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Mathematical modelling *Treponema* infection in free-ranging Olive baboons (*Papio anubis*) in Tanzania

Diamond Hawkins [a], Roland Kusi [b], Solomaya Schwab [c], Idrissa S. Chuma [d], Julius D. Keyyu [e], Sascha Knauf [f,*,1], Filipa M.D. Paciência [g], Dietmar Zinner [g,i,j], Jan Rychtář [h,*,2], Dewey Taylor [h]

[a] *Department of Mathematics, Bridgewater College, Bridgewater, VA 22812, USA*
[b] *College of Engineering, Virginia Commonwealth University, Richmond, VA 23284, USA*
[c] *Department of Mathematics, Cedar Crest College, Allentown, PA 18104, USA*
[d] *Tanzania National Parks (Serengeti), P.O. Box 3134 Arusha, Tanzania*
[e] *Tanzania Wildlife Research Institute (TAWIRI), Arusha, Tanzania*
[f] *Institute of International Animal Health/One Health, Friedrich-Loeffler-Institut, Südufer 10, 17493 Greifswald - Insel Riems, Germany*
[g] *Cognitive Ethology Laboratory, German Primate Center, Leibniz Institute for Primate Research, 37077 Göttingen, Germany*
[h] *Department of Mathematics and Applied Mathematics, Virginia Commonwealth University, Richmond, VA 23284, USA*
[i] *Department of Primate Cognition, Georg-August-Universität Göttingen, 37083 Göttingen, Germany*
[j] *Leibniz Science Campus Primate Cognition, 37077 Göttingen, Germany*

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ABSTRACT

Yaws is a chronic infection caused by the bacterium *Treponema pallidum* susp. *pertenue* (*TPE*) that was thought to be an exclusive human pathogen but was recently found and confirmed in nonhuman primates. In this paper, we develop the first compartmental ODE model for *TPE* infection with treatment of wild olive baboons. We solve for disease-free and endemic equilibria and give conditions on local and global stability of the disease-free equilibrium. We calibrate the model based on the data from Lake Manyara National Park in Tanzania. We use the model to help the park managers devise an effective strategy for treatment. We show that an increasing treatment rate yields a decrease in disease prevalence. This indicates that *TPE* can be eliminated through intense management in closed population. Specifically, we show that if the whole population is treated at least once every 5-6 years, a disease-free equilibrium can be reached. Furthermore, we demonstrate that to see a substantial decrease of *TPE* infection to near-elimination levels within 15 years, the whole population needs to be treated every 2-3 years.

1. Introduction

Yaws is a neglected tropical disease and currently subject to eradication efforts (WHO, 2020). The disease is caused by the bacterium *Treponema pallidum* susp. *pertenue* (*TPE*), which until recently, was believed to be an exclusive human pathogen (Knauf et al., 2018; Zimmerman et al., 2019). Our research has shown that African nonhuman primates (NHPs) are infected with *TPE* strains that are identical to strains that cause yaws in humans. While eradication of the latter is still believed possible, it is obvious that the bacterium itself will continue to exist in African NHPs. Based on current data, there is an extremely low, but non-negligible risk for spill-over from NHPs to humans (Knauf et al., 2018; Mubemba et al., 2020b; Chuma et al., 2019). Sustainable yaws eradication in the human population would require long-term control of *TPE* infection in our closest relatives, following a One Health approach, at least, until it will be demonstrated that current NHP infecting *TPE* strains do not possess a risk to humans.

We still know little about the biology of *TPE* and its interaction with its wild primate host. We could, however, show that in wild olive baboon (*Papio anubis*) female mate choice was affected by the infectious status of their male partners, i.e., females reduced sexual contacts with obviously infected males (Paciência et al., 2019). These infection related behavioural changes in combination with the fact that many NHP taxa including great apes are critically endangered (Estrada

* Corresponding authors.
E-mail addresses: dhawkins2@eagles.bridgewater.edu (D. Hawkins), kusir@vcu.edu (R. Kusi), sfschwab@cedarcrest.edu (S. Schwab), idrissa.chuma@tanzaniaparks.go.tz (I.S. Chuma), julius.keyyu@gmail.com (J.D. Keyyu), Sascha.Knauf@fli.de (S. Knauf), fmdpaciencia@gmail.com (F.M.D. Paciência), dzinner@gwdg.de (D. Zinner), rychtarj@vcu.edu (J. Rychtář), dttaylor2@vcu.edu (D. Taylor).
[1] Corresponding author for *TPE* infections.
[2] Corresponding author for mathematical modelling.

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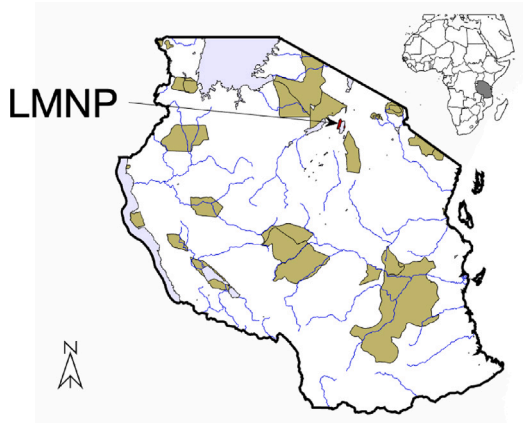

Fig. 1. Lake Manyara National Park (LMNP) and other national parks and protected areas in Tanzania, Africa. Map drawn in Matlab using the mapping toolbox and using the shapefiles from http://landscapesportal.org/layers/geonode:tz_protected_areas, https://datacatalog.worldbank.org/dataset/world-bank-official-boundaries, https://datacatalog.worldbank.org/dataset/africa-water-bodies-2015, https://www.arcgis.com/home/item.html?id=a13e9697ceb644b3a52b58df15c142f7.

et al., 2017) raise concerns on species survival. In some cases, it might be important to locally control or eliminate infection in wild primates to prevent the spread of the disease into critically endangered NHP populations. Few efforts have been reported at Gombe National Park, where treatment with penicillin has been used to control the disease in a habituated baboon group (Collins et al., 2011). Even though current treatment in humans is relatively easy to achieve with a single oral dose of azithromycin (Marks et al., 2018), treatment in NHPs will be far more challenging due to the cryptic lifestyle (e.g. timidity against humans) and uncooperative behaviour of wild primates paired with our knowledge gap on how *TPE* spreads within wild NHP populations.

Disease modelling is a modern tool that can help to predict (in-silico) the epidemiology of diseases as well as the outcome of different intervention strategies in wildlife before they are applied in the real world. Applying such a model to *TPE* infection in NHPs could help to better understand the impact of epidemiological and behavioural parameters on the disease spread. While similar models have already been published for human yaws treatment in rural communities (Gart and DeVries, 1966; Mushayabasa et al., 2012; Fitzpatrick et al., 2014; Marks et al., 2017; Fitzpatrick et al., 2018; Dyson et al., 2018, 2019; Holmes et al., 2020), for obvious reasons, they cannot be applied to wild NHPs which live under different ecological conditions and in different social settings and without voluntarily consulting health care. Moreover, since *TPE* infection occurs in low-income countries and conservation areas are often underfunded, mathematical models can be of great value to prioritized management options, including treatment, based on costs and benefits. While mathematical models are always a simplification of reality, their predictive value significantly increases with the proportion of data that are included from the real world. In this study, we aimed to develop a mathematical model for *TPE* infection in olive baboons and which includes the most recent knowledge on *TPE* infection in NHPs. Our goal was to quantify whether treating wild NHPs will result in lower *TPE* infection prevalence and at what rates the treatment must be applied to eliminate *TPE* from the target population at Lake Manyara National Park in Tanzania; see Fig. 1.

2. Material and methods

2.1. Data from yaws infection in wild olive baboons from Tanzania

Our mathematical model was designed based on current knowledge on *TPE* infection in olive baboons (*Papio anubis*). In contrast to human yaws infection, olive baboons in Tanzania show a genital-associated clinical manifestation, which together with the onset of the disease during sexual maturity is suggestive for a sexual transmission mode (Paciência et al., 2019; Chuma et al., 2019). Whether or not infection in baboons follows the classical human disease stages – primary, secondary and tertiary yaws and latent stage infection (Marks et al., 2017) – is unknown. We do know, however, that infection in olive baboons becomes systemic (Gogarten et al., 2016) and based on the biology of *Treponema pallidum* should not be clearable by the host without antimicrobial treatment (reviewed in Šmajs et al., 2018). In severe cases in olive baboons at Lake Manyara National Park in Tanzania—the most detailed studied *TPE* infected NHP population, tissue necrosis results in the loss of the corpus penis and the vagina, respectively (Knauf et al., 2012). The disease impact on mating behaviour in baboons has been demonstrated (Paciência et al., 2019). Model relevant demographic, behavioural and epidemiological parameters largely based on our study population at Lake Manyara National Park are summarized and referenced in (Table 1).

2.2. Mathematical model

We distinguish between males (subscript M) and females (subscript F). Individuals are born at rate Λ_M and Λ_F into pre-susceptible classes P_M and P_F, respectively. The young individuals are not yet sexually active and therefore they cannot get infected. As the individuals age at rate α_M and α_F, they become susceptible (S_M and S_F) at the onset of their sexual activity. A susceptible male gets clinically infected at rate $\beta_M \frac{I_F}{N_{AF}}$, where $\frac{I_F}{N_{AF}}$ is the proportion of clinically infected sexually active females; similarly, a susceptible female becomes clinically infected at rate $\beta_F \frac{I_M}{N_{AM}}$. The lesions on the infected individuals heal at rate λ_M and λ_F and the individuals become latently infected (L_M and L_F). The latently infected individuals cannot infect others, but they still carry the infection and relapse to the clinically infected stage at rate ρ_M and ρ_F. For simplicity, we assume that without treatment, all clinically infected individuals eventually relapse. All individuals die (of disease unrelated causes) at rates μM and μ_F.

The individuals are treated by antibiotics at rate τ. A treated individual becomes susceptible (if old enough).

The scheme of the dynamics is shown in Fig. 2 . The parameters and symbols are summarized in Tables 1 and 2.

3. Model analysis

The transmission dynamics described in Section 2.2 yields the following system of ODEs

$$\frac{dP_M}{dt} = \Lambda_M - (\alpha_M + \mu_M)P_M \tag{3.1}$$

$$\frac{dS_M}{dt} = \alpha_M P_M + \tau L_M + \tau I_M - \left(\beta_M \frac{I_F}{N_{AF}} + \mu_M\right) S_M \tag{3.2}$$

$$\frac{dI_M}{dt} = \beta_M \frac{I_F}{N_{AF}} S_M + \rho_M L_M - (\tau + \lambda_M + \mu_M) I_M \tag{3.3}$$

$$\frac{dL_M}{dt} = \lambda_M I_M - (\tau + \rho_M + \mu_M) L_M \tag{3.4}$$

$$\frac{dP_F}{dt} = \Lambda_F - (\alpha_F + \mu_F)P_F \tag{3.5}$$

$$\frac{dS_F}{dt} = \alpha_F P_F + \tau I_F + \tau L_F - \left(\beta_F \frac{I_M}{N_{AM}} + \mu_F\right) S_F \tag{3.6}$$

$$\frac{dI_F}{dt} = \beta_F \frac{I_M}{N_{AM}} S_F + \rho_F L_F - (\tau + \lambda_F + \mu_F) I_F \tag{3.7}$$

$$\frac{dL_F}{dt} = \lambda_F I_F - (\tau + \rho_F + \mu_F) L_F. \tag{3.8}$$

The system (3.1)–(3.8) has two equilibria, the disease-free equilibrium and an endemic equilibrium as discussed below.

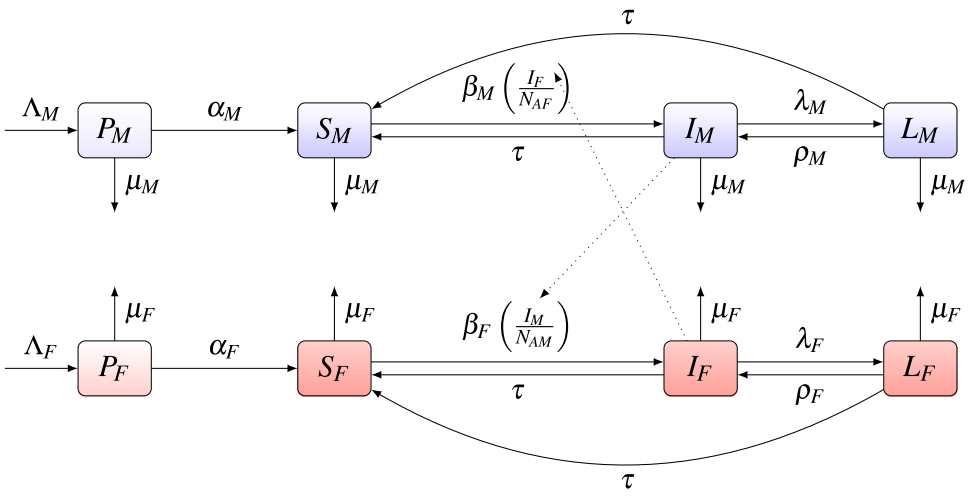

Fig. 2. Scheme of the dynamics. Blue: males, red: females. Full arrows denote transitions between the compartments. The letters next to the arrows specify the rates of the transitions. The dotted arrows show the influence on transmission rates. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Model parameters and their values. All times in years, all rates per year.

Symbol	Meaning	Males	Females	Source
Λ	Birth rate	0.075	0.075	Smuts and Nicolson (1989)
α^{-1}	Age of first sexual activity	3	6	Packer (1975), Bercovitch (1987), Smuts and Nicolson (1989)
μ^{-1}	Expected lifespan	12	15	Assumed
β	Contact rate	0.25	0.75	Assumed
λ^{-1}	Duration of the infectious period	1.5	4	Assumed
ρ^{-1}	Expected time to relapse	3	3	Assumed
τ	Treatment rate	variable	variable	(0 at the baseline)

Table 2
Model compartments. Subscript M indicates males, subscript F indicates females.

Symbol	Meaning	Description/clinical manifestation
P	Pre-susceptible	Not sexually active and not susceptible to infection
S	Susceptible	Sexually active and at risk of infection
I	Clinically infected	Infectious lesion or lesions, typically afflicting genital region. Seropositive and PCR positive
L	Latently infected	Non-infectious but can relapse to infectious lesions. Seropositive but not PCR positive

3.1. Disease-free equilibrium and the effective reproduction number

The disease-free equilibrium $\mathscr{E}^0 = (P_M^0, S_M^0, I_M^0, L_M^0, P_F^0, S_F^0, I_F^0, L_F^0)$ is given by

$$\mathscr{E}^0 = \left(\frac{\Lambda_M}{\alpha_M+\mu_M}, \frac{\Lambda_M}{\mu_M}\frac{\alpha_M}{\alpha_M+\mu_M}, 0, 0, \frac{\Lambda_F}{\alpha_F+\mu_F}, \frac{\Lambda_F}{\mu_F}\frac{\alpha_F}{\alpha_F+\mu_F}, 0, 0\right). \tag{3.9}$$

The effective reproduction number, $\mathcal{R}_e$, is given by

$$\mathcal{R}_e = \sqrt{\beta_F T_M \beta_M T_F}, \tag{3.10}$$

where

$$T_M = \frac{\rho_M+\mu_M+\tau}{(\lambda_M+\mu_M+\tau)(\rho_M+\mu_M+\tau)-\lambda_M\rho_M} \tag{3.11}$$

is the average time a male spends in the infectious compartment I_M and similarly,

$$T_F = \frac{\rho_F+\mu_F+\tau}{(\lambda_F+\mu_F+\tau)(\rho_F+\mu_F+\tau)-\lambda_F\rho_F} \tag{3.12}$$

is the average time a female spends in the infectious compartment I_F.

The formula (3.10) is derived using the next-generation matrix method (van den Driessche and Watmough, 2002) in Appendix.

It follows from van den Driessche and Watmough (2002) and Castillo-Chavez et al. (2002) that the disease-free equilibrium is locally and globally asymptotically stable if $\mathcal{R}_e < 1$ and it is unstable if $\mathcal{R}_e > 1$.

3.2. Endemic equilibrium

When $\mathcal{R}_e > 1$, there is an endemic equilibrium $\mathscr{E}^* = (P_M^*, S_M^*, I_M^*, L_M^*, P_F^*, S_F^*, I_F^*, L_F^*)$. The number of infected males is given by

$$I_M^* = \frac{N_{AM}^*(\mathcal{R}_e^2-1)}{T_F\beta_F(\beta_M T_M \pi_M + \pi_F)} \tag{3.13}$$

where

$$N_{AM}^* = \left(\frac{\Lambda_M}{\mu_M}\right)\left(\frac{\alpha_M}{\alpha_M+\mu_M}\right), \tag{3.14}$$

$$\pi_F = 1 + \frac{\lambda_F}{\tau+\rho_F+\mu_F}, \tag{3.15}$$

$$\pi_M = 1 + \frac{\lambda_M}{\tau+\rho_M+\mu_M}. \tag{3.16}$$

Furthermore,

$$P_M^* = \frac{\Lambda_M}{\alpha_M+\mu_M}, \tag{3.17}$$

$$L_M^* = \frac{\lambda_M}{\tau+\rho_M+\mu_M} I_M^*, \tag{3.18}$$

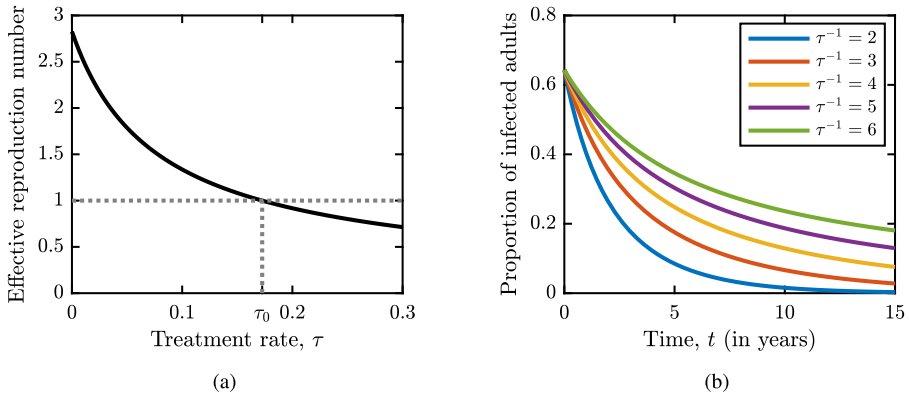

Fig. 3. (a) $\mathcal{R}_e$ is decreasing in τ. The treatment rate $\tau_0 \approx 0.173$ per year at which $\mathcal{R}_e$ reaches 1 is the minimal treatment rate that is needed for the elimination of *TPE* infections. For the parameters as in Table 1, treating the baboons once in just under six years ($1/0.173 \approx 5.78$), the infections can be eliminated. (b) The rate of elimination increases with the treating frequency. When the treatment happens about once in 4 years (or less often), the infections are still quite prevalent in the population after 15 years from the start of the treatment. To generate the Figure, we assumed that the population without any treatment had enough time to reach endemic equilibrium (with proportions of individuals as in Table 3. Then, starting at time $t = 0$, the treatment is applied with frequency τ^{-1}. We solve the system (3.1)–(3.8) numerically and plot $(I_M+L_M+I_F+L_F)/(S_M+I_M+L_M+S_F+I_F+L_F)$.

Table 3
Comparison of the model predictions with data on olive baboons collected by Chuma et al. (2018). The model predictions are based on endemic equilibrium values from Section 3.2 normalized in such a way that the total number of males is 63 and the total number of females is 74.

Compartment	Real data	Model prediction
S_M, Susceptible males, seronegative	29	27
I_M, Clinically infected males, seropositive and PCR positive	12	14
L_M, Latently infected males, seropositive and PCR negative	22	22
S_F, Susceptible females, seronegative	22	21
I_F, Clinically infected females, seropositive and PCR positive	31	32
L_F, Latently infected females, seropositve and PCR negative	21	21

$$S_M^* = N_{AM}^* - I_M^* - L_M^*. \tag{3.19}$$

The formulas for P_F^*, S_F^*, I_F^* and L_F^* are analogous with appropriate changes of subscripts M and F. Detailed calculations are shown in Appendix.

4. Results

Increasing the treatment rate τ yields a smaller number of infected males and females. It also results in a smaller effective reproduction number. These results follow from the facts that (a) by (3.11) and (3.12), T_M and T_F are decreasing in τ, (b) by (3.10), $\mathcal{R}_e$ is increasing in T_M and T_F, and thus (c) $\mathcal{R}_e$ is decreasing in τ. Consequently, by (3.13), I_M^* and also I_F^* are decreasing in τ.

Moreover, since $\lim_{\tau\to\infty} \mathcal{R}_e = 0$, there is a threshold treatment rate τ_0 such that $\mathcal{R}_e < 1$ whenever $\tau > \tau_0$, i.e., the population will reach the disease-free equilibrium. In other words, if the treatment rate is high enough, the *TPE* infection will be eliminated in a closed population. For the parameter values as in Table 1, $\tau_0 \approx 0.173$, i.e., the whole population would have to be treated once every $0.173^{-1} \approx 5.78$ years. This is illustrated in Fig. 3(a). However, realistically, the treatment rate needs to be much higher than τ_0 (in our particular case, the whole population should be treated once every 2–3 years), otherwise *TPE* infection will still be significantly present in the population even after 15 years; see Fig. 3(b).

We validated the model by comparing the predictions (under no treatment regime, i.e., $\tau = 0$) with the data collected in Chuma et al. (2018). As shown in Table 3, the model agrees with data very well and the difference can be easily attributed to randomness in data collection.

We also performed sensitivity analysis based on Arriola and Hyman (2009) and Table 4 shows the sensitivity of the effective reproduction number, $\mathcal{R}_e$, and the threshold treatment rate, τ_0, on model parameters. Both variables are most sensitive to the (unknown) contact rates β_F and β_M between the sexes. If the true contact rate is 1% more than we assumed, the threshold treatment rate increases by about 0.9% (and the effective reproduction number increases by about 0.5%) (see Fig. 4).

Table 4
The sensitivity indices $SI_{\mathcal{R}_e}$ and SI_{τ_0}. The index SI_y of a variable y on a parameter x was calculated as $\left(\frac{x}{y}\right)\cdot\left(\frac{\partial y}{\partial x}\right)$ (Arriola and Hyman, 2009). The numbers were rounded to the three decimal places. Parameters are as specified in Table 1. The sensitivity index −0.5 means that a 1% increase of a parameter value x will result in the 0.5% decrease of the variable y.

Parameter	$SI_{\mathcal{R}_e}$	SI_{τ_0}
β_F	0.499	0.912
β_M	0.499	0.911
ρ_M	0.218	0.260
ρ_F	0.160	0.180
λ_F	−0.192	−0.290
λ_M	−0.272	−0.433
μ_M	−0.454	−0.286
μ_F	−0.467	−0.263

5. Conclusions and discussion

We created an ODE compartmental model for sexual transmissions of *TPE* infection in olive baboons. We analysed the model and found expressions for the disease-free and endemic equilibria. We derived an expression for the effective reproduction number ($\mathcal{R}_e$) and determined conditions on local and global stability of the disease-free equilibrium. We validated the model by seeing a good fit with real world data (Chuma et al., 2018) and performed sensitivity analysis. Our model predicts that NHPs need to be treated at least once every two to three years in order to eliminate *TPE* within 15 years.

While our current mathematical model for yaws transmission in olive baboons is still limited by our understanding of yaws infection in NHP populations, it is already useful for the testing of effectiveness of yaws treatment in wild baboon populations. It should be seen as a starting point for the epidemiological modelling of *TPE* infection in wild primates, which is a requirement for the prioritization of possible

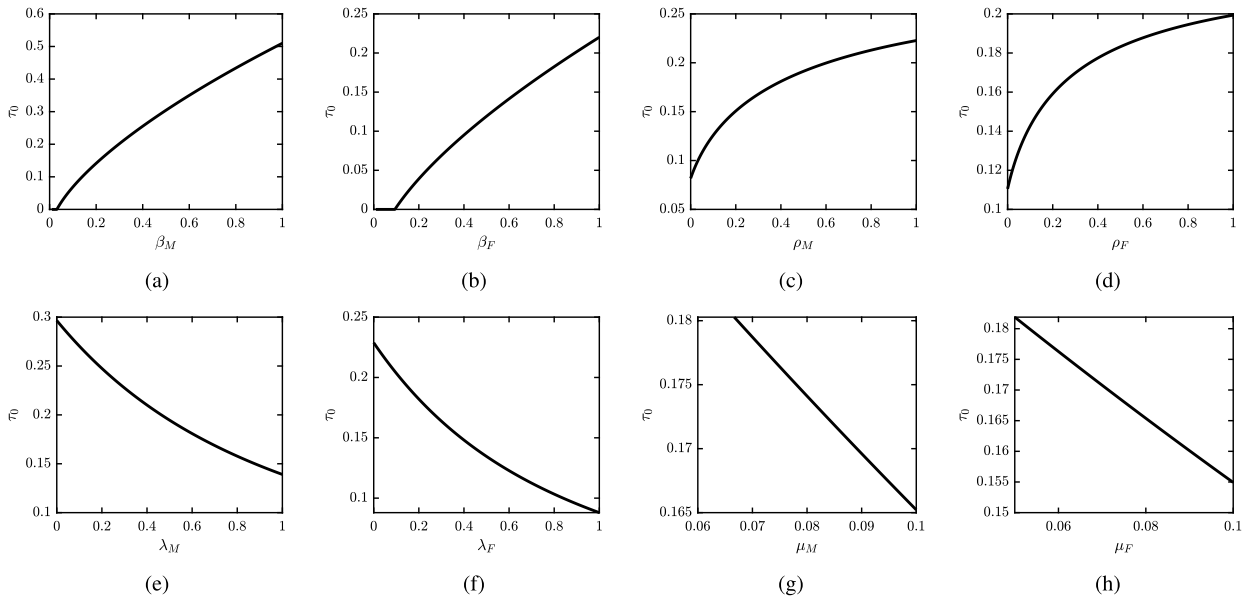

Fig. 4. Dependence of the threshold treatment rate τ_0 on model parameters; the parameters that do not vary are as specified in Table 1. As β_M, β_F, ρ_M or ρ_F increase, so does τ_0. This means that if any of these parameters is larger than we assumed, the treatment rate needed to eliminate *TPE* would have to be larger. In contrast, τ_0 is decreasing in $\lambda_M, \lambda_F, \mu$M and μ_F, i.e., if any of these parameters are larger, then the treatment rate could be smaller. Note that τ_0 is constant in Λ_M, Λ_F, α_M and α_F.

management options. Obviously, the model will benefit from evidence-based parameters collected from target populations. In particular olive baboons have a huge geographic range in sub-Saharan Africa that spans from West Africa across the northern savanna belt to East Africa. Within this large range, regional differences have been reported in terms of ecology and social organization (e.g., group size and demography) (Swedell, 2011). Moreover, *TPE* infection in East Africa is mostly associated with skin ulcers at the genital region, whereas in Central and West Africa infection is often associated with facial lesions or ulcers on the extremities (Knauf et al., 2018; Chuma et al., 2018, 2019; Levréro et al., 2007; Mubemba et al., 2020a). The latter argues for transmission through skin-to-skin contact independent of the mating behaviour. As a result, it will increase the predictive power of our model if it is fed with real data obtained from the population that should be treated against yaws infection. These data include but are not limited to male migration rates, mating behaviour, reproductive key parameters, infection rates and life-history parameters.

Many values of currently included model parameters are based on empirical knowledge that we obtained from our decade long field research with baboons and *TPE* infected primate populations. As a consequence, some of the parameters may include a sampling bias (e.g., preferential sampling of infected individuals, Chuma et al. (2018)) which might be an effect of the observed visibility of the external genital skin area in females compared to males. The model parameters, specifically the duration of infectious period, had to have a significant difference between males and females so that the model could produce more acutely infected females. If the true reality is that there is about the same number of acutely infected females as there are males, the model parameters would have to be adjusted accordingly. The increase of the accuracy of model predictions when real data are used warrants long-term field studies that combine behavioural and infectious disease research in target populations. This, unfortunately, is often challenged by a lack of funding for long-term projects.

Although yaws infection can be treated in humans with a single oral dose of azithromycin Mitjà et al. (2012), it is unrealistic to think that yaws eradication can be achieved through treatment of wild baboons and other NHP species which often avoid human contact or show an uncooperative behaviour. Nevertheless, our model predicts that *TPE* infection in baboons can be controlled or even eliminated in a defined population that is accessible for treatment intervention. Even in NHPs oral doses of penicillin or azithromycin can be used to treat bacterial infection (Gamble, 2018). We show that an increasing treatment rate yields a decrease in prevalence and the effective reproduction number ($\mathcal{R}_e$) indicating that a disease-free equilibrium can be reached through intense management in closed populations. This is an important finding for the conservation of species and important NHP populations (e.g. habituated animals) as well as for yaws eradication since our data on NHP infection suggest that the control of yaws in NHPs will be important to reach the WHO goal to eradicate human yaws by 2030 (WHO, 2020). For wildlife management authorities it is important to note that our ODE compartment model for sexual transmission of *TPE* infection in baboons indicates that for a true visible effect within a realistic time frame (15 years) one has to treat the animals at much higher rate than the smallest rate needed to achieve elimination. Although the full support of robustness is beyond the scope of this study, the result seems to be robust and not dependent on parameter values or details of the model.

Despite the encouraging results from our model that *TPE* infection in NHPs can be controlled using mass drug administration, a possible serious consequence of antibiotic treatment is the emergence of antibiotic resistant strains. In Papua New Guinea, where the new WHO yaws treatment strategy of mass azithromycin treatment followed by targeted treatment programmes was applied, a number of treatment failures with azithromycin became obvious (Mitjà et al., 2018). This was further proven by an increased PCR-detection of the mutations in the 23S ribosomal RNA genes of *T. pallidum* that are known to code for macrolide-resistance (Grimes et al., 2012). Since *TPE* in NHPs is more difficult to control and because of the zoonotic potential of *TPE* strains of NHP origin, the emergence of antibiotic resistant strains must be avoided at all costs. Any treatment in NHPs must be long-term monitored and scientifically evaluated with a clear cost–benefit analysis. Current NHPs strains show no macrolide resistance (Chuma et al., 2019) but we know that *T. pallidum* infection in humans is a dynamic process with multiple sublineages that can become extinct or being replaced by newer more dominant sublineages (Chuma et al., 2019; Beale et al., 2021). Management authorities must be aware that antibiotic treatment in NHPs would significantly impact the selection pressure for *TPE* with, yet, unknown ecological consequences for animal and human health.

In conclusion, current genetic data indicate that interspecies transmission of *TPE* in NHPs is rare (Mubemba et al., 2020b; Chuma et al., 2019). In light of the proven zoonotic potential of NHP infecting *TPE* strains (Smith et al., 1971) there is, however, a non negligible risk for human health. For this reason, the control of *TPE* infection especially in baboons in areas where they interact with humans paired with ongoing disease surveillance in NHPs and humans will become an important management tool to prevent potential spillovers and possible reemergence of human yaws. Six decades after the first description of the yaws bacterium in nonhuman primates (reviewed in Šmajs et al., 2018), it is clear that a One Health approach is needed to sustainably eliminate yaws infection in humans. Under no circumstance treatment in humans should be hindered by the fact that the bacterium is naturally found in NHPs (Knauf et al., 2018). Our mathematical model indicates that treatment in NHPs can result in disease free-populations and is therefore supportive for the sustainable elimination of human yaws when a One Health approach is applied.

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CRediT authorship contribution statement

Diamond Hawkins: Formal analysis, Software, Visualization, Investigation, Writing – original draft, Writing – review & editing. **Roland Kusi:** Formal analysis, Software, Writing – original draft, Writing – review & editing. **Solomaya Schwab:** Formal analysis, Software, Writing – original draft, Writing – review & editing. **Idrissa S. Chuma:** Providing data on *TPE* infection and baboon behaviour, Writing – original draft, Writing – review & editing. **Julius D. Keyyu:** Providing data on *TPE* infection and baboon behaviour, Writing – original draft, Writing – review & editing. **Sascha Knauf:** Providing data on TPE infection and baboon behaviour, Writing – original draft, Writing – review & editing. **Filipa M.D. Paciência:** Providing data on TPE infection and baboon behaviour, Writing – original draft, Writing – review & editing. **Dietmar Zinner:** Providing data on TPE infection and baboon behaviour, Writing – original draft, Writing – review & editing. **Jan Rychtář:** Writing – original draft, Writing – review & editing, Software, Methodology, Supervision, conceptualization. **Dewey Taylor:** Writing – original draft, Writing – review & editing, Methodology, Supervision, Conceptualization, Formal analysis, Validation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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Appendix. Calculations

A.1. Calculations of the effective reproduction number $\mathcal{R}_e$

Here we show the calculations of the effective reproduction number $\mathcal{R}_e$ using the next generation matrix method (van den Driessche and Watmough, 2002). We will assume the order of the compartments to be I_M, I_F, L_M, L_F, S_M, S_F, P_M, P_F; the first four are the infected compartments. The new infections are represented by a column vector

$$\mathscr{F} = \left(\beta_M \frac{I_F}{N_{AF}} S_M, \beta_F \frac{I_M}{N_{AM}} S_F, 0, 0,\right)^T, \tag{A.1}$$

while the changes in compartments that do not result in any new infections are represented by

$$\mathscr{V} = \begin{pmatrix} (\tau + \lambda_M + \mu_M) I_M - \rho_M L_M \\ (\tau + \lambda_F + \mu_F) I_F - \rho_F L_F \\ (\tau + \rho_M + \mu_M) L_M - \lambda_M I_M \\ (\tau + \rho_F + \mu_F) L_F - \lambda_F I_F \end{pmatrix}. \tag{A.2}$$

At the disease-free equilibrium, the Jacobians are given by

$$F = \begin{pmatrix} 0 & \beta_M \frac{S_M^0}{N_{AF}} & 0 & 0 \\ \beta_F \frac{S_F^0}{N_{AM}} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \tag{A.3}$$

$$V = \begin{pmatrix} \lambda_M + \mu_M + \tau & 0 & -\rho_M & 0 \\ 0 & \lambda_F + \mu_F + \tau & 0 & -\rho_F \\ -\lambda_M & 0 & \mu_M + \rho_M + \tau & 0 \\ 0 & -\lambda_F & 0 & \mu_F + \rho_F + \tau \end{pmatrix}. \tag{A.4}$$

Using symbolic computation capabilities of MATLAB, we calculated V^{-1}, FV^{-1} and the eigenvalues of FV^{-1}. The eigenvalues of FV^{-1} are 0 and $\pm\mathcal{R}_e$ where $\mathcal{R}_e$ is given by (3.10).

A.2. Calculations of the endemic equilibria

When solving for equilibria of the dynamics, i.e., the constant solutions of (3.1)–(3.8), we set the left-hand sides of the equations to zero and solve the following system of algebraic equations.

$$0 = \Lambda_M - (\alpha_M + \mu_M) P_M \tag{A.5}$$

$$0 = \alpha_M P_M + \tau L_M + \tau I_M - \left(\beta_M \frac{I_F}{N_{AF}} + \mu_M\right) S_M \tag{A.6}$$

$$0 = \beta_M \frac{I_F}{N_{AF}} S_M + \rho_M L_M - (\tau + \lambda_M + \mu_M) I_M \tag{A.7}$$

$$0 = \lambda_M I_M - (\tau + \rho_M + \mu_M) L_M \tag{A.8}$$

$$0 = \Lambda_F - (\alpha_F + \mu_F) P_F \tag{A.9}$$

$$0 = P_F \alpha_F + \tau I_F + \tau L_F - \left(\beta_F \frac{I_M}{N_{AM}} + \mu_F\right) S_F \tag{A.10}$$

$$0 = \beta_F \frac{I_M}{N_{AM}} S_F + \rho_F L_F - (\tau + \lambda_F + \mu_F) I_F \tag{A.11}$$

$$0 = \lambda_F I_F - (\tau + \rho_F + \mu_F) L_F \tag{A.12}$$

By (A.5) and (A.9)

$$P_M = \frac{\Lambda_M}{\alpha_M + \mu_M}, \tag{A.13}$$

$$P_F = \frac{\Lambda_F}{\alpha_F + \mu_F}. \tag{A.14}$$

By adding (A.6)–(A.8), we get

$$N_{AM} = \frac{\alpha_M}{\mu_M} P_M = \left(\frac{\Lambda_M}{\mu_M}\right)\left(\frac{\alpha_M}{\alpha_M + \mu_M}\right). \tag{A.15}$$

Similarly, by adding (A.10)–(A.12), we get

$$N_{AF} = \frac{\alpha_F}{\mu_F} P_F = \left(\frac{\Lambda_F}{\mu_F}\right)\left(\frac{\alpha_F}{\alpha_F + \mu_F}\right). \tag{A.16}$$

In the disease-free equilibrium we have $I_M = L_M = 0$ and thus $S_M = N_{AM}$. Similarly, $I_F = L_F = 0$ and thus $S_F = N_{AF}$. The formulas above thus provide disease-free equilibrium.

To continue solving the system for the endemic equilibrium, note that, by (A.8) and (A.12),

$$L_M = \frac{\lambda_M}{\tau + \rho_M + \mu_M} I_M, \tag{A.17}$$

$$L_F = \frac{\lambda_F}{\tau + \rho_F + \mu_F} I_F. \tag{A.18}$$

Since $S_M = N_{AM} - I_M - L_M$ and $S_F = N_{AF} - I_F - L_F$, we get, by (A.7) and (A.11),

$$\beta_M \frac{I_F}{N_{AF}}(N_{AM} - I_M - L_M) = (\tau + \lambda_M + \mu_M) I_M - \rho_M L_M, \tag{A.19}$$

$$\beta_F \frac{I_M}{N_{AM}}(N_{AF} - I_F - L_F) = (\tau + \lambda_F + \mu_F) I_F - \rho_F L_F. \tag{A.20}$$

Set

$$\pi_F = 1 + \frac{\lambda_F}{\tau + \rho_F + \mu_F}, \tag{A.21}$$

$$\pi_M = 1 + \frac{\lambda_M}{\tau + \rho_M + \mu_M}, \tag{A.22}$$

$$T_F = \left((\tau + \lambda_F + \mu_F) - \frac{\rho_F \lambda_F}{\tau + \rho_F + \mu_F}\right)^{-1}, \tag{A.23}$$

$$T_M = \left((\tau + \lambda_M + \mu_M) - \frac{\rho_M \lambda_M}{\tau + \rho_M + \mu_M}\right)^{-1}. \tag{A.24}$$

Then, (A.19)–(A.20) becomes

$$\beta_M \frac{I_F}{N_{AF}}(N_{AM} - \pi_M I_M) = \frac{I_M}{T_M}, \tag{A.25}$$

$$\beta_F \frac{I_M}{N_{AM}}(N_{AF} - \pi_F I_F) = \frac{I_F}{T_F}. \tag{A.26}$$

This yields

$$I_M = N_{AM} \frac{\beta_F \beta_M T_F T_M - 1}{T_F \beta_F (T_M \beta_M \pi_M + \pi_F)}, \tag{A.27}$$

$$I_F = N_{AF} \frac{\beta_F \beta_M T_F T_M - 1}{T_M \beta_M (T_F \beta_F \pi_F + \pi_M)}. \tag{A.28}$$

References

Arriola, L., Hyman, J.M., 2009. Sensitivity analysis for uncertainty quantification in mathematical models. In: Mathematical and Statistical Estimation Approaches in Epidemiology. Springer, pp. 195–247.

Beale, M.A., Marks, M., Cole, M.J., Lee, M.-K., Pitt, R., Ruis, C., Balla, E., Crucitti, T., Ewens, M., Fernández-Naval, C., 2021. Global phylogeny of *Treponema pallidum* lineages reveals recent expansion and spread of contemporary syphilis. Nat. Microbiol. 6 (12), 1549–1560.

Bercovitch, F.B., 1987. Reproductive success in male savanna baboons. Behav. Ecol. Sociobiol. 21 (3), 163–172.

Castillo-Chavez, C., Feng, Z., Huang, W., et al., 2002. On the computation of R_0 and its role in global stability. IMA Vol. Math. Appl. 125, 229–250.

Chuma, I.S., Batamuzi, E.K., Collins, D.A., Fyumagwa, R.D., Hallmaier-Wacker, L.K., Kazwala, R.R., Keyyu, J.D., Lejora, I.A., Lipende, I.F., Lüert, S., 2018. Widespread *Treponema pallidum* infection in nonhuman primates, Tanzania. Emerg. Infect. Diseases 24 (6), 1002.

Chuma, I.S., Roos, C., Atickem, A., Bohm, T., Collins, D.A., Grillová, L., Hallmaier-Wacker, L.K., Kazwala, R.R., Keyyu, J.D., Lüert, S., 2019. Strain diversity of *Treponema pallidum* subsp. *pertenue* suggests rare interspecies transmission in African nonhuman primates. Sci. Rep. 9 (1), 1–9.

Collins, D., Sindimwo, A., Wallis, P., 2011. Reproductive disease of olive baboons (*Papio anubis*) of Gombe National Park: Outbreak, time-course, and attempts to limit recurrence. In: Msuha, M., Nindi, S., Kakengi, V., Ntalwila, J., Kohi, E. (Eds.), Proceedings of the Eighth TAWIRI Scientific Conference. Climate Change: Challenges and Opportunities Towards Sustainable Wildlife Conservation and Development. Tanzania Wildlife Research Institute, Arusha (Tanzania), pp. 236–248.

Dyson, L., Marks, M., Crook, O.M., Sokana, O., Solomon, A.W., Bishop, A., Mabey, D.C., Hollingsworth, T.D., 2018. Targeted treatment of yaws with household contact tracing: How much do we miss? Am. J. Epidemiol. 187 (4), 837–844.

Dyson, L., Mooring, E.Q., Holmes, A., Tildesley, M.J., Marks, M., 2019. Insights from quantitative and mathematical modelling on the proposed 2030 goals for yaws. Gates Open Res. 3.

Estrada, A., Garber, P.A., Rylands, A.B., Roos, C., Fernandez-Duque, E., Di Fiore, A., Nekaris, K.A.-I., Nijman, V., Heymann, E.W., Lambert, J.E., 2017. Impending extinction crisis of the world's primates: Why primates matter. Sci. Adv. 3 (1), e1600946.

Fitzpatrick, C., Asiedu, K., Jannin, J., 2014. Where the road ends, yaws begins? The cost-effectiveness of eradication versus more roads. PLoS Negl. Trop. Dis. 8 (9), e3165.

Fitzpatrick, C., Asiedu, K., Solomon, A.W., Mitja, 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 Negl. Trop. Dis. 12 (12), e0006953.

Gamble, K.C., 2018. Primates. In: Exotic Animal Formulary. Elsevier, pp. 575–615.

Gart, J.J., DeVries, J., 1966. The mathematical analysis of concurrent epidemics of yaws and chickenpox. J. Hyg. 64, 431–439.

Gogarten, J.F., Düx, A., Schuenemann, V.J., Nowak, K., Boesch, C., Wittig, R.M., Krause, J., Calvignac-Spencer, S., Leendertz, F.H., 2016. Tools for opening new chapters in the book of *Treponema pallidum* evolutionary history. Clin. Microbiol. Inf. 22 (11), 916–921.

Grimes, M., Sahi, S.K., Godornes, B.C., Tantalo, L.C., Roberts, N., Bostick, D., Marra, C.M., Lukehart, S.A., 2012. Two mutations associated with macrolide resistance in *Treponema pallidum*: Increasing prevalence and correlation with molecular strain type in Seattle, Washington. Sex. Transm. Dis. 39 (12), 954.

Holmes, A., Tildesley, M.J., Solomon, A.W., Mabey, D.C., Sokana, O., Marks, M., Dyson, L., 2020. Modeling treatment strategies to inform yaws eradication. Emerg. Infect. Diseases 26 (11), 2685.

Kimball, P., Levenson, J., Moore, A., Rychtář, J., Taylor, D., 2021. An ODE model of yaws elimination in Lihir Island, Papua New Guinea. Preprint.

Knauf, S., Batamuzi, E., Mlengeya, T., Kilewo, M., Lejora, I., Nordhoff, M., Ehlers, B., Harper, K., Fyumagwa, R., Hoare, R., 2012. Treponema infection associated with genital ulceration in wild baboons. Vet. Pathol. 49 (2), 292–303.

Knauf, S., Gogarten, J.F., Schuenemann, V.J., De Nys, H.M., Düx, A., Strouhal, M., Mikalová, L., Bos, K.I., Armstrong, R., Batamuzi, E.K., 2018. Nonhuman primates across sub-Saharan Africa are infected with the yaws bacterium *Treponema pallidum* subsp. *pertenue*. Emerg. Microbes Inf. 7 (1), 1–4.

Levréro, F., Gatti, S., Gautier-Hion, A., Ménard, N., 2007. Yaws disease in a wild gorilla population and its impact on the reproductive status of males. Am. J. Phys. Anthropol. 132 (4), 568–575.

Marks, M., Mitjà, O., Bottomley, C., Kwakye, C., Houinei, W., Bauri, M., Adwere, P., Abdulai, A.A., Dua, F., Boateng, L., et al., 2018. Comparative efficacy of low-dose versus standard-dose azithromycin for patients with yaws: A randomised non-inferiority trial in Ghana and Papua New Guinea. Lancet Glob. Health 6 (4), e401–e410.

Marks, M., Mitjà, O., Fitzpatrick, C., Asiedu, K., Solomon, A.W., Mabey, D.C., Funk, S., 2017. Mathematical modeling of programmatic requirements for yaws eradication. Emerg. Infect. Diseases 23 (1), 22–28.

Mitjà, O., Godornes, C., Houinei, W., Kapa, A., Paru, R., Abel, H., González-Beiras, C., Bieb, S.V., Wangi, J., Barry, A.E., 2018. Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: A longitudinal study. Lancet 391 (10130), 1599–1607.

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. Lancet 379 (9813), 342–347.

Mubemba, B., Chanove, E., Mätz-Rensing, K., Gogarten, J.F., Düx, A., Merkel, K., Röthemeier, C., Sachse, A., Rase, H., Humle, T., 2020a. Yaws disease caused by *Treponema pallidum* subspecies *pertenue* in wild chimpanzee, Guinea, 2019. Emerg. Infect. Diseases 26 (6), 1283–1286.

Mubemba, B., Gogarten, J.F., Schuenemann, V.J., Düx, A., Lang, A., Nowak, K., Pléh, K., Reiter, E., Ulrich, M., Agbor, A., 2020b. Geographically structured genomic diversity of non-human primate-infecting *Treponema pallidum* subsp. *pertenue*. Microb. Genom. 6 (11), mgen000463.

Mushayabasa, S., Bhunu, C., Webb, C., Dhlamini, M., 2012. A mathematical model for assessing the impact of poverty on yaws eradication. Appl. Math. Model. 36 (4), 1653–1667.

Paciência, F., Rushmore, J., Chuma, I., Lipende, I., Caillaud, D., Knauf, S., Zinner, D., 2019. Mating avoidance in female olive baboons (*Papio anubis*) infected by *Treponema pallidum*. Sci. Adv. 5 (12), eaaw9724.

Packer, C., 1975. Male transfer in olive baboons. Nature 255 (5505), 219–220.

Šmajs, D., Strouhal, M., Knauf, S., 2018. Genetics of human and animal uncultivable treponemal pathogens. Infect. Genet. Evol. 61, 92–107.

Smith, J.L., David, N., Indgin, S., Israel, C., Levine, B., Justice Jr., J., McCrary 3rd, J., Medina, R., Paez, P., Santana, E., 1971. Neuro-ophthalmological study of late yaws and pinta. II. The caracas project. Br. J. Venereal Dis. 47 (4), 226–251.

Smuts, B., Nicolson, N., 1989. Reproduction in wild female olive baboons. Am. J. Primatol. 19 (4), 229–246.

Swedell, L., 2011. African apionins: Diversity of social organization and ecological flexibility. In: Campbell, C., Fuentes, A., MacKinnon, K., Bearder, S., Stumpf, R. (Eds.), Primates in Perspective. Oxford University Press, pp. 241–277.

van den Driessche, P., Watmough, J., 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. 180, 29–48.

WHO, 2020. Ending the Neglect To Attain the Sustainable Development Goals: A Road Map for Neglected Tropical Diseases 2021–2030: Overview. World Health Organization.

Zimmerman, D.M., Hardgrove, E.H., von Fricken, M.E., Kamau, J., Chai, D., Mutura, S., Kivali, V., Hussein, F., Ambala, P., Surmat, A., et al., 2019. Endemicity of yaws and seroprevalence of *Treponema pallidum* antibodies in nonhuman primates, Kenya. Emerg. Infect. Diseases 25 (11), 2147.