An ODE model of yaws elimination in Lihir Island, Papua New Guinea

Presley Kimball[1], Jacob Levenson[2], Amy Moore[3], Jan Rychtar[4] and Dewey Taylor[4]

[1] Department of Mathematics, Creighton University, Omaha, NE, United States of America
[2] Department of Mathematics, Washington and Lee University, Lexington, VA, United States of America
[3] Department of Mathematics and Statistics, Elon University, Elon, NC, United States of America
[4] Department of Mathematics and Applied Mathematics, Virginia Commonwealth University, Richmond, VA, United States of America

ABSTRACT

Yaws is a chronic infection that affects mainly the skin, bone and cartilage and spreads mostly between children. The new approval of a medication as treatment in 2012 has revived eradication efforts and now only few known localized foci of infection remain. The World Health Organization strategy mandates an initial round of total community treatment (TCT) with single-dose azithromycin followed either by further TCT or by total targeted treatment (TTT), an active case-finding and treatment of cases and their contacts. We develop the compartmental ODE model of yaws transmission and treatment for these scenarios. We solve for disease-free and endemic equilibria and also perform the stability analysis. We calibrate the model and validate its predictions on the data from Lihir Island in Papua New Guinea. We demonstrate that TTT strategy is efficient in preventing outbreaks but, due to the presence of asymptomatic latent cases, TTT will not eliminate yaws within a reasonable time frame. To achieve the 2030 eradication target, TCT should be applied instead.

INTRODUCTION

Yaws is an infectious disease spread by skin to skin contact mostly amongst children (*Marks, Solomon & Mabey, 2014*). It is caused by bacteria *Treponema pallidum* ssp. *pertenue*, and begins at an abrasion or open wound which then develops into the "primary papule" or "mother yaw" (*Perine et al., 1984*). This initial stage is known as primary yaws and the lesion persists for three to six months (*Marks et al., 2015a*). A short latency period may occur after primary yaws if the primary papule naturally heals before secondary lesions develop (*Perine et al., 1984*). Secondary yaws begins with the appearance of other lesions anywhere on the body (*Mitjà, Asiedu & Mabey, 2013*). These lesions heal spontaneously resulting in a noninfectious latent period that, in some cases, may last the remaining lifetime of the person (*Perine et al., 1984*). During the latent period, previously infected individuals may relapse into secondary yaws up to 5 years after recovering from infection (*Marks et al., 2015b*). Up to 10% of yaws cases may develop into late yaws (*Mitjà, Asiedu & Mabey,*

2013), also known as tertiary yaws. Tertiary lesions tend to be very harmful with massive necrotic tissue destruction; yet they are noninfectious (*Marks, Solomon & Mabey, 2014*).

Yaws was the first disease to be targeted for eradication by the World Health Organization (*Marks et al., 2015a*). Before this initiative, 90 countries were reported as endemic, totaling about 50 million cases worldwide (*Kazadi et al., 2014*). The mass screening and treatment programmes led by WHO reduced the global prevalence by >95% between 1950 and 1964, but yaws has reemerged as a public health problem (*Asiedu et al., 2008*). In 2018, Papua New Guinea and the Solomon Islands reported over 10,000 suspected cases each (*WHO, 2018b*). According to the most recent report (*WHO, 2020*), 15 countries are considered as currently endemic for yaws; 87,877 suspected yaws cases were reported to WHO in 2020 from 11 countries from which 81,369 cases were in Papua New Guinea. Solomon Islands reported 13,694 cases in 2019. Figure 1 shows the most recent status of yaws endemicity.

A single oral dose of azithromycin was shown to be just as effective as the previous treatment of injectable penicillin (*Mitjà et al., 2012*). This initiated a new wave of interest in eradication of yaws (*Marks et al., 2015a*) and, in 2012, the WHO implemented the Morges Strategy to combat yaws transmission with the goal of eradicating the disease by 2020 (*WHO, 2012*). The Morges Strategy includes one or more rounds of total community treatment (TCT) where treatment is given to all members of the community and followed by the total targeted treatment(TTT) where treatment is administered to all actively infected individuals and their close contacts as a response to a local outbreak (*WHO, 2012*). This strategy continues to be the primary plan to eradicate yaws, but the timeline has been stretched to eradication by 2030 after the original 2020 goal was not met (*Dyson et al., 2019*).

Mathematical modelling is now a standard and indispensable tool for understanding disease dynamics and control (*Anderson & May, 1992*), yet there is a surprising lack of models of yaws transmission. Until 2012, the only math model of yaws considered the effect of the chicken pox virus on yaws (*Gart & De Vries, 1966*). More recently, the model from *Mushayabasa et al. (2012)* divides the population into rich and poor and preforms a theoretical analysis of disease-free and endemic equilibria. In *Muench (2013)*, the authors fitted a simple catalytic model to age structured yaws data. All other models of yaws are stochastic and were designed to estimate various aspects of yaws eradication. In *Fitzpatrick, Asiedu & Jannin (2014)*, the authors were concerned with the economic side of eradication and concluded that the eradication would not be expensive; yet there is still a large degree of uncertainty for the lack of available data (*Dyson et al., 2019*). In *Dyson et al. (2017)*, the authors created a model to estimate the fraction of individuals that are missed during treatment in the Morges strategy. In modeling effectiveness of the Morges Strategy, *Marks et al. (2017)* investigated the probability of eradication. *Fitzpatrick et al. (2018)* created a linear regression model in order to predict the probability of case reporting in different previously affected countries based on different parameters. *Mooring et al. (2019)* builds off of the work of *Marks et al. (2017)*, using the same compartment model and modeling the effects of different combinations of TTT and TCT. The most recent model comes from *Holmes et al. (2020)* in which the authors adapted the model from *Dyson et al. (2017)* to again
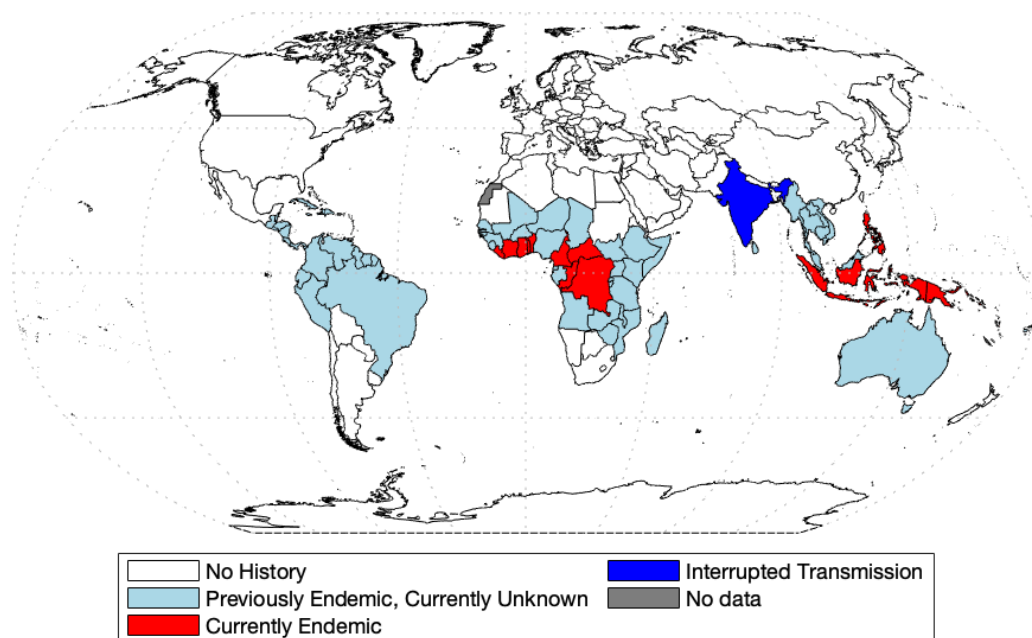
Figure 1 **World map of endemic history and prevalence of yaws.** Data collected from *WHO (2018b)* and *WHO (2020)* and map was made with the aid of borders.m file (*Greene et al., 2019*) in MATLAB.
Full-size ⬜ DOI: 10.7717/peerj.13018/fig-1

simulate different combinations of TTT and TCT. It was found that different populations require different treatments, but in general, TCT was more effective in eradication.

The stochastic models such as recent *Marks et al. (2017)*; *Mooring et al. (2019)*; *Holmes et al. (2020)* are generally more suitable for the eradication end game than the deterministic compartmental models. Yet, the deterministic models are typically simple and easy to analyze, while still reasonably accurate and realistic. Given the lack of deterministic models of yaws transmission in general, our goal is to develop a deterministic model of yaws transmission and then use the model to compare the effectiveness of TTT and TCT strategies. We use the model to derive a formula for the basic reproduction number and to obtain simulated times needed for yaws elimination. Our model can be used as a quick estimate of the effectiveness of a particular treatment strategy.

METHODS

We created a compartmental model shown in Fig. 2. Individuals are born as susceptible (S) at rate Λ. The susceptible individuals become exposed (E) after coming in contact with individuals having primary (Y_1) or secondary (Y_2) yaws; the transmission rate is β. After an incubation period lasting a time σ^{-1}, the exposed individual develops primary yaws and becomes infectious. The primary yaws lasts a time λ_1^{-1}, after which the individual may either develop secondary yaws (Y_2) with probability $p_{Y_1 Y_2}$, or go into a first latency period (L_1) with probability $p_{Y_1 L_1} = 1 - p_{Y_1 Y_2}$. This means that the rate of progression from Y_1 to L_1 is $p_{Y_1 L_1} \lambda_1$ while the rate of progression from Y_1 to Y_2 is $p_{Y_1 Y_2} \lambda_1$.
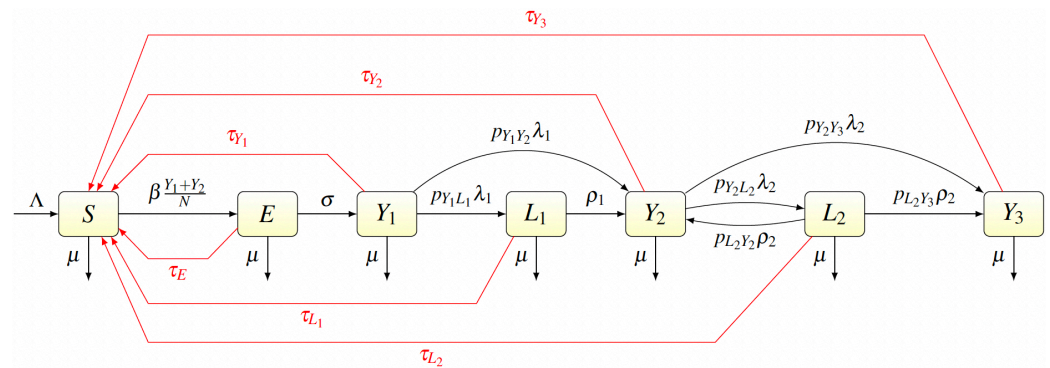
Figure 2 Scheme of the yaws dynamics. The arrows denote transitions between the compartments. The letters next to the arrows specify the per capita rates of the transitions. The red arrows denote a treatment. The black arrows show a natural disease progression (without any treatment), from susceptible (S) to exposed (E) and then to primary yaws (Y_1). After the primary yaws, a majority of cases goes through a short latent period (L_1) before progressing to secondary yaws (Y_2). A small portion develops secondary yaws directly. Most secondary yaws heals and the infection becomes latent (L_2). The latent cases can relapse to secondary yaws for the rest of their lives. Only a negligible number of individuals develop non-infectious tertiary yaws (Y_3).

Full-size 🖼 DOI: 10.7717/peerj.13018/fig-2

The average duration of the first latency period is ρ_1^{-1}; after that an individual develops secondary yaws. The average duration of secondary yaws is λ_2^{-1}. After this period, one could either develop rare, debilitating and very painful, but non-infectious, tertiary yaws (Y_3) with probability $p_{Y_2 Y_3}$, or go into the second latent period with probability $p_{Y_2 L_2} = 1 - p_{Y_2 Y_3}$. The average length of the second latency period is ρ_2^{-1}. Afterwards, individuals can relapse into secondary yaws with a probability $p_{L_2 Y_2}$, or develop tertiary yaws with a probability $p_{L_2 Y_3} = 1 - p_{L_2 Y_2}$.

Individuals can be treated and return to susceptible at a rate of τ_I for individuals in a compartment $I \in \{E, Y_1, Y_2, Y_3, L_1, L_2\}$. Treatment of each compartment depends on the elimination strategy and the specific values are discussed below.

Finally, all individuals are assumed to die at rate μ.

The parameters are summarized in Table 1. Most parameter values were estimated directly from the literature. The only two exceptions are the transmission rate β and the treatment rates τ. Details are shown in Appendix B.

The transmission rate β was obtained by fitting the endemic equilibrium to baseline data (prior the mass treatment, *i.e.,* when all $\tau_I = 0$) from Lihir Island in Papua New Guinea (*Mitjà et al., 2015b*).

To model TCT, we assume $\tau_I = 1/6$ for all I, corresponding to treating the whole population every six months. To model TTT, we assume the best case scenario, *i.e.,* $\tau_E = \tau_{Y_1} = \tau_{Y_2} = \tau_{Y_3} = \tau_{L_1} = 1/6$ while $\tau_{L_2} = 0.1/6$, *i.e.,* we assume that the TTT strategy finds and treats only 10% of secondary latent cases every six months but otherwise finds and treat every other infected individual. This again corresponds to treating active yaws cases and all their closed contacts (that will be either exposed or at most the first latency period) once in six months. We assume that 90% of secondary latent cases are omitted in

Table 1 Notation —Parameters, controls and their values. All times are expressed in months and rates are expressed per month. Details behind model calibration are explained in B.

Symbol	Meaning	Value	Range	Source
Λ	Birth rate	$\frac{27.2}{12*1000}$	$[0.001, 0.003]$	*United Nations (2019)*
μ^{-1}	Expected life span	$65*12$	$[600, 1200]$	*World Bank (2019)*
β	Transmission rate	0.0166	$[0.01, 0.02]$	Estimated
σ^{-1}	Length of the incubation period	$\frac{21}{30}$	$[\frac{9}{30}, \frac{90}{30}]$	*Perine et al. (1984)*
λ_1^{-1}	Length of primary yaws	3	$[3, 6]$	*Perine et al. (1984)*
λ_2^{-1}	Length of secondary yaws	3	$[0, 60]$	*Mitjà, Asiedu & Mabey (2013)*
ρ_1^{-1}	Length of latency after primary yaws	1.5	$[1, 2]$	*Marks et al. (2015a)*
ρ_2^{-1}	Length of second latency	30	$[1, 60]$	*Perine et al. (1984)*
$p_{Y_1 Y_2}$	Probability of immediate secondary yaws infection after primary yaws	0.12	$[0.09, 0.15]$	*Mitjà, Asiedu & Mabey (2013)*
$p_{Y_1 L_1}$	Probability of latency period after primary yaws	$1 - p_{Y_1 Y_2}$		
$p_{Y_2 Y_3}$	Probability of immediate tertiary yaws infection after secondary yaws	0.0001	$[0, 0.0002]$	*Mitjà, Asiedu & Mabey (2013)*
$p_{Y_2 L_2}$	Probability of latency period after secondary yaws	$1 - p_{Y_2 Y_3}$		
$p_{L_2 Y_2}$	Probability of relapsing to secondary yaws during latent period after secondary yaws	0.9999	$[0.9998, 1]$	*Mitjà, Asiedu & Mabey (2013)*
$p_{L_2 Y_3}$	Probability of developing tertiary yaws during latent period	$1 - p_{L_2 Y_2}$		
τ_I	Rate of treatment for the group $I \in \{E, Y_1, Y_2, Y_3, L_1, L_2\}$	variable		See text

the treatment because the were infected independently many months or even years ago and are not close contacts to the currently acutely infected individuals. We adopted these assumptions since we can then demonstrate that even these high coverage, yaws will persist in the population for long time under TTT strategy. The protocol of *Mitjà et al. (2015b)* study also included a 2 year period of non-strategic treatment. For that period, we assumed $\tau_E = \tau_{Y_1} = \tau_{Y_2} = \tau_{Y_3} = \tau_{L_1} = 1/24$ with coverage as in TTT.

We validated our model on data from the mass treatment trial in Lihir Island (*Mitjà et al., 2018*); see Fig. 3. The fitted curve follows general trends of the data. However, the real data for latent infections exhibits oscillation with peaks and dips every 6 months and our simple model cannot exhibit such oscillations.

We used the compartmental model from Fig. 2 to create a system of ordinary differential equations. We found disease-free and endemic equilibria. Using the next generation matrix method (*van den Driessche & Watmough, 2002*), we found the basic reproduction number. We performed the stability analysis of the disease-free equilibria based on methods from *van den Driessche & Watmough (2002)* and *Castillo-Chavez et al. (2002)*.

We did simulations in MATLAB, the code is made available in supplementary material. We adhered to responsible coding practices as outlined in *Lucas et al. (2020)*.

The global uncertainty and sensitivity analysis by the partial rank correlation coefficients, PRCC was based on *Marino et al. (2008)*. We randomly selected 1000 parameter values
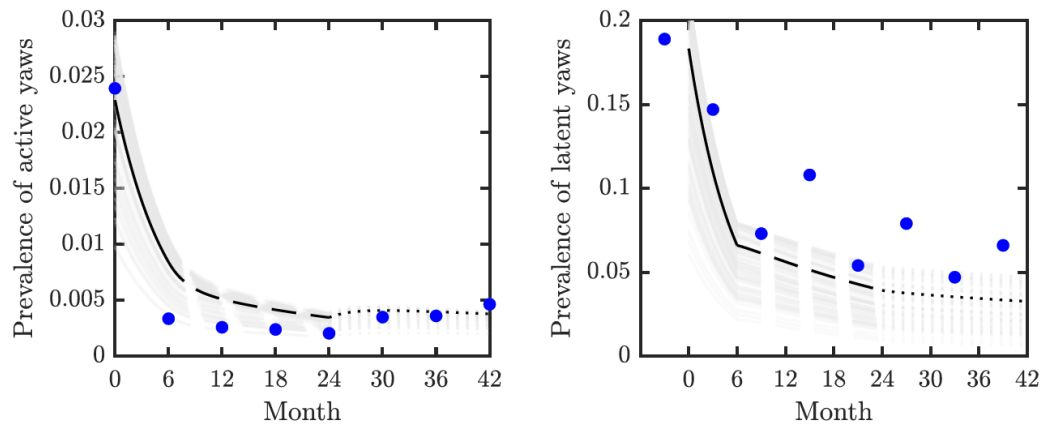
Figure 3 Model validation. Data from *Mitjà et al. (2018)* (blue circles) track active (left) and latent (right) yaws prevalence on Lihir Island. The study protocol was one round of TCT at time 0, followed by three rounds of TTT every six months till month 24 and then non-strategic treatment till month 42 (*Mitjà et al., 2015b*). The latent cases data (right) are plotted 3 months earlier to account for the continued seropositivity of latent infections until 3–6 months after treatment (*Mitjà et al., 2012*). The model predictions show one round of TCT (solid line, months 0–6) followed by TTT (dashed line, months 6–24) and then a period of non-strategic treatment (dotted line, during months 24–42). The black lines represent the model predictions for the parameters as in Table 1. The gray lines represent model predictions when the parameters value vary within the ranges specified in Table 1.

Full-size 🖾 DOI: 10.7717/peerj.13018/fig-3

within the ranges specified in Table 1. We used only those values that could fit to baseline data from Lihir Island (*Mitjà et al., 2015b*).

RESULTS

We obtained an explicit formula for the basic reproduction number, R_0. As shown in Eq. (9),

$$R_0 = \left(\frac{\beta\sigma}{v_E v_{Y_1}}\right)\left(1+\left(\frac{\lambda_1 v_{L_2}}{v_{L_1}}\right)\left(\frac{p_{Y_1 L_1}\rho_1 + p_{Y_1 Y_2} v_{L_1}}{v_{L_2} v_{Y_2} - p_{Y_2 L_2}\lambda_2 p_{L_2 Y_2}\rho_2}\right)\right) \tag{1}$$

where v_I denote the sum of all total rates out of the compartment I, *i.e.*,

$$v_E = \sigma + \tau_E + \mu \tag{2}$$

$$v_{Y_1} = \lambda_1 + \tau_{Y_1} + \mu \tag{3}$$

$$v_{Y_2} = \lambda_2 + \tau_{Y_2} + \mu \tag{4}$$

$$v_{Y_3} = \mu + \tau_{Y_3} \tag{5}$$

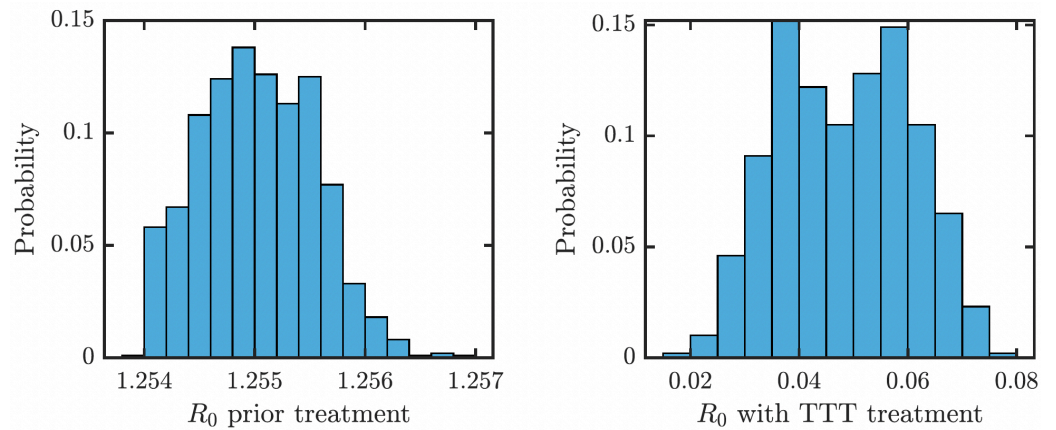$$v_{L_1} = \rho_1 + \tau_{L_1} + \mu \tag{6}$$

Figure 4 Distribution of R_0 for parameters that fit data from Lihir Island (*Mitjà et al., 2015b*). Left: Prior the treatment. Right: during TTT treatment.

Full-size 🖼 DOI: 10.7717/peerj.13018/fig-4

$$v_{L_2} = \rho_2 + \tau_{L_2} + \mu. \tag{7}$$

We estimated that without any treatment, $R_0 = 1.2548$. The uncertainty analysis showed that in order to fit data from Lihir Island, R_0 is between 1.24 and 1.27; see Fig. 4. With TTT treatment, the values of R_0 ranged between 0.02 and 0.08. This shows that TTT is quite effective in prevention of the spreading of the epidemics.

We proved (Theorem 1 in Appendix A.2) that the disease-free equilibrium is globally asymptotically stable when the basic reproduction number $R_0 < 1$. We also showed (Lemma 1 in Appendix A.2) that R_0 is decreasing in the treatment rate. If the treatment rate is high enough, the basic reproduction number drops below 1 even for a conservative TTT strategy when only active cases of yaws gets treated; see Fig. 5. This means that the Morges strategy can eventually eliminate yaws.

To understand how long the Morges strategy needs to be applied, we simulated two rounds of initial TCT and followed by subsequent rounds of TTT. We performed a global uncertainty analysis where we varied parameters within the ranges specified in Table 1. Figure 6 demonstrates the results. Our model predicts that it would take about 14 to 16 years to achieve a thousandfold decrease in cases (*i.e.*, less than 1 infected person in Lihir Island). The relatively high prevalence of latent cases in the population and the long latency period are the main culprits behind this long elimination time. The continuous application of TCT strategy every six months can achieve the same results in about 3.5 years; the improvement in speed is caused by the latent cases getting treated as well.

As illustrated in Fig. 7, the success or failure of TTT strategy significantly depends on how many latently infected individuals can be discovered and treated. The figure in fact shows expected elimination times for a whole family of strategies with TTT on one end (when the coverage of L_2 is low) and TCT on the other end (when the coverage of L_2 is 100%). It can take over 25 years to eliminate yaws if only 1% or less of latent cases are
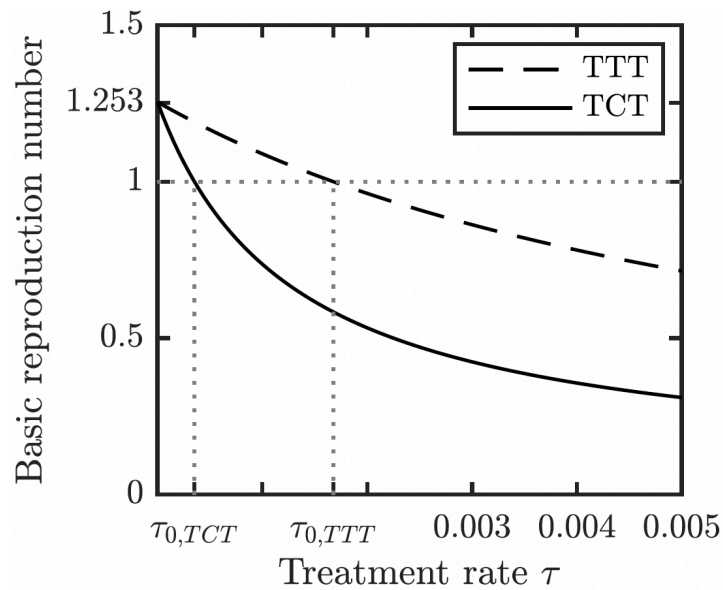
Figure 5 Dependence of R_0 on τ under TCT and TTT regimes. Once $\tau > \tau_0$ where τ_0 solves $R_0 = 1$, then the disease can be eliminated. For the parameters as in Table 1, $\tau_{0,TCT} \approx 3.5 \cdot 10^{-4}$ and $\tau_{0,TTT} \approx 1.68 \cdot 10^{-3}$.
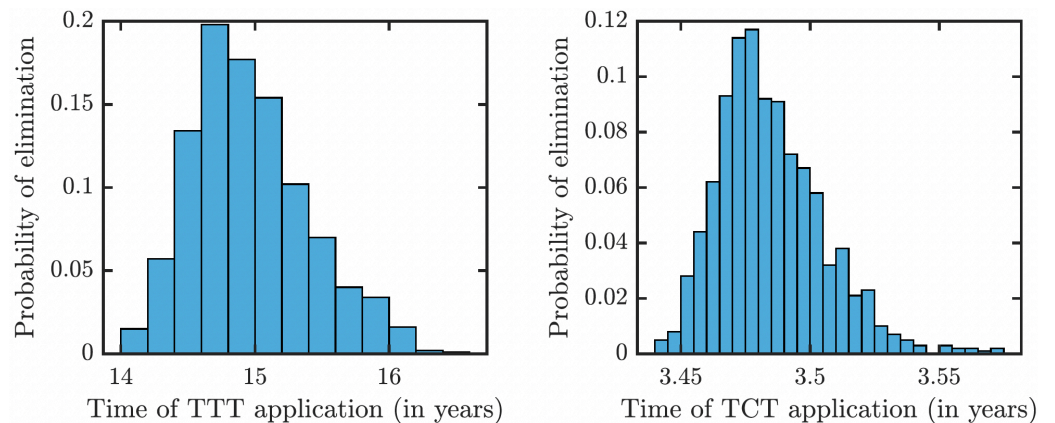Full-size 🖻 DOI: 10.7717/peerj.13018/fig-5

Figure 6 Distribution of times needed to decrease yaws cases thousand times using TTT (left) or TCT (right).
Full-size 🖻 DOI: 10.7717/peerj.13018/fig-6

found; it would take about about 10 years if 20% is found and about 5 years if about 50% of cases is found.

The sensitivity analysis shows a strong influence of the relapse rate, ρ_2, and the spontaneous healing rate of the secondary yaws, λ_2, on the elimination time under the TTT regime; see Fig. 7. The higher the relapse rate and the lower the healing rate, the less it takes to eliminate yaws. This initially counter-intuitive result is caused by the fact that spontaneous healing increases the pool of latently infected individuals that can be missed by the TTT strategy. However, if infected individuals do not heal spontaneously, they can
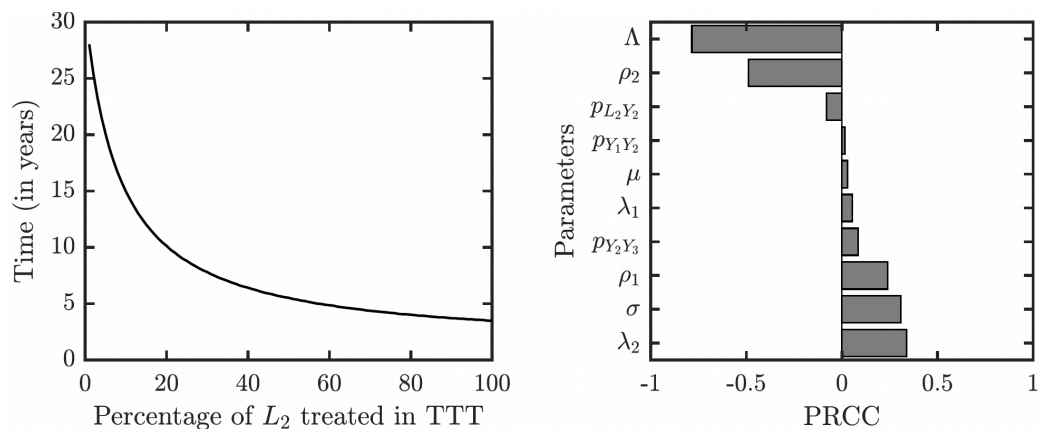
Figure 7 **Sensitivity analysis of the time needed to eliminate yaws under TTT.** We showed the dependence on the percentage of treated L_2 cases explicitly. The analysis of other parameters is done by partial rank correlation coefficients, PRCC (*Marino et al., 2008*).

Full-size 🖼 DOI: 10.7717/peerj.13018/fig-7

be discovered and treated. This again indicates that the latent individuals are the weakest point of the TTT strategy. A higher birth rate also reduces the time to elimination. This is mainly because a higher birth rate increases the influx of healthy individuals while the active yaws of young children are caught on time before progressing to latency. Naturally, a shorter incubation periods increases the time needed for the elimination as they increase the number of yaws cases. The effects of other parameters are relatively mild and not significant.

Finally, let us note that when $R_0 > 1$, the disease-free equilibrium is not stable and there exists an endemic equilibrium given explicitly in Eq. (10). We run numerical simulations for parameter values with ranges in Table 1 and the numerical solutions of the ODE model always converged to the endemic equilibrium. Moreover, motivated by *Yang et al. (2017)* and *LaSalle (1976)*, we considered a Lyapunov function $\mathcal{L} = \sum_C \left(C - C^* - C^* \ln\left(\frac{C}{C^*}\right) \right)$, where the summation is taken over all compartments $C \in \{S, E, Y_1, Y_2, Y_3, L_1, L_2\}$ and C^* is an endemic equilibrium value. It follows that $\mathcal{L} \geq 0$ and $\mathcal{L} = 0$ iff $C = C^*$ for all compartments. Also, we evaluated $\mathcal{L}' = \sum_C \left(1 - \frac{C^*}{C} C' \right)$ at 10^5 randomly selected values of the compartments. We always saw that $\mathcal{L}' < 0$. Thus, we believe that the endemic equilibrium is globally stable whenever $R > 1$, although we do not have an analytical proof of this fact. However, as it has been shown in Fig. 4, even with the weaker TTT treatment, R_0 is significantly less than 1 and thus, for the purpose of the elimination (which is the main focus of this paper), the stability of the disease-free equilibrium is much more important.

DISCUSSION

To model TTT strategy, we made a conservative assumption that not many latent cases are treated. We argue that this is a reasonable reflection of a reality in the eradication endgame. The latent cases represent reservoir of future infections *Dyson et al. (2019)*. By treating a recently relapsed latent case with all its close contacts, TTT strategy prevents outbreaks.

However, contact tracing does not identify many other latent cases in the population; they likely got infected independently many months or even years ago. Thus, TTT works quite slowly as an elimination strategy as it is equivalent to waiting for the latent cases to relapse instead of actively identifying and treating them while still asymptomatic.

Our model predicts very little variation of eradication times when using TCT strategy. This is natural as the whole population gets treated and most factors of yaws dynamics thus do not play any crucial role. The variability is much larger for the TTT regime which could potentially eliminate yaws in as little as 14 years but it may also take 16 years. The two key factors responsible for the large variation are the duration of the latent period (which is positively correlated with the elimination time) and the duration of the secondary yaws (which is negatively correlated with the elimination times). Gaining more knowledge about these two parameters would reduce the uncertainty of the model predictions.

Our model differs from previous models in two crucial aspects. First, we developed a deterministic ODE model, in contrast to recent stochastic models developed in *Fitzpatrick, Asiedu & Jannin (2014)*; *Marks et al. (2017)*; *Dyson et al. (2017)*; *Fitzpatrick et al. (2018)*; *Holmes et al. (2020)*. While stochastic simulations can incorporate higher degrees of realism, there is a natural simplicity in the ODE models that allows for an easy estimation of the basic reproduction number. Even with different model parameters, we do not necessarily have to rerun the simulations to be able to predict the model outcomes. Our model can thus serve as a first and reasonably reliable estimate of what will happen under different elimination strategies.

Second, our model incorporates all of the known stages of yaws. All models of yaws should consider susceptible individuals, infectious stage(s) of yaws (possibly divided into primary and secondary yaws) and the asymptomatic latent yaws that can relapse. Similarly to *Fitzpatrick, Asiedu & Jannin (2014)*, we also considered tertiary yaws; and as *Mushayabasa et al. (2012)*, we included exposed individuals. Finally, as in *Marks et al. (2017)* we included a possibility of a latent period between the primary and secondary yaws.

There are several limitation of our model. Most of the limitations stem from the fact that our model is a simple deterministic ODE model in homogeneous population. It thus cannot capture the true eradication endgame when only very small, often just a single digit, number of individuals are infected. The model also cannot capture household dynamics as done in *Dyson et al. (2017)* or the population structured into hamlets as done in *Mooring et al. (2019)*.

Unlike in stochastic simulations used in *Marks et al. (2017)*; *Dyson et al. (2017)*; *Mooring et al. (2019)*; *Holmes et al. (2020)*, we do not explicitly consider treatment coverage. An independent coverage is implicitly incorporated in our model—a rate $\tau_I = 1/6$ can mean that the whole (100%) population is treated once every 6 months, as well as that the attempt to treat the whole population is made every m months but at each attempt, only $p * 100\%$ of the population is reached with $m/p = 6$. A systematic failure of the treatment could be included in the model by duplicating each compartment into "treatment adherent" and "treatment non-adherent". Setting the birth rate as $(1-p)\Lambda$ and $p\Lambda$, respectively, into

the susceptible treatment adherent and treatment non-adherent, respectively, would then achieve a systematic failure of treatment for $p*100\%$ of the population.

Economics plays a key role in the feasibility of yaws eradication. Our model should be extended by explicitly optimizing control strategies, *i.e.,* the proper combination of TCT and TTT at the appropriate time intervals. The extensions need to take into the account that underdeveloped areas are more prone to transmission and are harder to screen for active infections.

CONCLUSIONS

Our paper is the first ODE compartment model specifically applied to yaws elimination. We investigated two strategies, the total community treatment (TCT) and the total targeted treatment (TTT). In agreement with previous models (*Dyson et al., 2017*; *Marks et al., 2015c*), we found that due to the high prevalence of latent infections, it is very hard to eliminates yaws by using TTT. Our model predicts that it would take about 15 years to reduce the prevalence thousandfold from the current levels. On the other hand, it would take only about 3.5 years if the whole community was treated once every six months. This is in a quantitative agreement with a recent detailed stochastic model (*Holmes et al., 2020*). We also note that due to the global stability of the disease-free equilibrium, and the fact that R_0 is significantly less than 1 even under TTT treatment, the initial levels of yaws in the population do not play a crucial role for the eradication.

In the light of above findings, we thus recommend using total community treatment as the primary yaws elimination strategy. This recommendation is further supported by the fact that (a) TCT provides additional benefits such as reduction in trachoma prevalence (*Solomon et al., 2015*), (b) the cost of TCT is not much larger that the cost of TTT (*Fitzpatrick, Asiedu & Jannin, 2014*), and (c) TTT requires active surveillance (*Fitzpatrick et al., 2018*), possibly further erasing the difference between the costs of these two approaches. As a note of caution, our model did not consider emergence of antibiotic resistant strains (*Mitjà et al., 2018*). It is a question whether a large scale application of TCT could eliminate yaws before the antibiotic resistance becomes a true obstacle.

APPENDIX A. MODEL ANALYSIS

The transmission dynamics described in Section yields the following system of ODEs

$$\frac{dS}{dt} = \Lambda + \tau_E E + \tau_{Y_1} Y_1 + \tau_{Y_2} Y_2 + \tau_{Y_3} Y_3 + \tau_{L_1} L_1 + \tau_{L_2} L_2 - \left(\beta \frac{Y_1 + Y_2}{N} + \mu \right) S \tag{8}$$

$$\frac{dE}{dt} = \beta \frac{Y_1 + Y_2}{N} S - (\sigma + \tau_E + \mu) E \tag{9}$$

$$\frac{dY_1}{dt} = \sigma E - \left(\lambda_1 + \tau_{Y_1} + \mu \right) Y_1 \tag{10}$$

$$\frac{dY_2}{dt} = p_{Y_1 Y_2} \lambda_1 Y_1 + \rho_1 L_1 + p_{L_2 Y_2} \rho_2 L_2 - (\lambda_2 + \tau_{Y_2} + \mu) Y_2 \tag{11}$$

$$\frac{dY_3}{dt} = p_{Y_2 Y_3} \lambda_2 Y_2 + p_{L_2 Y_3} \rho_2 L_2 - (\mu + \tau_{Y_3}) Y_3 \tag{12}$$

$$\frac{dL_1}{dt} = p_{Y_1 L_1} \lambda_1 Y_1 - (\rho_1 + \tau_{L_1} + \mu) L_1 \tag{13}$$

$$\frac{dL_2}{dt} = p_{Y_2 L_2} \lambda_2 Y_2 - (\rho_2 + \tau_{L_2} + \mu) L_2. \tag{14}$$

A.1 Positivity and boundedness of solutions

All parameters in the model are non-negative and it can be shown that the solutions of the system Eqs. (8)–(14) are non-negative, given non-negative initial values. Indeed, let $N = S + E + Y_1 + Y_2 + Y_3 + L_1 + L_2$. The biologically feasible region consists of $\mathcal{D} \subset \mathbb{R}^7_+$ such that $N \leq \frac{\Lambda}{\mu}$. Adding Eqs. (8)–(14) yields

$$\frac{dN}{dt} = \Lambda - \mu N \tag{15}$$

and thus

$$N(t) = \frac{\Lambda}{\mu} - \left(\frac{\Lambda}{\mu} - N(0) \right) e^{-\mu t}. \tag{16}$$

Consequently, the region $\mathcal{D}$ is positively invariant and the model is epidemiologically and mathematically well-posed (*Hethcote, 2000*). We also see that $\lim_{n \to \infty} N(t) = \frac{\Lambda}{\mu}$.

The system Eqs. (8)–(14) has two equilibria, the disease-free equilibrium and an endemic equilibrium as discussed below.

A.2 Disease-free equilibrium and the basic reproduction number

It follows from Eq. (17) general that the disease-free equilibrium, $\mathcal{E}^0 = (S^0, E^0, Y_1^0, Y_2^0, Y_3^0, L_1^0, L_2^0)$, is given by

$$\mathcal{E}^0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0 \right). \tag{17}$$

We calculate the basic reproduction number, R_0, using the next generation method (*van den Driessche & Watmough, 2002*). Let the column vector $I = (E, Y_1, Y_2, Y_3, L_1, L_2)^T$ represent the order of compartments with infection.

We define $\mathcal{F}$ and $\mathcal{V}$ as follows. The column vector $\mathcal{F} = (\beta \frac{Y_1 + Y_2}{N} S, 0, 0, 0, 0, 0)^T$ represents new infections that are introduced into each compartment. The column vector

$$\mathcal{V} = \begin{pmatrix} (\sigma + \tau_E + \mu)E \\ (\lambda_1 + \tau_{Y_1} + \mu)Y_1 - \sigma E \\ (\lambda_2 + \tau_{Y_2} + \mu)Y_2 - (p_{Y_1 Y_2}\lambda_1 Y_1 + \rho_1 L_1 + pL_2 Y_2 \rho_2 L_2) \\ (\mu + \tau_{Y_3})Y_3 - (p_{Y_2 Y_3}\lambda_2 Y_2 + pL_2 Y_3 \rho_2 L_2) \\ (\rho_1 + \tau_{L_1} + \mu)L_1 - p_{Y_1 L_1}\lambda_1 Y_1 \\ (\rho_2 + \tau_{L_2} + \mu)L_2 - p_{Y_2 L_2}\lambda_2 Y_2 \end{pmatrix} \tag{18}$$

represents difference between transfer out of the compartment and the transfer into that compartment that does not result from new infection.

Let F be the Jacobian matrix of $\mathcal{F}$ at the disease-free equilibrium, *i.e.*,

$$F = \begin{pmatrix} 0 & \beta & \beta & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}. \tag{19}$$

Let V be the Jacobian of $\mathcal{V}$ at the disease-free equilibrium, *i.e.*,

$$V = \begin{pmatrix} \sigma + \tau_E + \mu & 0 & 0 & 0 & 0 & 0 \\ -\sigma & \lambda_1 + \tau_{Y_1} + \mu & 0 & 0 & 0 & 0 \\ 0 & -p_{Y_1 Y_2}\lambda_1 & \lambda_2 + \tau_{Y_2} + \mu & 0 & -\rho_1 & -pL_2 Y_2 \rho_2 \\ 0 & 0 & -p_{Y_2 Y_3}\lambda_2 & \mu + \tau_{Y_3} & 0 & -pL_2 Y_3 \rho_2 \\ 0 & -p_{Y_1 L_1}\lambda_1 & 0 & 0 & \rho_1 + \tau_{L_1} + \mu & 0 \\ 0 & 0 & -p_{Y_2 L_2}\lambda_2 & 0 & 0 & \rho_2 + \tau_{L_2} + \mu \end{pmatrix} \tag{20}$$

Let v_I denote the sum of all total rates out of the compartment I, *i.e.*,

$$v_E = \sigma + \tau_E + \mu \tag{21}$$

$$v_{Y_1} = \lambda_1 + \tau_{Y_1} + \mu \tag{22}$$

$$v_{Y_2} = \lambda_2 + \tau_{Y_2} + \mu \tag{23}$$

$$v_{Y_3} = \mu + \tau_{Y_3} \tag{24}$$

$$v_{L_1} = \rho_1 + \tau_{L_1} + \mu \tag{25}$$

$$v_{L_2} = \rho_2 + \tau_{L_2} + \mu. \tag{26}$$

Using symbolic computation capabilities of MATLAB, we can calculate V^{-1}, FV^{-1} and eigenvalues of FV^{-1}. The code is available in the supplementary material. Since only the first row of F is non-trivial, the same is true about FV^{-1}. Thus, FV^{-1} has only one non-zero eigenvalue given by

$$R_0 = \left(\frac{\beta\sigma}{v_E v_{Y_1}}\right)\left(1 + \left(\frac{\lambda_1 v_{L_2}}{v_{L_1}}\right)\left(\frac{p_{Y_1 L_1}\rho_1 + p_{Y_1 Y_2}v_{L_1}}{v_{L_2}v_{Y_2} - p_{Y_2 L_2}\lambda_2 p_{L_2 Y_2}\rho_2}\right)\right). \tag{27}$$

Lemma 1 $\quad R_0 \geq 0$.
R_0 *is decreasing in* τ.
$\lim_{\tau\to\infty} R_0 = 0$. *Specifically, there is* τ *large enough such that* $R_0 < 1$.

Proof 1. Since $v_{Y_2} = \lambda_2 + \tau_{Y_2} + \mu > p_{Y_2 L_2}\lambda_2$ and $v_{L_2} = \rho 2 + \tau_{L_2} + \mu > p_{L_2 Y_2}\rho_2$, all terms in Eq. (27) are non-negative.
2. We get $\frac{\partial R_0}{\partial \tau_E} = -\frac{R_0}{(\sigma + \tau_E + \mu)} < 0$. Similarly, $\frac{\partial R_0}{\partial \tau_{Y_1}} = -\frac{R_0}{(\lambda_1 + \tau_{Y_1} + \mu)} < 0$. Also, since τ_{Y_2} appears only in the denominator of R_0, $\frac{\partial R_0}{\partial \tau_{Y_2}} < 0$. It also follows that $\frac{\partial R_0}{\partial \tau_{L_1}} < 0$ because

$\frac{\partial}{\partial \tau_{L_1}}\left(\frac{p_{Y_1 L_1}\rho_1 + p_{Y_1 Y_2}(\rho_1 + \tau_{L_1} + \mu)}{\rho_1 + \tau_{L_1} + \mu}\right) < 0$. Finally, $\frac{\partial R_0}{\partial \tau_{L_2}} < 0$ because

$\frac{\partial}{\partial \tau_{L_2}}\left(\frac{\rho_2 + \tau_{L_2} + \mu}{(\rho_2 + \tau_{L_2} + \mu)(\lambda_2 + \tau_{L_2} + \mu) - p_{Y_2 L_2}\lambda_2 p_{L_2 Y_2}\rho_2}\right) < 0$.

More generally, it can also be shown that $R0$ decreases directly with respect to τ. Since

$$\frac{dR_0}{d\tau} = \sum_I \frac{\partial R_0}{\partial \tau_I} \cdot \frac{\partial \tau_I}{\partial \tau} \tag{28}$$

and $\tau_I = c_I \tau$, we have, by previous calculations, $\frac{dR_0}{d\tau} < 0.3$. This follows directly from Eq. (27). $\square$

Theorem 1 *If* $R_0 < 1$, *then the disease-free equilibrium is globally asymptotically stable. If* $R_0 > 1$, *the disease-free equilibrium is unstable.*

Proof When $R_0 > 1$, the disease-free equilibrium is unstable by *van den Driessche & Watmough (2002)*.
When $R_0 < 1$, the global stability follows from *Castillo-Chavez et al. (2002)*. First, by Eq. (16), $S^0 = \frac{\Lambda}{\mu}$, corresponding to the disease-free equilibrium, is globally asymptotically stable for Eq. (15). Thus, the assumption (H1) in *Castillo-Chavez et al. (2002)* is satisfied. Second, let $\mathbf{I} = (E, Y_1, Y_2, Y_3, L_1, L_2)^T$ be the vector corresponding to infected compartments. The dynamics of $\mathbf{I}$ could thus be described by

$$\frac{d\mathbf{I}}{dt} = (\mathcal{F} - \mathcal{V})(S, \mathbf{I}) = (F - V)\mathbf{I} - \widehat{G}(S, \mathbf{I}) \tag{29}$$

where F and V are given by Eq. (19) matrix and Eq. (20) matrix and $\widehat{G}(S, \mathbf{I}) = \left(\beta(Y_1 + Y_2)(1 - \frac{S}{N}), 0, 0, 0, 0, 0\right)^T$. Note that $F - V$ is an M-matrix (all the off-diagonal entries are non-negative) and all entries of $\widehat{G}(S, \mathbf{I})$ are non-negative since $S \leq N$. Also, $F - V = D_\mathbf{I}(\mathcal{F} - \mathcal{V})(S^0, \mathbf{0})$. Thus, the assumption (H2) of *Castillo-Chavez et al. (2002)* is satisfied. Hence, the disease-free equilibrium $(S^0, \mathbf{0})$ is globally asymptotically stable when $R_0 < 1$. $\square$

Remark.

It follows from *Castillo-Chavez et al. (2002)* that there is $C > 0$ such that $\|\frac{d\mathbf{I}}{dt}\| \leq C(R_0)^t$. Consequently, the time needed the infections to drop below a predetermined level is proportional to $(\ln(R_0))^{-1}$.

A.3 Endemic equilibrium

When solving for equilibria of the dynamics, *i.e.,* the constant solutions of Eqs. (8) –(14), we set the left-hand sides to zero and solve the following system of algebraic equations.

$$0 = \Lambda + \tau_{Y_1} Y_1 + \tau_{Y_2} Y_2 + \tau_E E + \tau_{Y_3} Y_3 + \tau_{L_1} L_1 + \tau_{L_2} L_2 - \left(\beta \frac{Y_1 + Y_2}{N} + \mu \right) S \tag{30}$$

$$0 = \beta \frac{Y_1 + Y_2}{N} S - (\sigma + \tau_E + \mu) E \tag{31}$$

$$0 = \sigma E - \left(\lambda_1 + \tau_{Y_1} + \mu \right) Y_1 \tag{32}$$

$$0 = p_{Y_1 Y_2} \lambda_1 Y_1 + \rho_1 L_1 + p_{L_2 Y_2} \rho_2 L_2 - (\lambda_2 + \tau_{Y_2} + \mu) Y_2 \tag{33}$$

$$0 = p_{Y_2 Y_3} \lambda_2 Y_2 + p_{L_2 Y_3} \rho_2 L_2 - (\mu + \tau_{Y_3}) Y_3 \tag{34}$$

$$0 = p_{Y_1 L_1} \lambda_1 Y_1 - (\rho_1 + \tau_{L_1} + \mu) L_1 \tag{35}$$

$$0 = p_{Y_2 L_2} \lambda_2 Y_2 - \left(\rho_2 + \tau_{L_2} + \mu \right) L_2. \tag{36}$$

Let

$$N = S + E + Y_1 + Y_2 + Y_3 + L_1 + L_2. \tag{37}$$

By adding Eqs. (30) –(36) and solving for N, we get

$$N = \frac{\Lambda}{\mu}. \tag{38}$$

By Eq. (32),

$$Y_1 = k_{Y_1} E \tag{39}$$

where

$$k_{Y_1} = \frac{\sigma}{v_{Y_1}}.$$

By Eqs. (35) and (39),

$$0 = p_{Y_1 L_1} \lambda_1 \frac{\sigma}{\nu_{Y_1}} E - \nu_{L_1} L_1 \tag{40}$$

and thus

$$L_1 = k_{L_1} E \tag{41}$$

where

$$k_{L_1} = \frac{p_{Y_1 L_1} \lambda_1 \sigma}{\nu_{Y_1} \nu_{L_1}}.$$

By Eq. (36),

$$L_2 = \frac{p_{Y_2 L_2} \lambda_2 Y_2}{\nu_{L_2}}. \tag{42}$$

By Eqs. (33), (39), (41), and (42),

$$0 = (p_{Y_1 Y_2} \lambda_1 k_{Y_1} + \rho_1 k_{L_1}) E + p_{L_2 Y_2} \rho_2 \frac{p_{Y_2 L_2} \lambda_2 Y_2}{\nu L_2} - \nu Y_2 Y_2.$$

Solving for Y_2 yields

$$Y_2 = k_{Y_2} E \tag{43}$$

where

$$k_{Y_2} = \frac{(p_{Y_1 Y_2} \lambda_1 k_{Y_1} + \rho_1 k_{L_1}) \nu_{L_2}}{\nu_{Y_2} \nu_{L_2} - p_{L_2 Y_2} \rho_2 p_{Y_2 L_2} \lambda_2}$$

Note that, as in Lemma 1, $k_{Y_2} > 0$. By Eqs. (42) and (43),

$$L_2 = k_{L_2} E \tag{44}$$

where

$$k_{L_2} = \frac{p_{Y_2 L_2} \lambda_2 k_{Y_2}}{\nu_{L_2}}.$$

By Eqs. (34), (43), and (44),

$$Y_3 = k_{Y_3} E \tag{45}$$

where

$$k_{Y_3} = \frac{p_{Y_2 Y_3} \lambda_2 k_{Y_2} + p_{L_2 Y_3} \rho_2 k_{L_2}}{\nu_{Y_3}}. \tag{46}$$

By Eqs. (31), (43), and (39),

$$S = N \frac{\nu_E}{\beta (k_{Y_1} + k_{Y_2})}. \tag{47}$$

Lemma 2 $\beta (k_{Y_1} + k_{Y_2}) = \nu_E R_0.$

Proof

$$\beta\left(k_{Y_1}+k_{Y_2}\right)=\beta\frac{\sigma}{v_{Y_1}}+\beta\frac{\sigma\lambda_1 v_{L_2}(p_{Y_1 Y_2}v_{L_1}+p_{Y_1 L_1}\rho_1)}{v_{Y_1}v_{L_1}(v_{Y_2}v_{L_2}-p_{Y_2 L_2}\lambda_2 p_{L_2 Y_2}\rho_2)} \tag{48}$$

$$=\left(\frac{\beta\sigma}{v_{Y_1}}\right)\left(1+\left(\frac{\lambda_1 v_{L_2}(p_{Y_1 Y_2}v_{L_1}+p_{Y_1 L_1}\rho_1)}{v_{L_1}(v_{L_2}v_{Y_2}-p_{Y_2 L_2}\lambda_2 p_{L_2 Y_2}\rho_2)}\right)\right) \tag{49}$$

$$=v_E\left(\frac{\beta\sigma}{v_E v_{Y_1}}\right)\left(1+\left(\frac{\lambda_1 v_{L_2}}{v_{L_1}}\right)\left(\frac{p_{Y_1 Y_2}v_{L_1}+p_{Y_1 L_1}\rho_1}{v_{L_2}v_{Y_2}-p_{Y_2 L_2}\lambda_2 p_{L_2 Y_2}\rho_2}\right)\right) \tag{50}$$

$$=v_E R_0.\ \square \tag{51}$$

Thus, by Lemma 2, Eqs. (47), (37), (39), (43), (45), (41), and (44), we have

$$N=\frac{N}{R_0}+(1+k_{Y_1}+k_{Y_2}+k_{Y_3}+k_{L_1}+k_{L_2})E.$$

The results of this section can be summarized in the following theorem.

Theorem 2 *The endemic equilibrium* $\mathcal{E}^*=(S^*,E^*,Y_1^*,Y_2^*,Y_3^*,L_1^*,L_2^*)$ *exists and is unique if* $R_0>1$. *It is given by*

$$S^*=\frac{\Lambda}{\mu R_0}, \tag{52}$$

$$E^*=\left(\frac{\Lambda}{\mu}\right)\left(1-\frac{1}{R_0}\right)\left(\frac{1}{1+k_{Y_1}+k_{Y_2}+k_{Y_3}+k_{L_1}+k_{L_2}}\right) \tag{53}$$

$$I^*=k_I E^*,\ \text{for}\ I\in\{Y_1,Y_2,Y_3,L_1,L_2\}, \tag{54}$$

where

$$k_{Y_1}=\frac{\sigma}{v_{Y_1}} \tag{55}$$

$$k_{L_1}=\frac{p_{Y_1 L_1}\lambda_1\sigma}{v_{Y_1}v_{L_1}} \tag{56}$$

$$k_{Y_2}=\frac{(p_{Y_1 Y_2}\lambda_1 k_{Y_1}+\rho_1 k_{L_1})v_{L_2}}{v_{Y_2}v_{L_2}-p_{L_2 Y_2}\rho_2 p_{Y_2 L_2}\lambda_2} \tag{57}$$

$$k_{L_2}=\frac{p_{Y_2 L_2}\lambda_2 k_{Y_2}}{v_{L_2}} \tag{58}$$

$$k_{Y_3}=\frac{p_{Y_2 Y_3}\lambda_2 k_{Y_2}+p_{L_2 Y_3}\rho_2 k_{L_2}}{v_{Y_3}}. \tag{59}$$

Kimball et al. (2022), *PeerJ*, DOI 10.7717/peerj.13018

17/23

APPENDIX B. MODEL CALIBRATION

With the exception of the transmission rate β, the model parameters listed in Table 1 can be found directly in the literature.

The birth rate in Papua New Guinea is 27.2 births per thousand per year (*United Nations, 2019*). The life expectancy of 65 years (*World Bank, 2019*). Should the model be used for other countries, we suggest to change these values appropriately since the uncertainty analysis suggest some sensitivity to these values as shown in Fig. 6.

The incubation period, σ^{-1}, after exposure to yaws lasts on average 21 days with a range from 9 to 90 days (*Perine et al., 1984*; *WHO, 2018a*). Primary lesions last for 3 to 6 months (*Perine et al., 1984*). We will assume $\lambda_1^{-1} = 3$ months since this allowed the best fit for our model; larger λ causes larger discrepancies between active and latent yaws cases. To estimate the length of the latent period after primary yaws, we note that secondary yaws occurs one to two months after the primary lesion heals (*Marks et al., 2015a*). We thus set $\rho_1^{-1} = 1.5$ months. All secondary yaws lesions subside in weeks to months (*Mitjà, Asiedu & Mabey, 2013*) and we will thus assume $\lambda_2^{-1} = 3$ months to be on par with the primary yaws. We note that we are primarily interested in the duration of the infectiousness. The estimated total duration of infectiousness for an untreated yaws patient, including relapses, is of the order of 12 –18 months (*Perine et al., 1984*). With $\lambda_1^{-1} = \lambda_2^{-1} = 3$ months, this would mean primary yaws, secondary yaws and two to four relapses into secondary yaws.

The second stage of latency ranges from zero to five years, and even up to ten years (*Perine et al., 1984*; *Marks et al., 2015b*). Thus, we assume $\rho_2^{-1} = 30$ months.

Up to 10% of individuals develop tertiary yaws after five to ten years of untreated infection, but the condition is now extremely rare (*Mitjà, Asiedu & Mabey, 2013*). We thus set $p_{Y_2 Y_3} = 0.0001$ and $p_{L_2 Y_2} = 0.9999$. With these values, our model estimates the prevalence of the tertiary yaws in the endemic equilibrium (of untreated population) under 0.1% of the total population and slightly under 5% of the number of secondary yaws cases.

About 9–15% of primary yaws cases progress into secondary yaws with the primary lesion still present (*Mitjà, Asiedu & Mabey, 2013*; *Marks et al., 2015b*). We thus assumed $p_{Y_1 Y_2} = 0.12$ for the probability that individual progresses directly from the primary yaws to secondary yaws without any noticeable latent period.

To estimate the value of the transmission rate β, we fitted our model to the baseline data from Lihir Island (*Mitjà et al., 2015b*). The study indicates that, before the mass treatment trial, 2.4% of the population had active yaws and 18.9% were in the latent stage. The endemic equilibrium of our model given by Theorem 2 can be expressed as a function of β. We used MATLAB's optimization toolbox to numerically find the value of β so that the endemic equilibrium distribution of $S+E$, $Y_1 + Y_2 + Y_3$, and $L_1 + L_2$ fits best the empirical values 0.797, 0.024, and 0.189. We got $\beta = 0.016581$. With this value, the data from Lihir Island were recovered with an error less than 0.005; most of the error was caused by underestimating active yaws cases.

We note that we ran a number of different scenarios and by allowing a non-zero probability for the individuals with primary or secondary yaws infections to completely recover from the infections and become susceptible, we were able to match data from Lihir

Island with the error less than 10^{-6} (and very similar model outcomes, in particular still 3.5 years to elimination by using TCT and about 20 years to elimination by using TTT).

APPENDIX C. GLOBAL UNCERTAINTY AND SENSITIVITY ANALYSIS

We performed the global uncertainty and sensitivity analysis by the partial rank correlation coefficients (*Marino et al., 2008*). For every parameter with the exception the treatment rate τ_I (that does not have any influence at the base prior the beginning of the treatment) and the unknown transmission rate β, we randomly assigned a value from the uniform distribution within the range specified in Table 1. We then tried to fit the transmission rate β to the baseline data while keeping the treatment rate 0. We used the Matlab optimization toolbox as described in the previous section. We then used 1000 sets of the values that could fit to baseline data from Lihir Island (*Mitjà et al., 2015b*) within an error of 0.005 or less. The actual distribution of the parameter values used in the uncertainty analysis is shown in Fig. 8.

For each of these parameter values, we calculated the basic reproduction number, and the time needed for yaws elimination under the TCT and TTT protocols. The resulting histograms are shown in the main body of the manuscript.

ADDITIONAL INFORMATION AND DECLARATIONS

Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Presley Kimball, Jacob Levenson, Amy Moore, Jan Rychtar and Dewey Taylor conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
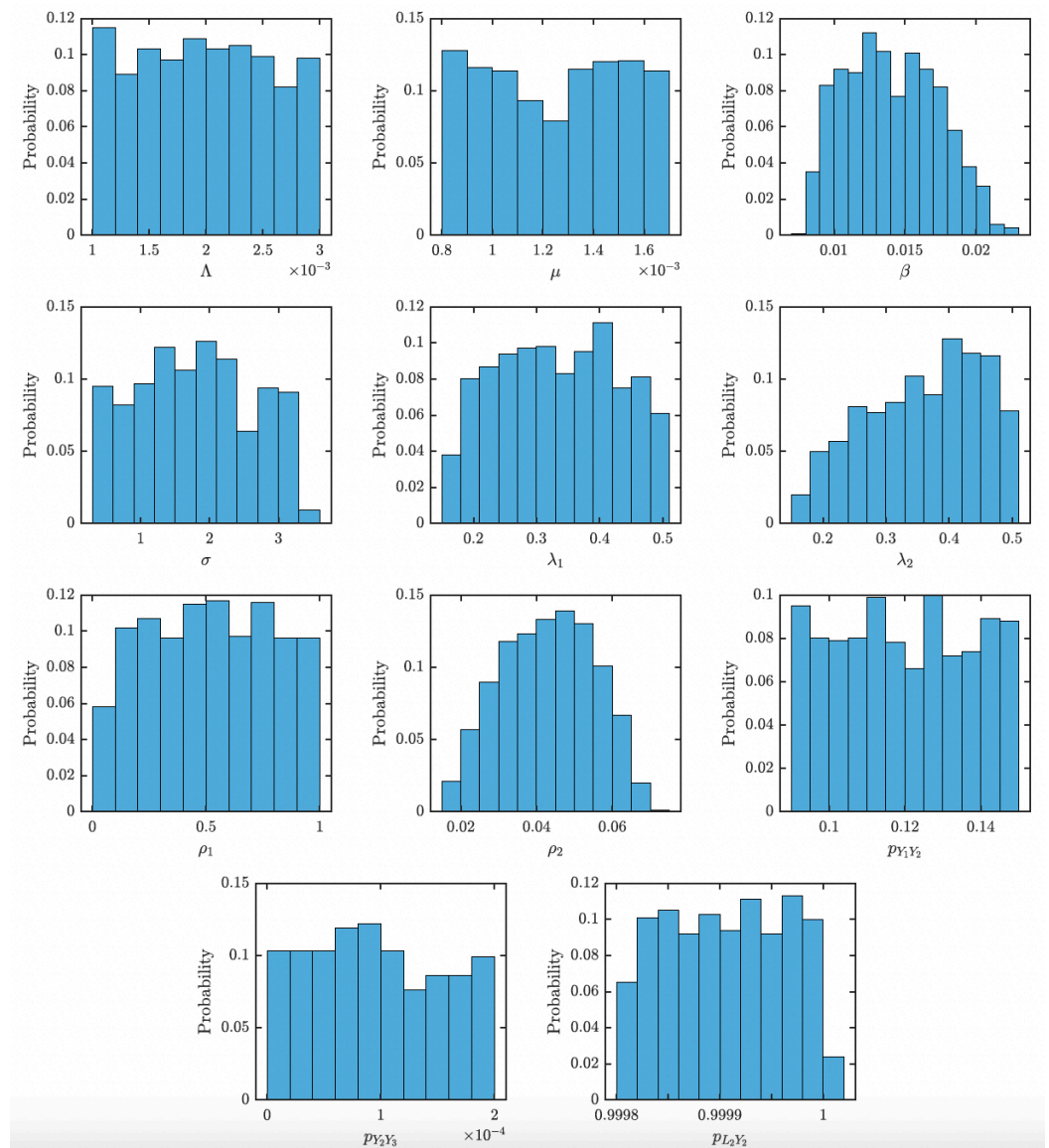
Figure 8 Distribution of the parameter values used in the uncertainty and sensitivity analysis. The parameters were chosen with ranges as specified in Table 1 such that the model fits the data from Lihir Island (*Mitjà et al., 2015b*).

Full-size ⤢ DOI: 10.7717/peerj.13018/fig-8

Data Availability

The following information was supplied regarding data availability:

The MATLAB code for running the numerical ODE solutions is available in the Supplemental Files. The data used in this study is available in Table 1.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.13018#supplemental-information.

REFERENCES

Anderson RM, May RM. 1992. *Infectious diseases of humans: dynamics and control.* Oxford University Press.

Asiedu K, Amouzou B, Dhariwal A, Karam M, Lobo D, Patnaik S, Meheus A. 2008. Yaws eradication: past efforts and future perspectives. *Bulletin of the World Health Organization* **86**:499–499A DOI 10.2471/BLT.08.055608.

Castillo-Chavez C, Feng Z, Huang W , et al. 2002. On the computation of R_0 and its role in global stability. *IMA Volumes in Mathematics and Its Applications* **125**:229–250 DOI 10.1007/978-1-4757-3667-0_13.

Dyson L, Marks M, Crook OM, Sokana O, Solomon AW, Bishop A, Mabey DC, Hollingsworth TD. 2017. Targeted treatment of yaws with household contact tracing: how much do we miss? *American Journal of Epidemiology* **187(4)**:837–844.

Dyson L, Mooring EQ, Holmes A, Tildesley MJ, Marks M. 2019. Insights from quantitative and mathematical modelling on the proposed 2030 goals for Yaws. *Gates Open Research* **3**:1576 DOI 10.12688/gatesopenres.13078.1.

Fitzpatrick C, Asiedu K, Jannin J. 2014. Where the road ends, yaws begins? The cost-effectiveness of eradication versus more roads. *PLOS Neglegted Tropical Diseases* **8(9)**:e3165 DOI 10.1371/journal.pntd.0003165.

Fitzpatrick C, Asiedu K, Solomon AW, Mitjà O, Marks M, Van der Stuyft P, Meheus F. 2018. Prioritizing surveillance activities for certification of yaws eradication based on a review and model of historical case reporting. *PLOS Neglected Tropical Diseases* **12(12)**:e0006953 DOI 10.1371/journal.pntd.0006953.

Gart JJ, De Vries J. 1966. The mathematical analysis of concurrent epidemics of yaws and chickenpox. *Epidemiology & Infection* **64(4)**:431–439 DOI 10.1017/S0022172400040730.

Greene CA, Thirumalai K, Kearney KA, Delgado JM, Schwanghart W, Wolfenbarger NS, Thyng KM, Gwyther DE, Gardner AS, Blankenship DD. 2019. The climate data toolbox for MATLAB. *Geochemistry, Geophysics, Geosystems* **20**:3774–3781 DOI 10.1029/2019gc008392.

Hethcote HW. 2000. The mathematics of infectious diseases. *SIAM Review* **42(4)**:599–653 DOI 10.1137/S0036144500371907.

Holmes A, Tildesley MJ, Solomon AW, Mabey DC, Sokana O, Marks M, Dyson L. 2020. Modeling treatment strategies to inform yaws eradication. *Emerging Infectious Diseases* **26(11)**:2685–2693 DOI 10.3201/eid2611.191491.

Kazadi WM, Asiedu KB, Agana N, Mitj O. 2014. Epidemiology of yaws: an update. *Clinical Epidemiology* **6**:119–128 DOI 10.2147/CLEP.S44553.

LaSalle JP. 1976. *The stability of dynamical systems.* Philadelphia: SIAM.

Lucas TC, Pollington TM, Davis EL, Hollingsworth TD. 2020. Responsible modelling: unit testing for infectious disease epidemiology. *Epidemics* **33**:100425.

Marino S, Hogue IB, Ray CJ, Kirschner DE. 2008. A methodology for performing global uncertainty and sensitivity analysis in systems biology. *Journal of Theoretical Biology* **254(1)**:178–196 DOI 10.1016/j.jtbi.2008.04.011.

Marks M, Lebari D, Solomon AW, Higgins SP. 2015a. Yaws. *British Medical Bulletin* **113**:91–100 DOI 10.1093/bmb/ldu037.

Marks M, Lebari D, Solomon AW, Higgins SP. 2015b. Yaws. *International Journal of STD & AIDS* **26**(10):696–703 DOI 10.1177/0956462414549036.

Marks M, Mitjà O, Fitzpatrick C, Asiedu K, Solomon AW, Mabey DC, Funk S. 2017. Mathematical modeling of programmatic requirements for yaws eradication. *Emerging Infectious Diseases* **23**(1):22–28 DOI 10.3201/eid2301.160487.

Marks M, Solomon AW, Mabey DC. 2014. Endemic treponemal diseases. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **108**(10):601–607 DOI 10.1093/trstmh/tru128.

Marks M, Vahi V, Sokana O, Puiahi E, Pavluck A, Zhang Z, Dalipanda T, Bottomley C, Mabey DC, Solomon AW. 2015c. Mapping the epidemiology of yaws in the Solomon Islands: a cluster randomized survey. *The American Journal of Tropical Medicine and Hygiene* **92**(1):129–133 DOI 10.4269/ajtmh.14-0438.

Mitjà O, Asiedu K, Mabey D. 2013. Yaws. *The Lancet* **381**(9868):763–773 DOI 10.1016/S0140-6736(12)62130-8.

Mitjà O, Godornes C, Houinei W, Kapa A, Paru R, Abel H, González-Beiras C, Bieb SV, Wangi J, Barry AE , et al. 2018. Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study. *The Lancet* **391**(10130):1599–1607 DOI 10.1016/S0140-6736(18)30204-6.

Mitjà O, Hays R, Ipai A, Penias M, Paru R, Fagaho D, De Lazzari E, Bassat Q. 2012. Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial. *The Lancet* **379**(9813):342–347 DOI 10.1016/S0140-6736(11)61624-3.

Mitjà OD, Hays RM, Ipai AH, Penias MH, Paru RB, Fagaho DB, de Lazzari EM, Bassat QP. 2012. Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial. *The Lancet* **379**(9813):342–347.

Mitjà O, Houinei W, Moses P, Kapa A, Paru R, Hays R, Lukehart S, Godornes C, Bieb SV, Grice T, Siba P, Mabey D, Sanz S, Alonso PL, Asiedu K, Bassat Q. 2015b. Mass treatment with single-dose azithromycin for yaws. *The New England Journal of Medicine* **372**(8):703–710 DOI 10.1056/NEJMoa1408586.

Mooring EQ, Marks M, Mitjà O, Castro M, Lipsitch M, Murray MB. 2019. Programmatic goals and spatial epidemiology influence the merit of targeted versus of population-wide interventions for yaws eradication. *BioRxiv*. 640326 DOI 10.1101/640326.

Muench H. 2013. *Catalytic models in epidemiology.* Cambridge: Harvard University Press.

Mushayabasa S, Bhunu C, Webb C, Dhlamini M. 2012. A mathematical model for assessing the impact of poverty on yaws eradication. *Applied Mathematical Modelling* **36**(4):1653–1667 DOI 10.1016/j.apm.2011.09.022.

Perine PL, Hopkins DR, Niemel PL, St John R, Causse G, Antal G. 1984. *Handbook of endemic treponematoses: yaws, endemic syphilis and pinta.* Geneva: World Health Organization.

Solomon AW, Marks M, Martin DL, Mikhailov A, Flueckiger RM, Mitjà O., Asiedu K, Jannin J, Engels D, Mabey DC. 2015. Trachoma and yaws: common ground? *PLOS Neglected Tropical Diseases* **9(12)**:e0004071 DOI 10.1371/journal.pntd.0004071.

United Nations. 2019. Crude birth rate data. *Available at https://population.un.org/wpp/ Download/Standard/Fertility/* (accessed on 02 July 2021).

Van den Driessche P, Watmough J. 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences* **180**:29–48 DOI 10.1016/S0025-5564(02)00108-6.

WHO. 2012. Eradication of yaws—the Morges strategy. *Weekly Epidemiological Record* **87(20)**:189–200.

WHO. 2018a. *Eradication of Yaws: a guide for programme managers.* Geneva: World Health Organization. *Available at https://apps.who.int/iris/bitstream/handle/10665/ 259902/9789241512695-eng.pdf* .

WHO. 2018b. Global Health Observatory data repository, Endemic treponematoses. Geneva: World Health Organization. *Available at https://apps.who.int/gho/data/node. main.NTDTREP?lang=en* (accessed on 14 June 2021).

WHO. 2020. Endemic treponematoses: Status of yaws endemicity 2018. World Health Organization. *Available at https://apps.who.int/neglected.diseases/ntddata/ treponematoses/treponematoses.html* (accessed on 28 June 2021).

World Bank. 2019. Life expectancy at birth, total (years). *Available at https://data. worldbank.org/indicator/SP.DYN.LE00.IN?view=chart* (accessed on 30 June 2021).

Yang C, Wang X, Gao D, Wang J. 2017. Impact of awareness programs on cholera dynamics: two modeling approaches. *Bulletin of Mathematical Biology* **79(9)**:2109–2131 DOI 10.1007/s11538-017-0322-1.