



OPEN LETTER

# Insights from quantitative and mathematical modelling on the proposed 2030 goals for Yaws [version 1; peer review: 2 approved]

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**v1** First published: 16 Oct 2019, 3:1576 (<https://doi.org/10.12688/gatesopenres.13078.1>)

Latest published: 16 Oct 2019, 3:1576 (<https://doi.org/10.12688/gatesopenres.13078.1>)

## Abstract

The World Health Organization is currently developing 2030 goals for neglected tropical diseases (NTDs). In these, yaws has been targeted for eradication by 2030, with 50% of member states certified free of yaws transmission by 2023. Here we summarise the yaws modelling literature and discuss the proposed goal and strategy. The current Morges strategy involves rounds of Total Community Treatment (TCT), in which all members of the community are treated, and Total Targeted Treatment (TTT), treating active cases and their contacts. However, modelling and empirical work suggest that latent infections are often not found in the same household as active cases, reducing the utility of household-based contact tracing for a TTT strategy. Economic modelling has also discovered uncertainty in the cost of eradication, requiring further data to give greater information. We also note the need for improved active surveillance in previously endemic countries, in order to plan future intervention efforts and ensure global eradication.

## Keywords

yaws, modelling, neglected tropical diseases

## Open Peer Review

Reviewer Status

	Invited Reviewers	
	1	2
<b>version 1</b> published 16 Oct 2019	 report	 report

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2 **David Šmajš**, Masaryk University, Brno, Czech Republic

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Any reports and responses or comments on the article can be found at the end of the article.



This article is included in the [2030 goals for neglected tropical diseases](#) collection.

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**Author roles:** **Dyson L:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Mooring EQ:** Conceptualization, Writing – Review & Editing; **Holmes A:** Conceptualization, Writing – Review & Editing; **Tildesley MJ:** Conceptualization, Writing – Review & Editing; **Marks M:** Conceptualization, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

**Grant information:** This work was supported by the Bill and Melinda Gates Foundation through funding to the NTD Modelling Consortium [OPP1184344] EQM was supported by the National Institutes of Health [T32 AI 007535].

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

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**How to cite this article:** Dyson L, Mooring EQ, Holmes A *et al.* **Insights from quantitative and mathematical modelling on the proposed 2030 goals for Yaws [version 1; peer review: 2 approved]** Gates Open Research 2019, 3:1576 (<https://doi.org/10.12688/gatesopenres.13078.1>)

**First published:** 16 Oct 2019, 3:1576 (<https://doi.org/10.12688/gatesopenres.13078.1>)

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## Background

Yaws is a bacterial infection causing lesions in the skin and bones, primarily found in tropical areas. It is caused by the bacteria *Treponema pallidum pertenue*, and spread by skin to skin contact with an infected lesion. While the initial lesion (“mother yaw”) may spontaneously heal without treatment, the individual remains infected and relapses to infectious yaws represent a reservoir of future infection. Such relapses can occur up to 10 years later, and symptoms deteriorate with additional relapses. Without treatment, progression to secondary and tertiary yaws can result in chronic disfigurement and disability. It is critical, therefore that any eradication strategy must successfully treat asymptomatic as well as infectious individuals.

Efforts to eradicate yaws in the 1950s used injections of benzylpenicillin to successfully reduce worldwide cases by 95% (Mitjà *et al.*, 2015). However, limited surveillance and resources unfortunately lead to resurgence in West Africa, Asia and the Pacific in the 1970s (Asiedu *et al.*, 2014). Renewed eradication efforts began in 2012, when a single dose of oral azithromycin was shown to be non-inferior to injection with benzylpenicillin (Mitjà *et al.*, 2012). In 2016 India became the first country to be declared by the World Health Organization (WHO) to be free of yaws.

Current eradication efforts follow the Morges strategy (World Health Organization, 2012), which recommends one or more rounds of total community treatment (TCT) followed by rounds of total targeted treatment (TTT), in which active cases and their contacts (household, frequent family friends, schoolmates and playmates) are treated. TTT is intended to ensure treatment of asymptomatic non-infectious individuals (latent infections), who can later relapse to infectious yaws. Azithromycin is effective in over 95% of cases, with intramuscular benzathine penicillin used as a second line treatment where necessary.

The WHO is currently developing the 2030 neglected tropical diseases (NTDs) Roadmap, detailing the goals for each disease and the strategies that should be used to reach these goals. Two rounds of consultations with endemic countries, partners, donors and other stakeholders were held to refine the proposed targets. The goal for yaws is to certify all member states free of yaws transmission by 2030, with 50% certified by 2023 and 70% by 2025 (World Health Organization, 2019). In this letter we discuss the insights gained from modelling work to date, the feasibility of the proposed goals and the strategies required to reach them.

## Mathematical modelling of yaws transmission

The mathematical modelling of yaws transmission is still in its early days, comprising just seven papers that include

modelling (Dyson *et al.*, 2018; Fitzpatrick *et al.*, 2014; Fitzpatrick *et al.*, 2018; Gart & De Vries, 1966; Marks *et al.*, 2017; Mooring *et al.*, 2019; Mushayabasa *et al.*, 2012) and a single example fitting a simple catalytic model to age structured yaws data (Muench, 1959). While some work comprises mostly theoretical research (Gart & De Vries, 1966; Mushayabasa *et al.*, 2012), more recent publications have used economic or transmission modelling to consider questions regarding the funding and implementation of eradication programmes.

## The costs of yaws eradication

Economic modelling undertaken by Fitzpatrick *et al.* (2014) revealed a high degree of uncertainty in the cost of eradication, costing USD 362 (75-1073) million in 12 endemic countries and USD 324 (47-522) million per disability-adjusted life year. This is calculated using a compartment model with primary, secondary and tertiary infection with gradual exit of the at risk population due to poverty reduction. There are many uncertain quantities in this calculation due to lack of data regarding the cost of TTT (here assumed to be 30-50% of the cost of TCT), lack of disability weights for early or late-stage yaws (DALYs were calculated using weights for comparable conditions) and uncertainties around the population at risk and the unit costs of delivery in different countries.

## Campaign strategies: TCT vs TTT

Two recent papers focussed on the feasibility of reaching eradication by the current strategy, and ways to determine how many rounds of TCT and TTT will be required. The first uses a stochastic model of community-level yaws transmission, and determined that to reach 80% probability of achieving eradication using 8 rounds of twice-yearly treatment (3 rounds of TCT followed by 5 rounds of TTT) 80% coverage in low transmission ( $R_0 = 1.45$ ) settings, and 95% coverage in high transmission ( $R_0 = 2.47$ ) settings was required (Marks *et al.*, 2017). Here TTT is modelled as having the potential to achieve different coverage levels in active and latent yaws. If only one round of TCT was conducted then 90% coverage was required, followed by 5 rounds of TTT at 90% coverage of active infections and 65% coverage of latent infections. In high transmission settings with yearly treatment no combination of variables or treatments achieved elimination of transmission (EOT) in the Marks *et al.* model.

A second paper used household model of infection, parameterised using data from the Solomon Islands, and indicated that latent infections are often not co-located in the same households as clinical infections. This would imply that treating clinical cases and their household contacts would miss a large fraction of latent infections (Dyson *et al.*, 2018). This work inferred the infection statuses of adults, for whom serological tests were not conducted and found that between 65% and 100% of latent infections were in households without a clinical infection present. The conclusion that latent infections are not closely connected to active cases is also supported by empirical studies showing that there may be as many as 6–10 latent cases for each active yaws case (Marks *et al.*, 2015)

and that in an implementation study of the Morges strategy (Mitjà *et al.*, 2015) the ratio of latent:active cases increased following several rounds of treatment suggesting that the intervention (single round of TCT followed by only TTT) was more effective at treating active cases than latent cases. Since latently infected individuals may relapse to infectious yaws as many as 10 years later, this represents a significant reservoir of infection. Indeed, even the time to relapse is uncertain, so that it is unclear how long it is necessary to observe zero cases for before we can be certain of elimination. Note that in the household model, even with 100% coverage of active cases, household-based TTT would achieve a maximum coverage in latent infections of 35% (Dyson *et al.*, 2018), far below the 65% coverage of latent infection required in the Marks *et al.* model.

A recent stochastic compartmental metapopulation model constructed by Mooring *et al.* (2019) also examined the performance of TCT vs TTT in reducing the prevalence of both active and latent yaws. The model simulated yaws transmission and intervention in populations averaging 20000 people divided among 200 “hamlets” that ranged in size from 75 to 125 people. In view of the finding from other modelling studies that a household definition of contact may be inadequate, the model of TTT assumed that cases of active disease were detected with a probability of 90% and that treatment was administered to, on average, 90% of all persons living in any hamlet with at least one detected active case. The model assessed the number of rounds of TTT required to achieve the same impact as an additional round of TCT across varying assumptions about spatial heterogeneity in transmissibility, mixing between hamlets, and the initial number of rounds of TCT (1 to 3). When the overall prevalence of yaws (both active and latent infection combined) was the outcome of interest, this model demonstrated that multiple rounds of TTT were likely to be required to match the impact of a single additional round of TCT even when TTT was administered to the entire population of a village.

### Yaws surveillance

The currently proposed goal for yaws is eradication by 2030, defined as interruption of transmission (absence of new cases) globally. This raises questions regarding the proposed strategy and means of certifying elimination. Recent regression modelling estimates that, for 66 out of the 86 countries whose current status is unknown, there is a less than 50% probability of reporting cases without an active surveillance program (Fitzpatrick *et al.*, 2018). Thus this indicates that to ensure global eradication by 2030, it is necessary to undertake surveillance in these previously endemic countries. Furthermore, surveillance during elimination campaigns is hindered by the cross-reactivity of the yaws serological test, so that only children can be reliably classed as having latent yaws from the testing. We note, however, that it is still the case that adults that are serologically negative are not carriers of latent yaws, and therefore tests in adults may still be of use.

### Where are there risks that need to be mitigated to achieve the goal?

The primary risk for yaws, is a general lack of political commitment and funding for yaws eradication. This lack of community buy-in and serious questions regarding whether yaws eradication should be a priority presents a serious risk to program success. The possibility of achieving eradication by 2030 is also highly dependent on what proportion of previously-endemic countries still contain cases of yaws as this will have significant implications for the scale of intervention required globally. In recent years two countries (Liberia and the Philippines) have been found to still be endemic (World Health Organization, 2018) highlighting the possibility that the number of countries requiring interventions for yaws eradication may grow substantially as surveillance is undertaken in a wider range of settings.

Systematic non-participation in both TCT and TTT may pose a hindrance to elimination. No measure has been made in this disease; however, previous modelling work shows that in mass drug administration campaigns systematic non-participation can have a significant effect, particularly when levels of reinfection are low (Dyson *et al.*, 2017). In the wider literature on MDA in infectious diseases, correlations between rounds were found of between 0.28 and 0.54 (Dyson *et al.*, 2017). Future modelling work could determine the effect of systematic non-participation on the outcome of elimination campaigns for yaws. In addition, drug resistance represents a risk to implementation of TCT and TTT with azithromycin. Resistance has been reported in Papua New Guinea in the context of a yaws eradication study (Mitjà *et al.*, 2018). Finally, as with many NTDs, it is important to require sufficient coverage of surveillance efforts to be sure that zero cases found represents interruption of transmission. As discussed above, in many countries it is unlikely that passive surveillance will result in reporting of new cases (Fitzpatrick *et al.*, 2018).

### Future work

Current modelling work is limited by the availability of suitable datasets, since a model fitted to data from a specific geographical location may not be directly applicable in another setting. In particular high-quality survey data is lacking from West and Central Africa, the region of the world where the second most cases arise (after the Pacific, where most current modelling data is derived from). It is this lack of setting-specific data that hinders country-specific predictions. In addition, given suitable data, modelling could also be undertaken that includes definitions of “contact” for TTT other than household contacts. For example, modelling school based contacts requires data in which the schools attended by children is included.

Other potential extensions include age-prevalence modelling, to determine whether serological testing in children aged 1–5 is necessary and sufficient for determining the interruption of transmission. Along with spatial modelling to assess

clustering, these models can be used to consider surveillance strategies. So far, most yaws modelling has focused on TCT and TTT, and not ongoing surveillance. Additional research should consider in greater depth ongoing community-based surveillance and the implications of treating suspected cases and, possibly, their contacts. Such research would shed light on the extent to which rapid identification of symptomatic cases should be a programmatic priority.

The dynamics of latent infection (i.e. the period during which infected individuals are at risk of reactivating and developing symptomatic and infectious yaws) deserves further study. Future modeling studies should further explore the extent to which results are sensitive to assumptions about the duration of latent infections. Most yaws models have implicitly assumed that the duration of latent infection is exponentially distributed. This distributional assumption deserves further study. Measuring the duration and distribution of latent infection is challenging, in part because it would be

unethical to prospectively follow-up untreated yaws patients. As a first step, models could be used to explore what sort of data would be required to indirectly infer the dynamics of latent infection.

Finally, further modelling may be undertaken to answer the question: “would achieving >90% coverage in children even if the overall population coverage is <90% be sufficient to interrupt transmission?” This work would need additional data regarding the amount of transmission between children and adults, which is difficult to obtain due to the problems with serological testing in adults. Without such data we could still ask the question: if adult transmission is very frequent we wouldn’t expect focusing coverage on children to interrupt transmission - how much rarer does it need to be for this strategy to be successful? Further economic modelling could also be undertaken given more data regarding the costs of TTT.

### Data availability

No data are associated with this article.

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## Open Peer Review

Current Peer Review Status:  

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### Version 1

Reviewer Report 12 December 2019

<https://doi.org/10.21956/gatesopenres.14217.r28252>

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#### David Šmajš

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The article summarizes 7 studies published on modelling of transmission of yaws, a disease targeted for eradication by WHO by 2030. Recently, some countries were declared to be free of yaws (India and Ecuador) indicating that elimination of yaws is an attainable goal. However, many factors affecting an achievement of this goal are not completely understood. The authors are well aware of the lack of the data allowing to specifically model yaws transmission in different geographical locations and to propose optimal eradication strategies for different countries or regions. The paper highlights main risks that can contribute to failure of the eradication efforts including lack of political commitment and funding, systematic non-participation in both TCT and TTT, selection of suboptimal strategy based on single or insufficient number of TCT rounds followed by TTT, possible emergence of azithromycin resistance of the yaws agent and the lack of sufficient surveillance to prove interruption of transmission. However, there are other potential risks that need to be considered and these include: 1) the role of migration and travel in reintroduction of infection to the treated population, 2) limited knowledge on proportion of latent and active yaws cases, efficiency of the treatment of latent yaws and its transmission routes in many areas and 3) the potential risk of transmission of yaws agent from non-human primates that were shown to have treponemal infections caused by strains similar to those causing yaws.

There are many studies describing a short-term effect of azithromycin MDA on reduction of active and latent yaws cases (e.g., Ghinai *et al.*, 2015<sup>1</sup>, Marks *et al.*, 2015<sup>2</sup>), however, there is only one longitudinal study using molecular detection and typing of *Treponema pallidum* subspecies *pertenue* (Mitja *et al.*, 2018<sup>3</sup>). This study showed that the active cases detected 42 months post single MDA round include the following patient categories: travelling residents, newly arrived migrants, MDA-treated non-travelling residents, and non-travelling residents absent from initial MDA. Most of the cases identified at this point were genotyped and belonged to the most frequent genotype found throughout the whole study. Although failure to achieve elimination of yaws is thought to be caused mainly by the proportion of individuals absent at the time of mass treatment, the presented facts indicate that other factors can contribute to this failure (in-migration, reinfection from other active cases, failure of treatment of latent cases).

As shown in the study of Mitja *et al.* (2017<sup>4</sup>), the serological cure of yaws was achieved in the same proportion of active and latent cases after 24 months. The data presented by Mitja *et al.* (2018<sup>3</sup>) showed that children with high titer latent yaws aged 6-15 years lowered from 19% at baseline to 7% at 42 months. However, it is not known if all the children were treated or not. Studies concentrating on the follow-up of latent cases should help to elucidate the treatment efficiency and dynamics of latent yaws infections as suggested by the authors of the open letter. The proportion of latent cases in the one round of TCT followed by 7 TTT treated population remains very high (> 5%) and represents potential risk of re-emergence of yaws. The successful strategy for elimination of yaws will have to implement additional steps to effectively target the remaining latent cases and the potential spread of yaws.

In recent years, reports describing infections of non-human primates with treponemes highly similar to the agent of human yaws have been published (Knauf *et al.*, 2018<sup>5</sup>, Chuma *et al.*, 2019<sup>6</sup>). Although the transfer from animals to humans has not been described yet, an active surveillance in areas of the risk should be planned as a part of the global yaws eradication program.

The planning of the yaws eradication program therefore requires future studies to predict the optimal ratio between TCT and TTT rounds, extent of TTT treatment, prediction of eradication costs and prediction of optimal strategy of active surveillance in the involved states and areas.

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**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**

Partly

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**

Yes

**Is the Open Letter written in accessible language?**

Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Treponema pallidum genomics, Molecular diagnostics of syphilis and endemic treponematoses

**We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 27 November 2019

<https://doi.org/10.21956/gatesopenres.14217.r28141>

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**Caroline Trotter** 

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Overall I found this article to be clearly structured and well written. There is not a large body of work on modelling yaws and the authors highlight that there is much more to be done. A key problem is the lack of data availability from certain regions to which models can be fitted. Given the uncertainties in the current costs of eradication, I wonder if the authors would consider proposing a value of information study to help target new data collection?

I noted one error - in the section "The costs of yaws eradication", the authors quote USD 324 million per DALY, whereas in fact the source cites USD 324 per DALY (a much more reasonable figure).

**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**

Yes

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**

Partly

**Is the Open Letter written in accessible language?**

Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**

Yes

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** Infectious disease epidemiology, mathematical modelling, (not yaws!)

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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