects of the each of its major components: mass treatment, surveillance, and certification.

We asked the following research questions: What are the drivers of cost for implementing mass treatment for yaws? What is the cost and cost-effectiveness of the eradication strategy based on mass treatment? What is the cost and cost-effectiveness of alternative strategies for yaws diagnosis and surveillance? What are the countries with a history of yaws that should be prioritized for active surveillance? Finally, what is the cost and cost-effectiveness of an eradication programme in the end game, including certification?

We tried to answer these research questions through a series of five interlinked papers. In this general discussion we will first summarize the main results, strengths and limitations of each paper, then address some additional questions that cut across all five papers, and finally give some recommendations for both policy and research.

Chapter 3.2 Main results, strengths and limitations

Mass treatment

With regard to mass treatment, in Paper 2.1.1, our review of the literature revealed 56 studies of the cost of mass treatment for 6 NTDs. We included in a meta-regression data from 34 studies from 23 countries and 91 sites. Unit costs were found to be very sensitive to economies of scale, and the decision of whether or not to use volunteers. Financial unit costs are predicted to be less than 2015 US$ 0.50 in most countries for programmes that treat 100 thousand people or more. However, for smaller programmes or those that cannot rely on volunteers, both economic and financial unit costs are expected to be higher. In small island states, it could cost as much as US$ 10 per person. A web-based software application was developed to generate country-specific benchmarks for the cost per person of mass treatment. These benchmarks can assist in monitoring value for money in NTD programme plans, budgets and accounts, or in setting pay-out for results-based financing mechanisms that is based on the predicted cost, plus an agreed markup.

It was noted as a limitation of the paper that most of the available costing studies consider only the early years of programme implementation. Some considered the cost of planning and mapping in these early years, but few considered longer-term monitoring and evaluation. A micro-costing study based on other sources (and therefore excluded from the meta-regression) estimated that the financial unit cost per treatment would increase two times towards the later phases of elimination of onchocerciasis in Africa.[68] This increase is driven by decreasing economies of scale, as our model predicts, but also increasing costs for surveillance. It was recognized that more evidence is needed on the cost of post-mass treatment surveillance, including Transmission Assessment Surveys for lymphatic filariasis, and verification of elimination or certification of eradication. Evidence on the latter is the subject of Paper 2.3.1, which finds that the cost of pre-certification and certification phases can be significant.

It is stated in the paper that “(w)hile many studies mentioned patient time and the use of volunteers, few reported their (economic) costs and they [the costs associated with volunteers] were therefore excluded from the analysis.” We do not consider this a major limitation of the study in the context of this thesis. We retained all eligible studies (whether they reported volunteer costs or not) and recorded the use of volunteers as a dummy variable for use in the meta-regression. In our subsequent application to the global yaws eradication strategy (in
Paper 2.1.2), we predicted unit costs by setting the dummy variable to zero. In other words, we based the prediction on costs from studies in which no volunteers were used and all workers were paid. We consider this to be a conservative application of the replacement cost approach described in Chapter 1.4, for when volunteer labor cannot be assumed to be available indefinitely.

In Paper 2.1.2, we combine economic unit cost benchmarks with resource needs for the global yaws eradication strategy and a Markov model of early- and late-stage yaws. We find that the economic cost of yaws eradication is uncertain but not high by the standards of disease elimination and eradication programmes. We estimate it at about US$ 362 (75-1073) million in the countries known to be endemic. Due to the global yaws eradication strategy, 13 (7.3-20) million years of life would be lived without early-stage yaws and 2.3 (1.1-4.2) million years of life without late-stage yaws. 1.3 (0.6-2.4) million DALYs would be averted. Eradication would cost US$ 26 (4.2-78) for each year of life lived without disability or disfigurement due to yaws, or US$ 324 (47-936) per disability-adjusted life year (DALY). Excluding drugs, existing staff and assets, the financial cost benchmark is US$ 213 (74-522) million.

We acknowledged that there remained considerable uncertainty about costs to be incurred countries of unknown yaws endemicity. Given that some of these countries share borders with the countries known to be endemic for yaws, cross-border issues will incur, at the very least, some additional coordination costs. While we included the cost of clinical surveillance in these countries, we did not include the cost of the tests that would be required during surveillance for the purpose of certification. It was recognized that more evidence is needed on what level of surveillance is required in what countries. This issue is addressed in Paper 2.2.2, which finds that no less than 83 countries and areas had a history of yaws but are no longer reporting cases to WHO and that active surveillance will be needed in at least 66 of them.

**Surveillance**

With regard to surveillance, in Paper 2.2.1, our economic model suggests that at current prices of the treponemal and trep/non-trep RDT’s, the sequential strategy is cost-saving for individual diagnosis at prevalence of past/current infection less than 85% (81-90); it is cost-saving for surveillance at less than 100%. The threshold price of the trep/non-trep RDT (below which the sequential strategy would no longer be cost-saving) is US$ 1.08 (1.02-1.14) for individual diagnosis at high prevalence of past/current infection (51%) and US$ 0.54 (0.52-0.56) for community surveillance at low prevalence (15%). Importantly, cost savings do not come at the expense of diagnostic accuracy or, by extension, programme outcomes. More than 900 correct diagnoses are made for every 1000 people tested under both strategies.

A major limitation of the study is that treponemal RDTs have not been assessed for yaws, and that we have therefore had to infer sensitivity and specificity from test performance for syphilis. Performance in syphilis is likely to be better than it is in yaws, as the trep/non-trep RDT also performs better in syphilis than in yaws. Although titers are often higher in syphilis compared with yaws (especially asymptomatic disease), it is unclear why Marks et al (2016) found that trep/non-trep performance was worse for yaws even when controlling for titer. It was highlighted that community surveillance is needed not only in known endemic countries but also a much larger number of countries with a history of yaws, as elaborated in Paper 2.2.2.

In Paper 2.2.2, our systematic review of the literature since the year 1945 revealed that yaws has been reported in at least 103 countries and areas. Reported cases peaked in the
1950s, with 55 countries reporting at least one case in 1950 and a total of 2.5 million cases reported in 1954. All but 15 countries and areas stopped reporting cases by the mid-1990s and 2 are thought to have interrupted transmission. Our regression model suggests that case reporting during periods of ongoing transmission is positively associated with socioeconomic development and, in the short-term, negatively associated with independence and armed conflict. Among 86 countries whose current status is unknown, we identified a group of 20 with more than a 50% probability of reporting cases if there was ongoing transmission – in these countries, passive surveillance might be sufficient. For the other 66 countries, international support for more active surveillance will be required.

The model was limited by the availability of historical data back to 1945 and we may be omitting important explanatory variables. For example, we would have liked to include variables more directly related to strength of health information systems, and to poverty or income inequality. In high income countries where economic wealth and access to health services is unequally distributed over geographic areas, there may remain neglected communities with a high probability of endemicity and inadequate passive surveillance capacity.

Certification

With regard to certification, in Paper 2.3.1, we used data from the guinea worm eradication programme (GWEP). We found that certification costs about US$1.50-4.10 per 1000 population per year, plus up to US$ 4-6 million per year in global and regional costs. In spite of these costs, the cost per DALY averted (relative to doing nothing) is estimated at US$ 280 in the period 1986-2020. The cost of certification can be high, but the cost of continuing control will be higher than that of eradicating. In the period 2015-2030, the GWEP (with certification) is more cost-effective than simple control (without certification) if willingness to pay for one year of life lived without the risk of guinea worm disease exceeds US$ 0.10.

The study does have limitations. Projected costs to complete eradication in 2016-2020 might be too low. If eradication is not achieved by 2020, then the cost of the end game will increase further. There is also the issue of the generalizability of this evidence from the GWEP to the yaws eradication programme, not addressed explicitly in the paper, but which we detail in Chapter 3.3. We conclude that much of the certification process, and its costs, can be generalized across disease programmes.

Chapter 3.3 Cross-cutting questions

We wish to address some additional questions that cut across all five papers contained in this thesis. We group these in three categories.

What is the generalizability of evidence from other neglected tropical diseases for yaws eradication?

In two studies, we have relied on data and other evidence from other NTDs to make projections for yaws.

First, in our analysis of the cost per person reached by mass treatment programmes, we included data from five other NTDs. These included another bacterial infection treated with azithromycin (trachoma), but mainly parasitic infections (lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminthiases). Their inclusion could be justified in spite of the diverse epidemiology by the fact that, excluding the medicines, mass treatment is implemented in much the same way, after controlling for the use of school-based platforms.
Even for the vector-borne among these five diseases, the primary intervention for elimination purposes remains mass treatment.

Most of the available costing studies are of control programmes. Control refers to the reduction of disease incidence, prevalence, morbidity, and/or mortality to a locally acceptable level as a result of deliberate efforts; elimination, by contrast, refers to reduction below a certain threshold.[18] Of the 34 studies identified in our review, only 8 referred explicitly to eradication (yaws) or elimination (lymphatic filariasis, onchocerciasis) as a programme objective.[69][70][71][72][73][74][75][76] Only one of those directly compared the costs of control and elimination strategies (for onchocerciasis), involving annual and biannual (twice yearly) mass treatment respectively.[76] No study has been conducted in a country where elimination has actually been achieved. We come back to this issue in our recommendations for future research.

Second, in our analysis of the cost and cost-effectiveness of an eradication programme in the end game, we were forced to rely on data from the GWEP. Clearly, the cost-effectiveness of the GWEP, which faces a different epidemiology and uses a different intervention, cannot be generalized in its entirety to the yaws eradication strategy. However, mechanisms and processes for certification will be similar and, excluding the cost of diagnostic tests (not required in the GWEP), the costs of certification are probably generalizable. Again, the potential problem is not that we used data from another disease, but that the countries covered by that analysis (limited to the African Region) may not be representative of yaws-endemic countries as a whole. In practice, however, with the possible exception of the small island states of the Western Pacific (only 3 of the 14 yaws-endemic countries), this should not be a major cause for concern.

What does the economics of yaws eradication look like in the context of other mass treatment programmes?

Policy decisions on yaws are not made in isolation, and the cost and cost-effectiveness of yaws eradication should be seen in the context of that of other NTD programmes employing mass treatment as a strategy.

The results of a review and synthesis of cost-effectiveness analyses of mass treatment programmes are presented in Table 1. Average cost-effectiveness ratios have been standardized for prices in the year 2012, and whenever possible relative to a null scenario (i.e. doing nothing). All of the cost-effectiveness ratios are well below the threshold of one half of GDP per capita in low income countries, implying that they are cost-effective in most settings.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment/care</th>
<th>Setting</th>
<th>Target population</th>
<th>2012 US$ per DALY averted, relative to doing nothing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic filariasis</td>
<td>Stone and others (2016)</td>
<td>Albendazole + Ivermectin</td>
<td>Global</td>
<td>All</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mesoendemic areas (microfilarial prevalence: 40%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperendemic areas (60%)</td>
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<td></td>
<td></td>
<td></td>
<td>Hyperendemic areas (80%)</td>
</tr>
<tr>
<td></td>
<td>Turner and others (2014)</td>
<td>Ivermectin, annual</td>
<td>Africa</td>
<td></td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td></td>
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<tr>
<td>Schistosomiasis and STH</td>
<td>Lo and others (2015)</td>
<td>Albendazole + Praziquantel</td>
<td>Côte d'Ivoire</td>
<td>School-age children</td>
</tr>
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<td></td>
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<tr>
<td>Trachoma</td>
<td>Baltussen and others (2012)</td>
<td>Mass treatment with azithromycin + trichiasis surgery</td>
<td>sub-Saharan Africa</td>
<td>95% coverage</td>
</tr>
<tr>
<td>Yaws</td>
<td>Fitzpatrick and others (2014)</td>
<td>Azithromycin</td>
<td>Global</td>
<td>All</td>
</tr>
</tbody>
</table>

* Stone and others (2016) did not report the number of DALYs averted relative to a null (do nothing) scenario, only relative to current situation (under which many DALYs are already being averted).

** Baltussen and others (2012) used market prices of 2012 for azithromycin; an assumption of zero cost would be closer to the reality of the current situation.

*** Fitzpatrick and others (2014) included the cost of azithromycin as it was not yet donated, as well as clinical surveillance in 71 countries no longer reporting cases.

Annual mass treatment with ivermectin is estimated to cost 2012 US$ 3-15 per DALY averted depending on the degree of onchocerciasis endemicity.[77] The cost-effectiveness of preventive chemotherapy for soil-transmitted helminthiases (STH) has been the subject of some controversy.[78] However, mass treatment of school-age children in Côte d'Ivoire for STH and schistosomiasis together costs 2014 US$ 118 (2012 US$ 114) per DALY averted relative to doing nothing.[79] Combination with other interventions is also possible. Mass treatment for STH costs 2012 US$13 per DALY averted when added to a vitamin A supplementation campaign for children 6 months to 14 years old in Uganda.[80]

The cost-effectiveness of mass treatment for trachoma depends crucially on assumptions about the cost of azithromycin. Of the medicines delivered as preventive chemotherapy, azithromycin, a broad-spectrum antibiotic, has the greatest market value. Applying the market price of azithromycin, Baltussen and others (2012) found that mass treatment combined with trichiasis surgery costs about 2012 US$ 83 per DALY averted in sub-Saharan Africa, relative
to doing nothing.[81] In practice, azithromycin is available as a free donation to trachoma elimination programmes worldwide. An earlier study suggested a 73% decrease in the cost per DALY averted with donated azithromycin.[82] Therefore, the cost per DALY averted is probably closer to 2012 US$ 22.

In Paper 2.1.2, we estimated that yaws eradication would cost about 2012 US$ 324 per DALY averted. However, we assumed that the full cost of azithromycin would be borne by the global eradication programme. We acknowledged that the cost to the programme would be significantly reduced by donations of azithromycin for yaws, as for trachoma. Our result also included the cost of clinical surveillance in 71 countries of historic endemicity. Removing the cost of drugs and clinical surveillance outside the countries of known endemicity, the cost per DALY averted by yaws eradication is closer to 2012 US$ 280. This number is still higher than the cost-per DALY averted by mass treatment for the elimination or control of other NTDs, but falls well within the range estimated for the eradication of guinea worm disease.[83]

The cost-effectiveness of an eradication programme with upfront costs for long-term benefits is highly dependent on the time horizon (and discount rates) chosen in the analysis – more so, in any case, than that of a control programme, for which both costs and benefits are ongoing. WHO has typically used a horizon of 100 years for the purpose of generalized cost-effectiveness analysis for national priority-setting.[84] There is no “correct” horizon. For both guinea worm disease and yaws, we were fairly conservative in projecting only as far forward as 2030 and 2050, respectively. Choice of the horizons was driven in part by computational requirements of the probabilistic sensitivity analysis and Markov models, but also in part by the maximum time horizons of likely international funders.

What are the implications of developments in philanthropy, policy and research since the launch of the updated global strategy to eradicate yaws?

Since the launch of the Morges Strategy and overlapping with publication of the individual papers contained in this thesis, there have been developments that warrant a reinterpretation of the results.

At the Global Partners Meeting on Neglected Tropical Diseases, convened by WHO in Geneva on 19 April 2017, partners announced new or renewed support to defeat NTDs. These announcements included a groundbreaking pledge from EMS – the biggest domestic manufacturer of generic medicines in Brazil – to make the first ever donation of oral azithromycin for the eradication of yaws.[85] This development confirms that, in comparing the cost-effectiveness of the yaws eradication programme to mass treatment for other NTDs, it is appropriate to consider that the cost of the medicines will be borne outside of the programme.

Mathematical modelling that we undertook since our analysis of the cost and cost-effectiveness of mass treatment for yaws suggests that more than two rounds of total community treatment (TCT) and as many as 5 rounds of total targeted treatment (TTT) may be required to achieve eradication.[86] This is because in this recent analysis we considered the possibility of lower effective treatment coverage than in our cost-effectiveness analysis (>90%). The more conservative scenario was based on evidence from mass treatment for other NTDs. It remains to be seen in practice whether yaws eradication programmes can achieve higher effective coverage than these other programmes, given the relatively small size of yaws endemic communities, and the collateral and almost immediately perceptible benefits of azithromycin treatment.

At the same time, recent research suggests that more integrated approaches to disease mapping and mass treatment could lower the cost of the yaws eradication programme.[87] A
recent clinical trial suggests that the dose of azithromycin used for trachoma (20g/kg) may be sufficient for yaws (normally 30g/kg). Furthermore, another paper suggests that, rather than the 3-6 monthly treatment suggested by the Morges Strategy, once-yearly treatment may be adequate, as for trachoma.[88] Both of these findings will facilitate integration of total community treatment with other mass treatment programmes in some settings. The cost of total targeted treatment and surveillance may also be reduced by a new integrated approach to the individual treatment of a larger group of NTDs with skin manifestations, including Buruli ulcer, cutaneous leishmaniasis and leprosy.[89]

**What is the role of disease elimination or eradication programmes in strengthening health systems towards Universal Health Coverage?**

While NTD programmes historically have been structured and continue to be perceived as a collection of vertical programmes, WHO’s roadmap for the NTDs has long emphasized integrated interventions over individual diseases.[42] NTD programmes have increasingly adopted an integrated approach.[90] They are becoming diagonal programmes for the poorest – targeting disease-specific outcomes while strengthening health systems. This diagonal approach is particularly true for diseases amenable to preventive chemotherapy and other periodic outreach interventions. It is also reflected in WHO’s integrated approach to the individual treatment of a group of NTDs with skin manifestations, including yaws.[74]

The Sustainable Development Goals target “the end” of communicable diseases, including NTDs. However, they also emphasize the importance of strengthening health systems for Universal Health Coverage (UHC), with the target to “achieve UHC, including financial risk protection, access to quality essential health care services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all.”[91] Under the Millenium Development Goals, “global health initiatives” for HIV, tuberculosis and malaria were accused of undermining efforts to strengthen health systems.[92]

WHO’s Maximizing Positive Synergies Collaborative Group made a number of recommendations for global health initiatives.[93] These include the need to: 1) extend the health remit of global health initiatives and agree to indicators for health systems strengthening; 2) improve the alignment of planning processes and resource allocations between global health initiatives and with health systems; and 3) generate more evidence on the costs and benefits of strengthening health systems and a case for investments in health systems to complement those in global health initiatives.

Aligning the global yaws eradication strategy with UHC will require more than just the integration of drug procurement and delivery for yaws with that of other diseases. It will require that training for yaws treatment and surveillance be planned and coordinated with training for other health services. It will also require national adaptation and interpretation of global eradication strategy, building on existing organizational structures and management systems, including financial systems. Good practices in the alignment of yaws treatment and surveillance with health systems strengthening will need to be documented and shared across countries.

**What methodological issues in economic evaluation are relevant to other disease elimination or eradication programmes?**

Our application of the methods of economic evaluation to the global yaws eradication strategy has relevance for other global strategies to eliminate or eradicate a disease. As a general comment, first, economic evaluation should be undertaken before setting global targets for elimination or eradication. The sort of evidence produced – costs, DALYs and ICERs – is what is needed to get international partners, including funders, to sign onto a global target. Second, economic evaluation should look at all major components of a disease
elimination or eradication strategy, including not just the interventions required to interrupt transmission, but also surveillance and certification, as they are all integral and connected parts of any such strategy.

Specifically with regard to cost analysis, there is a need for greater transparency and consistency in the methods used to value volunteer time. The economic costs relating to volunteer time are often ignored or estimated inconsistently. Furthermore, many volunteers receive in-kind incentives or are paid per diems (sometimes upfront during trainings) that may cover more than the cost of participation. Mass treatment campaigns have tended to rely heavily on volunteers – a model that is unlikely to be sustainable if programmes move from control to elimination or eradication. A replacement cost approach to volunteer time is advisable, since volunteer labor cannot be assumed to be available indefinitely, or on the scale or with the quality required for successful implementation of an elimination or eradication strategy.

Econometric modelling can be particularly helpful in understanding the drivers of cost in mass treatment towards elimination or eradication. Mass treatment campaigns have targeted populations as small as 1 thousand people or as large as 1 million, and have integrated the delivery of medicines for as many as five diseases at a time. Cost analysis of an elimination or eradication strategy based on mass treatment or other periodic outreach must take into account the effect of economies of scale and scope. Econometric models of cost functions can help understand how costs will vary across countries, but also over time, as programmes scale up and then scale down in the end game, when efforts are focused on smaller hotspots on ongoing transmission, and at different rates for the different diseases being targeted.

Markov models are well-suited to the evaluation of elimination and eradication strategies as they allow longer time periods to be modelled. However, the nature of disease elimination and eradication is such that most of the benefit accrues to future cohorts. These Markov models must therefore capture initial as well as future cohorts. The remaining challenge, in converting the outputs of these models into outcome measures that can be compared across diseases, is that none of the NTDs targeted for elimination or eradication have formal disability weights from the available Global Burden of Disease studies. For regions or countries with a sufficiently high burden of those diseases, one may need to assess local health state valuations for the relevant sequelae.

As already discussed in Chapter 1.4, the cost-effectiveness of an eradication programme (with upfront costs for long-term benefits) is highly dependent on the time horizon and discount rates. WHO guidance with respect to the time horizon is quite clear: 10 years of programme implementation and up to 100 years of the associated costs and health effects. However, when it comes to NTDs and other diseases closely linked to poverty, a shorter time horizon might be justified on the basis that even if the health sector chooses the “do nothing” comparator, the burden of some of these diseases might disappear eventually anyway.

There is still no consensus about what discount rate to use, or indeed whether health effects should be discounted at all, given concerns about the morality of giving greater weight to current generations. When evaluating a global strategy that covers many countries (as any eradication strategy must), there will be legitimate and often substantial differences in time preferences for both health and wealth. While WHO recommends that uncertainty related to variables that carry value judgements should be subjected to one-way or multi-way analysis, there is a case that can be made that in the case of a global strategy, uncertainty around the global discount rate might best be dealt with using PSA.
Chapter 3.4 Recommendations for policy

On the basis of the findings of the papers contained in this thesis, and in spite of the abovementioned limitations, we make three broad recommendations.

Donors looking for cost-effective, affordable and equitable investments should consider investing in the global yaws eradication strategy.

The global yaws eradication strategy would cost US$ 324 (47-936) per disability-adjusted life year (DALY). It is cost-effective according to WHO thresholds based on GDP per capita. However, the health budget constraints of most low and middle income countries are too tight for them to afford all that is cost-effective according to those thresholds. Furthermore, the cost per DALY averted is an aggregate measure that provides no information about the equitable distribution of health benefits among population groups. The case for investment in mass treatment for yaws must be seen in the context of competing priorities of the global health community and a multi-criteria approach to setting priorities for UHC.

A ranking of 93 health interventions for low- and middle-income countries considered that mass treatment for yaws should be considered a priority intervention for Universal Health Coverage in lower-middle income countries based on a threshold of only (2012) US$ 500 per DALY averted. It was ranked at the level of intrapartum care, a package including safe abortion and surgical treatment of emergency obstetric care. However, it is important to note that the cost per DALY was taken from Paper 2.1.2 of this thesis, estimated in the context of a global yaws eradication strategy including both low and middle income countries. Had the ranking used country-specific estimates of the cost-effectiveness of mass treatment for yaws, it would also have been included in its essential package for low income countries.

Again, cost-effectiveness should not be the only important criterion in setting priorities for UHC. WHO’s Guidance for Priority Setting in Health Care (GPS-Health) incorporates criteria related to the disease and intervention (severity of disease, capacity to benefit, and past health loss); characteristics of social groups (socioeconomic status, area of living, gender; race, ethnicity, religion and sexual orientation); and non-health consequences (financial protection, economic productivity, and care for others). Increasingly, these dimensions of public choice are being considered more formally in the context of multi-criteria decision analysis.

The data are too scarce for formal analysis in this thesis, but yaws endemic communities are thought to be among the poorest and most remote, depending on subsistence and informal economies with no social protection. Interventions designed to serve these communities, such as periodic outreach including mass treatment for yaws, should therefore also be prioritized on the basis of the beneficiaries’ low socioeconomic status, area of living, and susceptibility to productivity losses that threaten lives as well as livelihoods. While couched in economic language, these additional criteria are drawn from equity and human rights, which have an important role in priority-setting for UHC.

The governments of endemic countries will make the decision of whether or not to prioritize national elimination of yaws. However, the global public good of yaws eradication will require global financing, including donations from the private sector. With the recent donation of azithromycin by a Brazilian pharmaceutical company, the programme is in need of a lead financing partner for delivery of the donated medicines. The Korea International Cooperation Agency (KOICA) became in 2017 the first bilateral to provide funding for yaws eradication, with seed funding to map the disease in East Timor. WHO should provide support to KOICA to ensure that the project in East Timor is a success, and one that KOICA will wish to repeat elsewhere.
Financial and in-kind resources should be harnessed also from the extractive industries (e.g. mining, logging) and others (e.g. cocoa and coffee) in endemic countries. These are industries with operations on or near the resource-rich lands where resource-poor populations still live with yaws. There is already some precedent for mining company support to yaws eradication implementation and research in Papua New Guinea.[36] Endemic country governments should approach these companies and explore possibilities for public-private partnership on yaws eradication.

Endemic countries should use the sequential strategy for diagnosis and surveillance while the global eradication programme advocates for a low cost dual test.

There are two situations of particular relevance in which savings could be substantial if endemic countries implemented the sequential testing strategy: first, during mass screening campaigns, before and after TCT; second, during final screening campaigns, including verification of the interruption of transmission. Cost savings from the sequential strategy should be reallocated to other essential interventions, such as sensitization to increase treatment coverage.

In the meantime, the global programme should negotiate with diagnostic manufacturers for a dual test costing about US$0.50-1.00. It can also explore alternative strategies with them. If a non-trep RDT were made available (alone, without the treponemal RDT), then an alternative strategy could involve the treponemal RDT followed by the non-treponemal RDT.

Indeed, it could advocate for outright donation of diagnostic tests – treponemal and/or non-treponemal. WHO has signed an agreement with Korea’s Standard Diagnostics for donation of rapid diagnostic tests for another NTD – human African trypanosomiasis; Standard Diagnostics is also producer of the treponemal test (SD Bioline) that could be used for yaws.

WHO should pursue surveillance for certification of those countries with the highest probability of having interrupted transmission.

WHO should initiate discussions with prioritized countries to assess their interest in and readiness for surveillance for certification of yaws eradication. Integration of surveillance with other large scale prevalence surveys for trachoma and other NTDs could be considered.[96] For 13 of the 14 WHO Member States currently reporting cases, a subnational mapping has been done.[10] The resulting maps were then overlaid with trachoma endemcity maps – looking for opportunities for integrated delivery of azithromycin.[87] A similar exercise should be done for the remaining 85 countries and areas, looking for opportunities for integrated surveillance.

The process of certification too could be better integrated across disease programmes. With so few human cases occurring, the GWEP needs to respond to demands from its long-standing donors to justify continued investment in countries in the pre-certification and certification stages, some of which have not seen cases in many years. The overall cost-effectiveness of the GWEP does not exempt it from such pressures. The fact that the cost of certification seems to be driven by inputs at the national and international level rather than at the community level suggests that there are savings to be had from integrating the certification across diseases, wherever possible, beginning with GWD and yaws.

Chapter 3.5 Recommendations for research

During implementation of the above policy recommendations, WHO should guide countries in undertaking operational research to address the following questions that remain from the health economic perspective:
What is the cost per person treated in the remotest villages of yaws endemic
countries and how does that cost evolve over subsequent rounds of total community
treatment (TCT) and total targeted treatment (TTT)?

As noted above, the available costing studies of mass treatment programmes consider only
the early years of implementation. Papua New Guinea and Vanuatu has now implemented
several years of TCT in very remote settings. Their data could be analyzed to assess how costs
have evolved over time and, in the case of Vanuatu, in the transition from TCT to TTT.

What effective coverage can be achieved and, as a result, what is the minimum
number and most cost-effective combination of rounds of TCT and/or TTT?

It is clear that at least one round of TCT is required in order to significantly reduce
asymptomatic infections.[97] In settings where it is not possible to achieve >90% coverage,
probably more than one round of TCT will be required.[86] In addition to increasing cost,
implementing numerous rounds of TCT could lead to antimicrobial resistance (discussed
below) and reduce effectiveness. The cost and effects of TTT will depend on how it is
implemented – for example, whether only household contacts, or extended families and
schoolmates are treated in these rounds.

What are the benefits and costs of integrating yaws TCT with mapping and
treatment for other NTDs?

The global yaws eradication programme still does not have the financial backing of a
large international donor. Realistically, it will have to leverage resources from other global
NTD programmes. Integrated mapping and mass treatment with trachoma could help reduce
the cost of TCT; integrated training for diagnosis and treatment with leprosy and Buruli ulcer
could help reduce the cost of TTT and post-treatment surveillance. However, there are
coordination costs, especially at the beginning of the integration process. The co-endemicity
of these diseases needs to be better measured in order to assess whether the benefits will
exceed the costs.

What is the actual performance of the treponemal RDT for yaws, and its
performance relative to the treponemal line of the trep/non-trep RDT?

The treponemal RDT has been assessed for syphilis, not for yaws. It is unlikely that the
actual performance of the treponemal RDT for yaws will affect the cost-effectiveness of the
sequential strategy recommended in this dissertation relative to the trep/non-trep RDT. It
could, however, affect the confidence with which sero-survey results can be interpreted for
the purpose of certification of eradication.

What is the appropriate probability cut-off, at which point to require countries of
historic yaws endemicity to undertake active yaws surveillance for the purpose of
certification?

Fifth, the 50% cut-off for the probability of reporting cases (if there was ongoing
transmission) was chosen arbitrarily. Threshold probabilities can be made more evidence-
based as active surveillance is undertaken. If no cases are found in countries with a low
probability of reporting, one might wish to decrease the cut-off to reduce the number of
countries requiring active surveillance. One might also wish to sample some of the countries
with a high probability of reporting and do active surveillance regardless; if cases are found,
there is reason to question the robustness of the model and/or cut-off.

What are the minimum required standards for “satisfactory surveillance” in order
to be certified as yaws-free?

Quality standards for “satisfactory surveillance” need to be established. In the case of
guinea worm disease eradication, the conditions were, for example, that 80% of population in
formerly endemic regions knew the amount of the reward for reporting cases. The challenge is that confirmation of yaws, unlike guinea worm disease, cannot be done on the basis of clinical examination alone.

**How might the development of antimicrobial resistance in yaws from mass treatment with azithromycin affect the cost and effectiveness of the global strategy?**

A recent study found for the first time emergence of azithromycin-resistant *T. p. pertenue* in an island setting where 84% coverage with TCT had been insufficient to achieve elimination.[98] But the Morges Strategy has always required more than just TCT (with >90% coverage). A few lessons from the study: 1) strict surveillance, including of populations moving across borders, will be required to ensure effectiveness of the global yaws eradication strategy; and 2) vigilance against antimicrobial resistance, including reporting of treatment failures and monitoring of any potential resistant cases, will need to be included in national plans and budgets of national yaws eradication programmes. In terms of cost, allowances will have to be made for treatment with injectable penicillin in cases of azithromycin-resistance.

**What are the potential benefits and costs of mass treatment for yaws for off-target diseases and health systems more broadly?**

As mentioned in Paper 2.1.2, our analysis does not take into account the potential knock-on benefits of total community treatment with azithromycin for trachoma, chancroid, chlamydia, syphilis, gastrointestinal and respiratory tract infections or malaria, nor of any of the other health services delivered during the campaigns. Reductions in child-mortality have been associated with mass administration of azithromycin for trachoma.[99] We have received anecdotal evidence of decreased in- and outpatient visits for diarrheal disease after mass treatment campaigns with azithromycin for yaws. However, the size of this benefit has not, to our knowledge, been evaluated in the literature.

At the same time, there is some evidence that vaccination campaigns can have a negative impact on routine services.[100] The question of the place of disease elimination or eradication programmes in strengthening health systems towards Universal Health Coverage was raised in Chapter 3.3. There is a need to monitor and evaluate impact on routine services of mass treatment campaigns for yaws.
References outside the published papers


Samenvatting

Framboesia tropica behoort tot een groep van bacteriële aandoeningen, de treponematosen, die ook endemische syfilis (bejel), pinta en syphilis omvat. De verwekker is de treponemale spirocheet (kurkentrekker vormig) Treponema pallidum subsp. pertenue. Regionaal is de ziekte ook bekend onder namen zoals buba (Spaans), pian (Frans), parangi of paru (Maleisisch). Framboesia (van “framboos” respectievelijk “framboise” in het Nederlands of het Frans), refereert naar het uiterlijke aspect van de veroorzaakte letsels. De Engelse benaming “yaws” kan zijn oorsprong vinden in een Afrikaanse woord voor bessen (yaw).

In 1948, bij de oprichting van de Wereldgezondheidsorganisatie (WGO), behoorde framboesia tropica tot de volksgezondheidsproblemen die het nieuwe agentschap als prioriteit vooropstelde. De tweede World Health Assembly in 1949 aanvaardde resolutie WHA 2.36 “bewust van het belang van de andere treponematosen, naast venerische syphilis”. De ruime geografische verspreiding en de hoge mortaliteit en invaliditeit veroorzaakt door framboesia tropica verantwoordde de internationale belangstelling. In 1950 werd het aantal wereldwijd door framboesia tropica geïnfecteerde personen door de WGO op 160 miljoen geschat.


Tussen 2008 en 2015 werden 450,000 nieuwe gevallen van framboesia tropica aan de WGO gerapporteerd. De populatie die risico loopt in de 13 landen die nu nog steeds gevallen aangeven wordt op 89 miljoen geschat. Ondanks het hoog aantal gevallen bestaan er geen gepubliceerde schattingen van de ziektebelast van framboesia uitgedrukt in DALYs (Disability Adjusted Life Years - levensjaren gecorrigeerd voor beperkingen). Er zijn ook geen gekende schattingen van de economische kosten van de aandoening in termen van gezondheidszorgkosten of productiviteitsverliezen.

In 2012, organiseerde de WGO een experten bijeenkomst die leidde tot de Morges strategie voor framboesia tropica eradication. Eradicatie wordt gedefinieerd als de “permanente daling tot nul van de wereldwijde incidentie van een infectie veroorzaakt door een specifiek agens als gevolg van gerichte maatregelen; verdere interventies zijn dan niet meer nodig”. In 2013 aanvaardde de 66ste WHA resolutie 66.12, die als doelstelling heeft framboesia tropica te radicieren tegen 2020.

De Morges strategie heeft drie belangrijke componenten: massabehandeling, surveillance en certificering. Massabehandeling staat voor behandeling van een ganse endemische bevolking ongeacht het aantal actieve klinische gevallen. Surveillance dient opgezet te worden in de 13 landen die nog steeds framboesia rapporteren, maar een groter nog onbekend aantal landen zal op een bepaald moment een of andere vorm van surveillance nodig hebben teneinde te certificeren dat alle landen inderdaad framboesia vrij zijn.

Populaties waarin framboesia tropica endemisch is behoren tot de armste ter wereld. Dit heeft tot gevolg dat een groot deel van de middelen die nodig zijn voor globale eradication zullen moeten gemobiliseerd worden door publieke instellingen, zowel nationaal als internationaal. Beleidsvormers zullen overtuigd moeten worden dat eradication van framboesia kosteneffectief en betaalbaar is vooraleer van start te gaan met de strategie.
Een economische evaluatie van de framboesia eradicatiestrategie kan hierbij helpen door informatie te verschaffen voor het operationaliseren van de strategie, door ze zo kosteneffectief mogelijk te maken, en door haar betaalbaarheid aan te tonen. Wij benaderen deze economische evaluatie in drie delen, die overeenkomen met de drie hoofdcomponenten van de framboesia eradicatiestrategie.

De economische aspecten van massabehandeling van framboesia worden onderzocht in twee publicaties. In de eerste gebruiken we een regressiemodel om vanuit de studie en synthese van gegevens over de kost van massabehandeling voor andere NTDs (Neglected Tropical Diseases - Verwaarloosde Tropische Ziekten) referentiepunten te bekomen voor de kost per capita van massabehandeling van framboesia. In het tweede artikel gebruiken wij deze referentiepunten in een Markov model van kosten en kosteneffectiviteit van de framboesia eradicatiestrategie in gekende endemische landen.

Ons systematisch literatuuroverzicht vond 56 studies rond de kost van massabehandeling voor 6 NTDs. We namen gegevens van 34 studies in 23 landen en 91 geografische locaties op in een meta-regressie. Eenheidskosten bleken zeer gevoelig te zijn voor schaalvoordelen en het al of niet inschakelen van vrijwilligers. De voorspelde financiële eenheidskosten bedragen in de meeste landen minder dan US$ 0.50 (2015 US$) voor programma’s die 100,000 of meer mensen behandelen. Voor kleinere programma’s of voor diegene die geen vrijwilligers kunnen inschakelen zullen de economische en financiële eenheidskosten echter hoger zijn. In kleine eilandstaten kunnen ze oplopen tot US$ 10 per persoon. We ontwikkelden een online software applicatie die landen-specifieke referentiepunten schat voor de kost per persoon voor massabehandeling.

Op basis van ons probabilistisch kosteneffectiviteitsmodel is de geschatte economische kost van framboesia eradicatie onzeker, maar niet hoog vergeleken met eradicatie programma’s van andere ziekten – ongeveer US$ 362 (75-1,073) miljoen voor de gekende endemische landen. Eradicatie zou US$ 26 (4.2-78) kosten per levensjaar doorgebracht zonder beperkingen te wijten aan framboesia, of US$ 324 (47-936) per DALY. Zonder medicatie, bestaand personeel en activa in rekening te brengen is de financiële kost US$ 213 (74-522) miljoen. De reële kost van “wachten tot er meer wegen zijn” (armoedereductie) zou tot 13 (7.3-20) miljoen levensjaren met het vroege stadium van framboesia oplopen en tot 2.3 (1.1-4.2) miljoen levensjaren getroffen door het late stadium.

De economische aspecten van framboesia surveillance worden eveneens in twee publicaties behandeld. In de eerste bepalen we de kosten en kosteneffectiviteit voor de diagnose van framboesia en voor surveillance van twee alternatieve test strategieën, met treponemale en gecombineerde treponemale/niet-treponemale snelle diagnostische testen. In het tweede artikel onderzoeken we de historische literatuur, sinds 1945, naar de rapportage van framboesia gevallen door alle landen. Op basis van een regressiemodel van factoren geassocieerd met rapportage identificeren wij prioriteiten voor surveillance onder landen die nu geen gevallen meer rapporteren aan de WGO.

Wat surveillance betreft, suggereert ons beslissingskundig model dat, bij de huidige prijzen van de treponemale en de treponemale/niet treponemale snelle diagnostische testen, de sequentiële teststrategie kostenbesparend is voor individuele diagnose bij een prevalentie van oude/huidige infectie beneden 85% (81-90); voor surveillance is ze altijd kostenbesparend. De drempelprijs van de treponemale/niet treponemale snelle diagnostische testen (beneden dewelke de sequentiële strategie niet meer kosteneffectief zou zijn) is US$ 1.08 (1.02-1.14) voor individuele diagnose bij hoge prevalentie van oude/huidige infectie (51%) en US$ 0.54 (0.52-0.56) voor surveillance in de ganse populatie bij lage prevalentie (15%).

Ons systematisch overzicht van de literatuur sinds 1945 toonde aan dat framboesia gerapporteerd is geworden in minstens 103 landen of zones. Het aantal gevallen was het
hoogst in de jaren 1950, met 55 landen die in 1950 minstens 1 geval aangaven en een totaal van 2,5 miljoen aangegeven gevallen in 1954. Rapportage stopte uit alle landen, op 15 na, midden de jaren 1990. Ons regressiemodel toont aan dat rapporteren van gevallen in periodes van transmissie positief geassocieerd is met socio-economische ontwikkeling en, op korte termijn, negatief met onafhankelijkheid. Voor 66 van de 86 ooit endemische landen waarvan de huidige status onbekend is, is de waarschijnlijkheid dat ze gevallen zouden rapporteren bij transmissie lager dan 50%. In deze landen zal meer actieve surveillance nodig zijn. Passieve surveillance is waarschijnlijk voldoende in de andere 20 landen.

De economische aspecten van certificatie worden behandeld in één publicatie. We maken gebruik van gegevens van het (nog lopende) Guinea worm eradicatie programma en onderzoeken daarmee de kost van certificatie van de onderbreking van ziekteoverdracht en de kosteneffectiviteit van het eindstadium van een eradicatie programme. Onze studie is de eerste formele kosten en kosteneffectiviteit analyse van een eradicatie programma in zijn eindfase, wanneer het aantal gevallen daalt en de meeste kosten voor surveillance en certificatie zijn.

Op basis van de gegevens van het Guinea worm eradicatie programma (GWEP) vonden wij dat de pre-certificatie en certificatie fasen ongeveer US$ 0,0041 en 0,0015 per capita per jaar kosten. We schatten de kost per vermeden DALY (relatief tot niets doen) op US$ 280 tijdens de periode 1986-2020. De kost van pre-certificatie en certificatie kan hoog zijn, maar de kost van aanhoudende bestrijdingsmaatregelen kan nog hoger uitvallen. In de periode 2015-2030, is het GWEP (met certificatie) meer kosteneffectief dan alleen bestrijding (zonder certificatie) indien de bereidheid tot betalen voor één levensjaar zonder risico op Guinea worm aandoening groter is dan US$ 0,10.

Op basis van onze bevindingen formuleren we drie brede beleidsaanbevelingen.

Ten eerste, donoren op zoek naar investeringen in de globale volksgezondheid met lage kost en hoge kosteneffectiviteit moeten overwegen om in het globale framboesia eradicatie programma te investeren.

Gezien de verwachte kosteneffectiviteit van het programma, is de grootste vraag die overblijft hoe de implementatie ervan te financieren. Regeringen van endemische landen worden aangespoord verantwoordelijkheid voor nationale inspanningen op zich te nemen, maar framboesia eradicatie is een wereldwijd collectief goed, wat ook globale financiering noodzaakt, inclusief schenkingen vanuit de private sector.

Op nationaal niveau kunnen financiële - en in natura middelen worden aangeboord van extractieve (mijnen, houtkap) en andere bedrijven (bijv. cacao en koffieplantages). De activiteiten van deze bedrijven situeren zich in gebieden die rijk zijn aan grondstoffen en waar nog steeds arme bevolkingsgroepen met framboesia leven.

Na de recente donatie van azythromycine aan de WGO door een Braziliaans farmaceutisch bedrijf heeft het programma nood aan een leidende financiële partner voor het afleveren van de gedoneerde medicijnen. De Koreaans hulponderste (KOICA) was de eerste bilaterale actor die, in 2017, financiële middelen ter beschikking stelde voor framboesia eradicatie, beginnend met startkapitaal om de ziekte in kaart te brengen in Oost-Timor. De WGO zou KOICA moeten steunen om te verzekeren dat het project in Oost-Timor een succes wordt dat KOICA elders wil herhalen.

Ten tweede, endemische landen zouden gebruik moeten maken van de sequentiële teststrategie voor diagnose en surveillance terwijl het globale eradicatie programma in parallel pleit voor een goedkope duale test.

In twee situaties kunnen substantiële besparingen worden gerealiseerd als endemische landen de sequentiële teststrategie toepassen: ten eerste tijdens massascreening, vóór en na massabehandeling; en ten tweede tijdens screeningscampagnes in de eindfase, inclusief
verificatie van de onderbreking van de transmissie. Kostenbesparingen gerealiseerd met de sequentiële strategie kunnen worden aangewend voor andere essentiële interventies zoals bewustmaking van de bevolking om de dekkingsgraad van massabehandeling te verhogen.

Ondertussen zou het globale programma moeten onderhandelen met producenten van diagnostica over een kostprijs van ongeveer 0.50-1.00 US$ voor een tweeledige test. Het programma kan met deze producenten ook alternatieve strategieën bekijken. Indien een snelle niet-treponemale diagnostische test beschikbaar zou komen (zonder de treponemale component), wordt een alternatieve strategie mogelijk waarbij een treponemale snelle test gevolgd wordt door een niet-treponemale snelle test.

Het programma zou ook ronduit kunnen pleiten voor volledig kosteloze donatie van diagnostische tests – treponemale en/of niet-treponemale. De WGO heeft een overeenkomst gesloten met het Koreaanse Standard Diagnostics voor de schenking van snelle diagnostische tests voor een andere verwaarloosde tropische ziekte - humane Afrikaanse trypanosomiase; Standard Diagnostics is ook de producent van de treponemale test (SD Bioline) die voor framboesia tropica zou kunnen worden gebruikt.

Ten derde, de WGO zou surveillance voor certificatie moeten nastreven van die landen waarvoor de kans het grootst is dat transmissie werd gestopt.

De Organisatie zou gesprekken moeten aangaan met de prioritaire landen om hun interesse en bereidheid voor surveillance voor certificatie van framboesia eradicatie te toetsen. Integratie van die surveillance met bestaande grootschalige prevalentiestudies voor trachoma en andere verwaarloosde tropische ziekten kan worden overwogen.

Gedurende de implementatie van de hogervermelde beleidsaanbevelingen zou de WGO landen moeten begeleiden bij operationeel onderzoek naar de volgende vragen die vanuit gezondheid-economic perspectief overblijven: Wat is de kost per behandelde persoon in de meest afgelegen dorpen in framboesia endemische landen en hoe evolueert deze kost met opeenvolgende ronden van massabehandeling? Welke effectieve dekkingsgraad kan worden bekomen en, daaruit voortvloeiend, wat is het minimum aantal en de meest kosteneffectieve combinatie van ronden van massabehandeling? Wat zijn de kosten en de baten van integreren van massabehandeling voor framboesia met massabehandeling voor andere tropische verwaarloosde ziekten, en van surveillance vanuit een dermatologische “huid-NTD” aanpak? Wat is de reële performantie van de treponemale snelle diagnostische tests, en wat is hun performantie in vergelijking met de treponemale component van de trep/non-trep snelle diagnostische tests? Wat is het aangewezen omslagpunt qua waarschijnlijkheid van rapportering om actieve surveillance nodig te hebben voor het opstarten van certificatie in landen die in het verleden endemisch waren voor framboesia? Wat zijn de minimaal vereiste standaarden voor “voldoende surveillance” teneinde als framboesia-vrij te worden gecertificeerd? Hoe zou ontwikkeling van antimicrobiële resistentie in framboesia ten gevolge van massabehandeling met azithromycine de kost en kosteneffectiviteit van de globale eradiciestrategie beïnvloeden?
Summary

Yaws belongs to a group of bacterial diseases known as treponematoses, including also bejel, pinta and syphilis. It is caused by the treponemal spirochete (cork-screw shaped) *Treponema pallidum subsp. pertenue*. The disease is known regionally by other names, such as buba (Spanish), pian (French), parangi or paru (Malay). It is also known as frambesia (from “framboise,” raspberry in French), due to its appearance. The name “yaws” may have originated from an African word for berry (yaw).

In 1948, when the World Health Organization (WHO) was established, yaws was among the major public health problems that the new health agency chose to prioritize. In 1949, the second World Health Assembly (WHA) adopted resolution WHA 2.36, “realiz[ing] the importance of treponematoses other than syphilis”. The extensive geographical range and the high morbidity and disability caused by yaws justified international attention. In 1950, WHO estimated that 160 million people were infected with yaws.

WHO piloted yaws elimination campaigns using penicillin in ten countries over 1948–1953. Success in these initial pilot projects supported for mass treatment using injectable penicillin in 46 countries from 1953–1963. These mass treatment campaigns reduced the estimated global prevalence of infection to 2.5 million by 1964. At the time, there was no formal certification process in place to confirm local elimination. Vertical yaws programmes were subsequently integrated into national primary health care systems. In 1995, WHO estimated the global prevalence at 460 000 infectious cases.

During 2008–2015, over 450 000 new cases were reported to WHO. The population at risk in the 13 countries still reporting cases is estimated at 89 million. In spite of the continued high number of cases, there are no published estimates of the burden of yaws in terms of Disability-Adjusted Life Years (DALYs). Similarly, there are no known estimates of the economic cost of the disease in terms of health care costs or productivity losses.

In 2012, a WHO-convened meeting of experts resulted in the Morges Strategy for yaws eradication. Eradication is the “permanent reduction to zero of the worldwide incidence of an infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed”. In 2013, the sixty-sixth WHA (2013) adopted resolution 66.12, with a target to eradicate yaws by 2020.

The Morges Strategy has three major components: mass treatment, surveillance, and certification. Mass treatment refers to treatment of an entire endemic community irrespective of the number of active clinical cases. Surveillance will need to be undertaken in the 15 countries and areas still reporting yaws cases. However, a larger but (as yet) unknown number of countries with a history of yaws will also at some point require some surveillance, to certify that all countries are in fact free from yaws.

Yaws-endemic communities are among the poorest in the world. As a result, much of the resources required for the eradications of yaws globally will need to be mobilized by public institutions, both domestic and international. Decision-makers will have to be convinced that yaws eradication is cost-effective and affordable, before embarking on such a strategy.

An economic evaluation of the yaws eradication strategy will help by informing the operationalization of the strategy, making it the most cost-effective possible, and demonstrating that it is affordable. We approach the economic evaluation in three parts, corresponding to the three major components of the yaws eradication strategy.

The economics of mass treatment for yaws is dealt with in two papers. In the first, using a regression model, we establish benchmarks for the cost per capita of mass treatment for yaws, reviewing and synthesizing evidence on the cost of mass treatment campaigns for other
NTDs. In the second, we use those benchmarks in a Markov model of the cost and cost-effectiveness of the yaws eradication strategy in the known endemic countries.

Our review of the literature revealed 56 studies of the cost of mass treatment for 6 NTDs. We included in a meta-regression data from 34 studies from 23 countries and 91 sites. Unit costs were found to be very sensitive to economies of scale, and the decision of whether or not to use volunteers. Financial unit costs are predicted to be less than 2015 US$ 0.50 in most countries for programmes that treat 100 thousand people or more. However, for smaller programmes or those that cannot rely on volunteers, both economic and financial unit costs are expected to be higher. In small island states, it could cost as much as US$ 10 per person. A web-based software application was developed to generate country-specific benchmarks for the cost per person of mass treatment.

Based on our probabilistic cost-effectiveness model, the estimate of the economic cost of yaws eradication is uncertain but not high by the standard of other disease eradication programmes – about US$ 362 (75-1073) million in the countries known to be endemic. Eradication would cost US$ 26 (4.2-78) for each year of life lived without disability or disfigurement due to yaws, or US$ 324 (47-936) per disability-adjusted life year (DALY). Excluding drugs, existing staff and assets, the financial cost is US$ 213 (74-522) million. The real cost of waiting for more roads (poverty reduction) would be 13 (7.3-20) million years of life affected by early-stage yaws and 2.3 (1.1-4.2) million years of life affected by late-stage yaws.

The economics of yaws surveillance is also addressed in two papers. In the first, we appraise the cost and cost-effectiveness of two alternative testing strategies using treponemal and dual treponemal/non-treponemal (non/non-trep) rapid diagnostic tests (RDTs) for yaws diagnosis and surveillance. In the second, we examine the historical literature on yaws case reports by all countries since 1945 and, on the basis of a regression model of factors associated with those reports, identify priorities for surveillance among countries no longer reporting cases to WHO.

With regard to surveillance, our decision analytic model suggests that at current prices of the treponemal and trep/non-trep RDTs, the sequential strategy is cost-saving for individual diagnosis at prevalence of past/current infection less than 85% (81-90); it is cost-saving for surveillance at less than 100%. The threshold price of the trep/non-trep RDT (below which the sequential strategy would no longer be cost-saving) is US$ 1.08 (1.02-1.14) for individual diagnosis at high prevalence of past/current infection (51%) and US$ 0.54 (0.52-0.56) for community surveillance at low prevalence (15%).

Our systematic review of the literature since the year 1945 revealed that yaws has been reported in at least 103 countries and areas. Reported cases peaked in the 1950s, with 55 countries reporting at least one case in 1950 and a total of 2.5 million cases reported in 1954. All but 15 countries and areas stopped reporting cases by the mid-1990s. Our regression model suggests that case reporting during periods of ongoing transmission is positively associated with socioeconomic development and, in the short-term, negatively associated with independence and armed conflict. Among 86 countries whose current status is unknown, we have identified a group of 20 countries with more than a 50% probability of reporting cases in the absence of active surveillance. For the other 66 countries, international support for active surveillance will likely be required.

The economics of certification is dealt with in a single paper. Using evidence from (ongoing) efforts to eradicate guinea worm disease (GWD), we consider the cost of certification of the interruption of transmission and the cost-effectiveness of an eradication programme in the end game. Ours is the first formal cost and cost-effectiveness analysis of an
eradication programme in the end game, when the number of cases decreases and much of the cost of the programme is for surveillance and certification.

Using data from the guinea worm eradication programme (GWEP), we found that certification costs about US$1.50-4.10 per 1000 population per year, plus up to US$ 4-6 million per year in global and regional costs. In spite of these costs, the cost per DALY averted (relative to doing nothing) is estimated at US$ 280 in the period 1986-2020. We found that the cost of certification can be high, but the cost of sustained control will be higher. In the period 2015-2030, the GWEP (with certification) is more cost-effective than simple control (without certification) if willingness to pay for one year of life lived without the risk of guinea worm disease exceeds US$ 0.10.

On the basis of the findings of the papers contained in this thesis, we make three broad policy recommendations.

First, donors looking for low cost and cost-effective investments in global public health should consider investing in the global yaws eradication programme.

Given the expected cost-effectiveness and affordability of the yaws eradication programme, the main question that remains is how to finance its implementation. The governments of endemic countries are encouraged to take ownership of national elimination efforts. But the global public good of yaws eradication also requires require global financing, including donations from the private sector.

At the national level, financial and in-kind resources could be better harnessed from the extractive industries (e.g. mining, logging) and others (e.g. cocoa and coffee). These are industries with operations on or near the resource-rich lands where resource-poor populations still live with yaws.

Today, with the recent donation of azithromycin to WHO by a Brazilian pharmaceutical company, the programme is in need of a lead financing partner for delivery of free medicines. The Korean aid agency (KOICA) become in 2017 the first bilateral to provide funding for yaws eradication, with seed funding to map the disease in East Timor. WHO should provide support to KOICA to ensure that the project in East Timor is a success, and one that KOICA will wish to repeat elsewhere.

Second, endemic countries should use the sequential strategy for diagnosis and surveillance while the global eradication programme advocates for a low cost dual test.

There are two situations of particular relevance in which savings could be substantial if endemic countries implemented the sequential testing strategy: first, during mass screening campaigns, before and after mass treatment; second, during final screening campaigns, including verification of the interruption of transmission. Cost savings from the sequential strategy should be reallocated to other essential interventions, such as sensitization to increase treatment coverage.

In the meantime, the global programme should negotiate with diagnostic manufacturers for a dual test costing about US$0.50-1.00. It can also explore alternative strategies with them. If a non-trep RDT were made available (alone, without the treponemal RDT), then an alternative strategy could involve the treponemal RDT followed by the non-treponemal RDT.

Indeed, the programme could advocate for outright donation of diagnostic tests – treponemal and/or non-treponemal. WHO has signed an agreement with Korea’s Standard Diagnostics for donation of rapid diagnostic tests for another NTD – human African trypanosomiasis; Standard Diagnostics is also producer of the treponemal test (SD Bioline) that could be used for yaws.
Third, WHO should pursue surveillance for certification of those countries with strong passive surveillance systems and the highest probability of having interrupted transmission. It should initiate discussions with countries with weak passive surveillance to assess their interest in and readiness for active surveillance for certification of yaws eradication. Integration of surveillance with other large scale prevalence surveys for trachoma and other NTDs could be considered. Certification should be integrated across diseases wherever possible.

During implementation of the above policy recommendations, WHO should guide countries in undertaking operational research to address the following questions that remain from the health economic perspective: What is the cost per person treated in the remotest villages of yaws endemic countries and how does that cost evolve over subsequent rounds of mass treatment? What effective coverage can be achieved and, as a result, what is the minimum number and most cost-effective combination of rounds of mass treatment? What are the costs and benefits of integrating mass treatment for yaws with mass treatment for other NTDs, and surveillance within a skin-NTD approach? What is the actual performance of the treponemal RDT, and its performance relative to the treponemal line of the trep/non-trep RDT? What is the appropriate probability cut-off, at which point to require countries of historic yaws endemicity to undertake active yaws surveillance for the purpose of certification? What are the minimum required standards for “satisfactory surveillance” in order to be certified as yaws-free? How might the development of antimicrobial resistance in yaws from mass treatment with azithromycin affect the cost and effectiveness of the global strategy? And finally, what are the potential benefits and costs of mass treatment for yaws for off-target diseases and health systems more broadly?
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Curriculum vitae

Education

2016–Present  Universiteit Gent, Ghent, Belgium
Doctor in Health Sciences

2003–2004  Universitat Pompeu Fabra, Barcelona, Spain
Master of Sciences in Economics (international economics)

2000–2002  École des Hautes Études Commerciales (HEC), Montréal, Canada
Maîtrise ès sciences en gestion (applied financial economics)

1997–2000  McGill University, Montréal, Canada
Bachelor of Commerce (joint honours economics & finance)

Work experience

1/2013–Present  World Health Organization, Geneva, Switzerland
Health Economist, Department of Control of Neglected Tropical Diseases (NTD)

Technical Officer, Tuberculosis Monitoring and Evaluation, Global TB Programme (GTB)

Technical Officer, Comprehensive Information for Tobacco Control, Tobacco Free Initiative (TFI)

Consultant, Armament and Arms Control

5/2002–10/2003  Towers Perrin, Montreal, Canada
Associate Consultant, Executive Compensation

Publications and citations

Google Scholar profile: https://goo.gl/c71yd3