Article Summary Line: A successful yaws eradication strategy is likely to require multiple rounds of whole community treatment, with targeted treatment being less effective. However, logistical implications should be taken into account. Further data are also needed to expand the model to different settings.

Running Title: Modelling Strategies to Inform Yaws Eradication

Keywords: Yaws, Mass Drug Administration, Treponema pallidum pertenue, Contact Tracing

Modelling Treatment Strategies to Inform Yaws Eradication

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Abstract - 148 words

Yaws is a neglected tropical disease targeted for eradication by 2030. To achieve eradication it is crucial to find and treat asymptomatic infections as well as clinical cases. The proposed plan, the Morges strategy, involves rounds of Total Community Treatment (TCT, treating the whole population) and Total Targeted Treatment (TTT, treating clinical cases and their contacts). However, modelling and empirical work suggests asymptomatic infections are often not found in the same households as clinical cases, reducing the utility of household-based contact tracing for a TTT strategy. We use a model fitted to data from the Solomon Islands to predict the likelihood of elimination of transmission (EOT) under different intervention schemes, and levels of systematic non-treatment present in the intervention. Our results indicate that it is more effective

to implement additional treatment rounds through TCT than to carry out additional rounds of treatment of high risk individuals through TTT.

Background/ Introduction

Yaws is an infectious disease found in South America, Asia, Africa and Oceania. It is caused by *Treponema pallidum* subspecies *pertenue (1)*, an organism morphologically identical to *T. pallidum pallidum*, which causes syphilis. Yaws can present with skin lesions, involvement of the bones and joints and eventually irreversible disfigurement. It is spread by direct contact between a susceptible individual and lesions of infectious individuals. It particularly affects 2–15-year-olds.

In the 1950s, the World Health Organization (WHO) and UNICEF led efforts to eradicate yaws through mass treatment with benzathine benzylpenicillin *(2)*, reducing the number of cases worldwide by about 95% *(3)*. Yaws then fell off the public health agenda, and has since resurged in several countries. Efforts were renewed when in 2012, a study *(4)* showed that treatment with a single oral dose of azithromycin was non-inferior to benzathine benzylpenicillin, while avoiding the need for cold chains, injection equipment and personnel trained to use it. This reduced the logistic barriers to mass drug administration, potentially making eradication more feasible.

In 2012, in response to this finding, member states of WHO committed to eradicate yaws by 2020 *(5)*, though more recently 2030 has been suggested as a more realistic target *(6)*. The primary reason for this change was the high number of countries still endemic, and the even higher number of previously endemic countries whose current endemicity status remains unknown at the time of writing. The current eradication strategy, known as the Morges strategy,

consists of treatment with single-dose oral azithromycin in two modes of community-based intervention: total community treatment (TCT), and total targeted treatment (TTT) *(7)*. TCT attempts to treat everyone in a given community (village or town) regardless of the number of active clinical cases, while TTT treats active clinical cases and their contacts, where contacts are those in the same household or school, or playmates of affected individuals *(8)*. In response to evidence from pilot studies that a single round of TCT is not sufficient to interrupt transmission, WHO has proposed revising the strategy *(9)*. The revised strategy suggests that in most circumstances 2-3 rounds of TCT are likely to be required, followed by TTT performed at 6-12-monthly intervals *(10)*. TCT is designed for situations in which a large proportion of the population is infected, while TTT is intended to treat a small number of remaining cases once elimination of transmission (EOT) appears close.

T. p. pertenue infection can be divided into active yaws and latent yaws. Active yaws can then be split further into primary, secondary and tertiary yaws *(11)*. After an incubation period averaging 21 (range 9–90) days, primary yaws initially presents as a papule at the site of inoculation. The papule then enlarges, lasting for 3–6 months. Early secondary yaws lesions may appear near the initial lesion and persist for more than 6 months. These lesions heal spontaneously, leading to a non-infectious latent period which could last the remaining lifetime of the individual *(12)*. However, the state of latency can end at any time by the reappearance of infectious lesions. Tertiary yaws lesions are now rarely seen *(13)*, but when present they appear years after primary yaws, are often destructive, but are non-infectious.

A considerable challenge for eradicating yaws is the existence of asymptomatic individuals, who together harbour a large reservoir of infection. There may be 6–10 cases of latent yaws for each active case *(14)*. If not treating the whole community, it is essential to

successfully treat both clinical cases and latently-infected individuals. The assumption conceptually underlying TTT is that asymptomatic individuals are likely to be close contacts of current clinical cases.

The difficulty of diagnosing latent yaws in adults also represents a challenge for researchers attempting to understand the dynamics of transmission. Serological testing cannot distinguish between syphilis and yaws infections, meaning it is usually only children below the age of 15 years that have serological tests performed *(3)*.

In this paper, we extend previous yaws modelling work by incorporating both household structure and simulations of eradication strategies into the model. We evaluate the Morges strategy, and variants of it, for their suitability in meeting the WHO goal of yaws eradication. We investigate the likely impact of different assumptions regarding coverage during rounds of TCT on the success of a strategy, and the impact systematic non-adherence could have on its effectiveness. Finally, we consider whether regular surveillance could be an effective component of a programme seeking to meet the WHO goal.

Methods

We adapted the Markov model developed by Dyson *et al. (15)*. The model consists of houses, each containing a number of inhabitants. Individuals may be classified as susceptible (S); infected and infectious (I); or asymptomatically infected (but not infectious) (A). Within each household, susceptible individuals may become infected by other individuals from within their household or from other households. From the infectious state, a person can either recover and re-enter the susceptible state, or they can develop a latent infection, entering the asymptomatic state. From the asymptomatic state, individuals can either recover, entering the susceptible state, or the infectious lesions can recur, causing them to re-enter the infectious state. These transitions

are summarised in Figure 1 and Table 1. In Dyson *et al.* this model was fitted at steady state to data from the Solomon Islands *(14)*, using a presumed constant rate of between-household infection. Here we extend the model to include a dynamic rate of between-household infection, which is assumed to be proportional to the total prevalence of infectious individuals in the population at a given time (see supplementary material). We take parameter values from posterior distributions with maximum posterior value (MPV) as given in Table 2, drawn from expert opinion and previous model-fitting to Solomon Islands data *(15)*.

We consider a population of 5000 households, with sizes distributed according to empirical data from the Solomon Islands (Figure 2), representing a population of approximately 20,000 individuals. Each treatment scheme consists of a number of rounds of TCT, followed by a number of rounds of TTT. During TTT, we define a contact to be anyone in the same household as an infectious individual. We assume an optimistic coverage of 100% of active cases and their contacts given treatment during rounds of TTT (a conservative assumption under the hypothesis that TTT is not an effective strategy), TCT coverage of 80% *(3)*, and azithromycin efficacy of 95% *(11)*. We consider up to 10 rounds of TCT, and up to 10 rounds of TTT. Treatment rounds are scheduled (following WHO guidelines, *(9)*) at 6-month intervals, with all rounds of TCT being performed before any TTT. Using the Gillespie Algorithm *(18)*, simulations were run to steady state before starting treatment, and then run for a further 150 months to simulate the time remaining to meet the 2030 deadline. We simulated each scenario 2240 times, and took the mean of the results.

We then considered the impact of population size on the probability of campaign success: whether a specific treatment campaign would be more successful in areas with greater or fewer

people. We considered population sizes ranging from 100–50,000 households, using two rounds of TCT followed by two rounds of TTT.

While coverage is likely to be important in determining how successful a mass treatment campaign would be, recent modelling work has shown that the quality of coverage is also critical *(19)*. Specifically, whether the same people receive treatment in each round has a significant impact on the likelihood of EOT. Treatment campaigns that repeatedly miss the same individuals are said to have a high level of systematic non-treatment. Models of treatment campaigns usually assume that a random selection of people receive treatment in each round. However, this likely overestimates the effectiveness of a TCT round. We therefore developed a framework (as laid out in *(17)*) for mass-drug administration in which we could control individual-level treatment correlation between rounds: if an individual is treated in one round, how likely are they to be treated in a subsequent round? For the sake of illustration, consider the special cases in which the correlation coefficient (ρ) is 0 or 1:

1) $\rho = 0$: Treatment status in one treatment round is not associated with the probability of treatment in subsequent treatment rounds, which are independent events.
2) $\rho = 1$: In each treatment round, the same people are treated, and the same people are not treated.

We investigated the impact of assigning different values to ρ on the modeled effectiveness of intervention. For $\rho > 0$, we considered treatment status only at household level. So for $\rho = 1$, the same households (and everyone in those households) would be treated every round, while for $0 < \rho < 1$, each person in the same household has the same probability of receiving treatment, which is different to the individuals in other households.

We also considered the use of more frequent, lower intensity treatment. This could be delivered by, for example, a volunteer offering azithromycin to people who the volunteer thinks have yaws. We investigated whether this would reduce the required number of rounds of TTT, using an estimated coverage of 5% of infectious individuals and their household contacts every month, in addition to six-monthly rounds of TCT/ TTT (up to 10 rounds of TCT, and up to 10 rounds of TTT).

Results

We first consider the dynamics under three different treatment strategies, chosen as strategies that have been previously discussed by yaws experts. These strategies, and the probability of EOT calculated for each, are summarised in Table 3. While an extra round of treatment of either kind is beneficial, an extra round of TCT outperforms an extra round of TTT (Figure 3). In Figure 4, we plot EOT probability for up to 8 additional rounds of TCT or TTT, from a base intervention of 2 rounds of TCT, and 2 rounds of TTT. Increasing the number of rounds of TCT increases the probability of EOT more rapidly than including additional rounds of TTT. In fact, it would take 4–5 additional TTT rounds to achieve the same effect as 1 additional round of TCT.

We extend this further by comparing the effectiveness of 120 different treatment strategies, plus a control strategy in which no antibiotic treatment is provided, in a population of 5000 households. Figure 5 shows that any strategy involving fewer than three rounds of TCT is unlikely to be effective in meeting the 2030 WHO goal for yaws. When we assume a TCT coverage of 90%, we still find that at least three rounds should be considered (see supplementary material). It is notable that TTT does not directly precipitate EOT by treating all cases. Instead, multiple rounds of TTT serve to keep infection prevalence low, so that in a small population

infection eventually disappears stochastically. Effective population size therefore influences the probability of EOT: infection in a smaller population is more susceptible to stochasticity. (Effective population size refers to the population that interacts, so that an isolated small village will have a small population size, whereas multiple villages sharing schools with substantial between-village intermingling have a larger effective size than the individual villages.)

Figure 6 displays EOT probability with changing effective population size using a fixed strategy of two rounds of TCT followed by two rounds of TTT. It shows that as the effective population size increases, the probability of EOT decreases, with the probability approaching zero at around 10,000 households.

As coverage becomes more systematic (so that treatments tend to be given repeatedly to the same individuals), the number of cases increases and the probability of EOT decreases significantly (Figure 7). While random coverage resulted in a probability of EOT of 15%, this fell to just 2% with fully systematic coverage. Here each scheme consists of two rounds of TCT followed by two rounds of TTT. As the correlation between rounds of treatment increases, the probability of EOT of transmission decreases substantially, particularly for lower correlations as we start moving away from random to more systematic treatment (Figure 8).

Since TTT primarily acts by keeping the infectious population at a sufficiently low level that stochasticity eventually leads to elimination, we hypothesise that a lower level of more frequent treatment may act as a potential replacement for TTT. We consider the strategies investigated in Table 3, this time incorporating a monthly volunteer treatment with a coverage of 5%. The results can be seen in Table 4. Under a strategy of 2 rounds of TCT followed by 2 rounds of TTT, the probability of elimination increased from 15% to 53% when we incorporated this low-level regular treatment, an increase of 38 percentage points. Similar increases were seen

for the other two strategies. Also of note is the very small increase in probability of elimination achieved when performing a third round of TTT. This suggests that TTT has very limited effect with this volunteer treatment. Extending this to the full range of strategies previously considered, we observe that additional rounds of TTT have a reduced impact compared to interventions without background treatment (Figure 9). Further reductions in impact are observed when more rounds of TCT are undertaken (Figure 10 and Figure 11). When performing two rounds of TCT, increasing volunteer coverage leads to increased probabilities of EOT unless greater than 5 rounds of TTT are undertaken. When using four rounds of TCT, increasing the number of rounds of TTT performed results in very little increase in the probability of EOT, regardless of the number of rounds of TTT performed.

Discussion

We used a stochastic household-level model of yaws transmission to consider the likely effectiveness of various treatment strategies in the eradication of yaws. As expected, we found that more rounds of TCT and TTT led to higher probability of EOT. However, in our model, EOT was not directly achieved through treatment itself. Rather, TTT served to keep the infection prevalence low, so that yaws eventually disappeared through chance events. That is, TCT acts to reduce the prevalence of infection to a low level, which is then maintained by TTT until elimination occurs. As such, TCT should be considered the principal driving force for EOT. To efficiently reach elimination, according to our model, multiple rounds of TCT need to be implemented, and TTT should not be considered an effective method for reducing prevalence of infection. Indeed, it would take up to 5 rounds of TTT to achieve the same impact as one additional round of TCT. The original Morges strategy, in which only a single round of TCT is advised, is unlikely to enable us to meet the WHO 2030 goal. However, the revised strategy, in

which 2-3 rounds of TCT are advised, is more likely to meet this goal if linked to appropriate ongoing surveillance following TCT. However, further rounds of TCT will likely be required if 90% coverage is not attained. This conclusion is consistent with the conclusions of previous modelling work (using the same data) *(15,16)*, and recent empirical findings from Papua New Guinea *(20)*.

Since the effect of chance events was found to be a critical factor in determining success, we next considered the impact of population size on the effectiveness of an eradication campaign. We found that, for a given treatment scheme, the size of the population had a considerable influence on the probability of EOT: a given strategy is more likely to be successful for smaller than larger populations. The corollary of this finding is that the intervention strategy used in any context should be influenced by the size of the population being treated. This conclusion should be considered in parallel with the one outlined above. For stochasticity to successfully drive EOT, the prevalence of infection after completion of the rounds of TCT needs to be sufficiently small. The larger the population, the greater will be the number of rounds of TCT required to reduce the infection prevalence to the appropriate threshold (Figure 6).

While the impact of varying treatment coverage levels is widely appreciated, it is less well understood that the quality of the coverage is also of critical importance. The effect of rounds of TCT will be modified by the coverage attained and the level of systematic non-treatment. When we assume treatment with some level of systematic non-treatment, we find that treatment is substantially less effective, as under these schemes the same people are treated many times, while others are never treated. Since it is likely that any treatment campaign will suffer from some level of systematic non-treatment (in terms of correlation of treatment status between

different treatment rounds) it is essential that programmes take this into account. As such, it is beneficial when undertaking a treatment campaign to maximise not just the coverage of the campaign, but also the quality of that coverage. In short, if we always treat the same people and miss the same people a perpetual reservoir of infection may be maintained, undercutting efforts to interrupt transmission.

Since TTT primarily acts by keeping the infectious population at a sufficiently low level that stochasticity eventually leads to elimination, we hypothesised that a lower level of more frequent treatment may act as a potential replacement for TTT. This could be accomplished via volunteers handing out azithromycin to infected individuals and their household contacts on a monthly (or more frequent) basis. We found this to be very effective (theoretically) in increasing the probability of EOT. Once the prevalence of infection was at a sufficiently low level, 5% coverage with ongoing treatment was sufficient to maintain that prevalence until infection was eliminated due to chance. After at least four rounds of TCT, this was true regardless of whether any TTT was performed, perhaps indicating that TTT might be redundant. This further supports the concept that additional rounds of TCT could be prioritised over TTT, particularly if low-level background antibiotic treatment could be subsequently deployed. Strategies to support ongoing community surveillance deserve further consideration and could link with ongoing regular surveillance for other NTDs *(21,22)*. This is supported by a successful elimination campaign in India, in which cash incentives were offered to people who identified confirmed cases.

The current study has a number of limitations which may be addressed in future work. First, we defined a TTT "contact" as an individual in the same household as an infectious individual. Extending this to include multiple nearby households, villages or schools may impact

model results. Treating school contacts could be particularly relevant because most new cases of yaws are found in children, which could suggest schools are important settings for transmission.

Second, the current model includes both adults and children in a single class, but given age-stratified data, we could model treatment effectiveness separately for adults and children. That might include, for example, age-dependent treatment strategies, such as only treating children, which has been empirically tested for the use of azithromycin in trachoma elimination *(23)*. Higher coverage could be more reasonably achieved in younger age groups by yaws programmes if the aforementioned extension to the "contact" definition was incorporated.

Spatial heterogeneities may play a role in affecting the transmission of yaws. In parts of the Solomon Islands, people generally live near the coast, and rarely walk through the centre of the island. Since an implementation unit is likely to consist of several villages, the population's spatial distribution and movement patterns may limit the spread of infection. Including this in our analyses could potentially more closely reflect real-world transmission dynamics.

Re-introduction of yaws from outside the implementation site, while not directly relevant to our research question (which relates to the optimal control strategy within a given area), is possible and should be kept in mind for future yaws modelling work. Similarly, recent reports suggest non-human primates (NHP) can be reservoirs for yaws bacteria. If further evidence that NHP to human transmission is possible is found , this should be considered in future models.

Recent reports have shown that as with syphilis, yaws can develop azithromycin resistance *(20,24)*. While penicillin would remain effective in this scenario, this is a significant concern for yaws eradication, and how likely implementation strategies are to generate resistance is a critical research question. Although drug resistance is currently a lesser concern than the relapse of latent infection (which is what we investigate in this work), collection of further data

on drug resistance should be prioritised to allow this to be investigated and incorporated into future models.

In summary, we have shown that the current iteration of the Morges strategy is unlikely to help programmes meet the 2030 goal of global yaws eradication. We have suggested alternative strategies that may increase the likelihood of achieving this goal. In particular, we found that further rounds of TCT should be preferred to TTT. We have also shown that population size and quality of coverage can significantly affect the success of a treatment campaign, and so need to be considered in programme design. Finally, further consideration should be given to strategies supporting ongoing community surveillance, which could be integrated with ongoing surveillance for other NTDs.

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Tables and Figures

Table 1: Permitted state transitions

Description	State transition	Rate

Infection (external (ε) and within-household (ß))	(S,I,A) → (S-1,I+1,A)	$\varepsilon + \frac{\beta I}{N-1}$
Treatment/ birth-death	(S,I,A) → (S+1,I-1,A)	δ
Remission	(S,I,A) → (S,I-1,A+1)	λ
Recurrence	(S,I,A) → (S,I+1,A-1)	ρ
Treatment/ birth-death	(S,I,A) → (S+1,I,A-1)	δ

Table 2: Parameter values*

Parameter	Value	Source
β	0.0516	*(14)*
δ	0.0513	*(14)*
λ	0.185	*(15, 16)*
ρ	0.0165	*(14)*
$\varepsilon^{\dagger}$	0.004	*(14)*
$\alpha^{\ddagger}$	0.1669	*Supplementary Material*

*Given parameter value is the maximum posterior value (MPV) of the distribution from which each parameter is drawn, with the exception of λ,which is consistent with expert opinion.
†: Steady state external force of infection.
‡: This is the between-household rate of infection corresponding to a steady state external force of infection ε.

Table 3: Summary of treatment strategies used in figure 3

Strategy	Rounds of TCT*	Rounds of TTT*	Probability of elimination
1	2	2	15%
2	3	2	57%
3	2	3	26%

*TCT, total community treatment; TTT, total targeted treatment.

Table 4: Summary of treatment strategies with and without regular surveillance.

Strategy	Rounds of TCT*	Rounds of TTT*	Volunteer treatment coverage	Probability of elimination
1a	2	2	0%	15%
1b	2	2	5%	53%
2a	3	2	0%	57%
2b	3	2	5%	71%
3a	2	3	0%	26%
3b	2	3	5%	56%

*TCT, total community treatment; TTT, total targeted treatment. Strategies labelled ‘a’ are those without any regular surveillance, while ‘b’ dnotes the corresponding strategy with regular surveillance.

Figure 1: Graphical representation of the model being used for yaws transmission. Each individual is either susceptible (S), infectious (I), or asymptomatic (A).

Figure 2: Distribution of household sizes, using data collected from the Solomon Islands (2013).

Figure 3: Dynamics of yaws transmission (clinical infectious and latent cases combined, averaged over 1000 simulations) under 3 different treatment strategies: 2 TCT, 2TTT (red), 3 TCT, 2TTT (blue), 2 TCT, 3TTT (green). Simulations are run to steady state before starting the first round of treatment. Times given are the amount of time (in years) since the first round of treatment.

Figure 4: Probability of local elimination of transmission under different intervention strategies consisting of at least 2 rounds of TCT and at least 2 rounds of TTT, with varying numbers of additional rounds of TTT (blue) or TCT (green). Each twice-yearly round of TCT has 80% coverage, while TTT has 100% coverage and treatment is assumed to have 95% efficacy. All rounds of TCT are performed first before any rounds of TTT begin, which are then also performed twice-yearly.

Figure 5: Probability of local elimination of transmission under different intervention strategies with varying numbers of rounds of TCT followed by rounds of TTT treating clinical cases and household contacts. Each rectangle in the figure represents a different strategy (consisting of some number of rounds of TCT followed by rounds of TTT). The colour of the rectangle shows the probability of EOT, using the colour bar to the right. Each twice-yearly round of TCT has 80% coverage, while TTT has 100% coverage and treatment is assumed to have 95% efficacy.

Figure 6: Probability of local elimination of transmission for varying population sizes after two rounds of TCT followed by two rounds of TTT, 6 months apart. TCT has 80% coverage and TTT has 100% coverage and treatment is assumed to have 95% efficacy.

Figure 7: Dynamics of infected yaws (clinical infectious cases and latent cases) under random (red) or fully systematic (blue) coverage when implementing mass drug administration. Simulations are run to steady state before starting the first round of treatment. Times given are the amount of time since the first round of treatment. Treatment involved 2 twice-yearly rounds of TCT, followed by 2 twice-yearly rounds of TTT. TCT has a coverage of 80%, while

TTT has a coverage of 100% of all infectious individuals and their household contacts. Azithromycin efficacy is assumed to be 95%. Shaded regions denote values within one standard deviation of the mean value.

Figure 8: Probability of local elimination of transmission under intervention strategy consisting of 2 rounds of TCT, followed by two rounds of TTT treating clinical cases and household contacts as correlation between treatment rounds varies. 0 correlation denotes random treatment, while a correlation of 1 denotes fully systematic treatment. Each twice-yearly round of TCT has 80% coverage, while TTT has 100% coverage and treatment is assumed to have 95% efficacy.

Figure 9: Probability of local elimination of transmission under different intervention strategies with varying numbers of rounds of TCT followed by rounds of TTT treating clinical cases and household contacts. Each rectangle in the figure represents a different strategy (consisting of some number of rounds of TCT followed by rounds of TTT). The colour of the rectangle shows the probability of EOT, using the colour bar to the right. Each twice-yearly round of TCT has 80% coverage, while TTT has 100% coverage and treatment is assumed to have 95% efficacy. An additional type of treatment round is administered once a month, giving treatment to 5% of infectious individuals and their household contacts.

Figure 10: Probability of eradication under a strategy of 2 rounds of TCT with a varying number of rounds of TTT. Additional treatment rounds have coverages of 0% (blue), 1% (yellow), 2% (green), 3% (red), 4% (purple), 5% (brown). Low coverage treatment of infected individuals and their household contacts occur once a month.

Figure 11: Probability of eradication under a strategy of 4 rounds of TCT with a varying number of rounds of TTT. Additional treatment rounds have coverages of 0% (blue), 1% (yellow), 2% (green), 3% (red), 4% (purple), 5% (brown). Low coverage treatment of infected individuals and their household contacts occur once a month.