Can culling to prevent monkeypox infection be counter-productive? Scenarios from a theoretical model

Jean M. Tchuenche*, Chris T. Bauch

Department of Mathematics and Statistics, University of Guelph, ON N1G 2W1, Canada

*Correspondence: jmtchuenche@gmail.com, cbauch@uoguelph.ca

Abstract

In the last two decades, monkeypox outbreaks in human populations in Africa and North America have reminded us that smallpox is not the only poxvirus with potential to cause harm in human populations. Monkeypox transmission is sustained in animal reservoirs, and animal-human contacts are responsible for sporadic outbreaks in humans. Here, we develop and analyze a deterministic epizootic (animal-based) transmission model capturing disease dynamics in an animal population, disease dynamics in an age-structured human population, and their coupling through animal-human contacts. We develop a single-patch model as well as a two-patch meta-population extension. We derive mathematical expressions for the basic reproduction number, which governs the likelihood of a large outbreak. We also investigate the effectiveness of culling strategies and the impact of changes in the animal-human contact rate. Numerical analysis of the model suggests that, for some parameter values, culling can actually have the counter-productive outcome of increasing monkeypox infection in children, if animal reproduction is a density-dependent process. The likelihood of this happening, as well as the prevalence of monkeypox in humans, depends sensitively on the animal-human contact rate. We also find that ignoring age structure in human populations can lead to overestimating the transmissibility of monkeypox in humans. In conclusion, the effectiveness of monkeypox control strategies such as culling can strongly depend on the details of demography and epidemiology in the animal reservoirs that sustain it. Therefore, to better understand how to prevent and control monkeypox outbreaks in humans, better empirical data from wild animal populations where monkeypox is endemic must be collected, and these data must be incorporated into highly structured theoretical models.

Introduction

Poxvirus infections in humans have an ancient history, and they remain one of the most dangerous families of viruses of livestock animals and humans. During the last two decades, there have emerged reports on human monkeypox outbreaks in Africa and North America (with over 90% occurring in young children) [1] as well as in non-human primates and rodents. Vaccinia, cowpox, and buffalopox virus outbreaks have also occurred in various countries in recent years [2]. Monkeypox is caused by a member of the orthopoxvirus genus that also includes camelpox, cowpox, rodentpox and vaccinia. Monkeypox virus was initially isolated in 1958 by von Magnus and coworkers [3] from outbreaks of disease in cynomolgus monkey colonies of Singapore origin in the State Serum Institute, Copenhagen, but human monkeypox was not recognized until 1970 in the equatorial region of Zaire (now the Democratic Republic of Congo, DRC) [4], one year after the last confirmed smallpox case had been detected in the area [1]. It is considered by some to be the most important orthopoxvirus infection in humans partly because it causes disease clinically indistinguishable from smallpox [5].

Monkeypox is a neglected but emerging infection and was not perceived as posing a global threat until accidentally introduced into the USA in 2003 [6, 12] and in South Sudan in 2005 [6]. These recent outbreaks (in the United States, the Republic of Congo and Sudan) highlight the capacity of this virus to appear where it has never before been reported. It is a zoonotic (animal-to-human transmission) disease, meaning the virus can penetrate the interspecies barrier [10]. Its transmissibility has slightly been on the increase in human hosts [3, 7]. This poses a great challenge as it is possible for humans to become sole natural hosts of pox viruses, as evidenced by the histories of the variola and molluscum contagiosum pox viruses. Human monkeypox has been recorded sporadically in the tropical rain forest of central and western Africa over the past 30 years [7, 8, 9]. It is endemic to central and western parts of Africa [11]. Concerns about the potential use of monkeypox virus as a bio-terrorism agent have arisen in the past, and its potential as a bio-terrorist weapon may need to be reassessed in the era of modern molecular biology [16, 17]. However, at present, monkeypox case imports from endemic countries (through the importation of exotic animals) remain the only source of potential sporadic outbreaks in other countries.

Monkeypox infection is preventable, but there is currently no proven treatment for the disease [10, 11, 12]. Eradication of the virus is complicated by the fact that a reservoir of infection is maintained in populations of sylvatic hosts outside the direct control of humans [15]. The primary reservoir for human infection remains unknown, however, studies point to several species of squirrels, specifically rope (or tree) squirrels of the African genus *Funisciurus* as playing a major role as a potential reservoir of the virus [18]. Indeed, the term monkeypox is something of a misnomer, because evidence suggests that rodents, and not monkeys, are actually its largest natural reservoir in terms of both absolute numbers and percentages [12, 14, 17]. Monkeys are probably sentinel animals, only occasionally infected with

this virus, rather than its principal reservoir host [20]. Its reservoir seems to be mostly confined to the tropical rain forest belt of Africa and the hosts are arboreal rodents from which sporadic transmissions occur to simians and humans. Man is therefore considered an incidental host [21, 22].

The systemic manifestations of monkeypox infection in humans are similar to those of smallpox. Previous vaccination with the smallpox (vaccinia) vaccine appears to confer protective immunity against monkeypox: the overall monkeypox attack rate for contacts without a smallpox vaccination scar differs significantly from the attack rate for contacts with a scar, indicating previous vaccination [7, 23]. The incidence of monkeypox has increased as immunity from smallpox vaccination has waned over time [7]. Although the monkeypox appears incapable of sustained secondary transmission in humans, evidence of human-to-human transmission exists [6, 17, 24]. The possibility that monkeypox virus could eventually evolve to the point of persistence in human communities is not excluded, particularly in communities with little pre-existing immunity from smallpox infection [23, 24].

Mathematical models of the dynamics of monkeypox are rare, although models assuming a natural history structure similar to what would be suitable for monkeypox (Susceptible-Infectious-Recovered type) exist in the literature [25, 26, 27, 28]. Jezek and colleagues [29, 24] study a stochastic model for inter-human spread of monkeypox using a Monte Carlo type model to assess the potential risk for significant changes in disease incidence as a result of the diminishing protection from smallpox vaccination. They predict that sustained monkeypox transmission on account of declining immunity from previous smallpox vaccinations was unlikely.

Here, we develop and analyze a deterministic monkeypox model that encompasses the disease dynamics in an animal population and a connected human population. Expressions for the threshold for endemic persistence of the disease are computed. A meta-population model extension (that describes multiple animal hosts or multiple spatial regions) is briefly discussed and several analytic results are presented for the two-patch case. Model parameters are estimated from the literature. Even though the number of infected individuals in monkeypox case clusters is very small, and human-to-human transmission is dominated by demographic stochasticity, a deterministic model can be solved explicitly to gain insight into its qualitative dynamics. We analyze the impact of age structure, culling strategies, variations in the animal-human contact rate parameter. There are different sources of uncertainty that may affect a modeling analysis: inherent or natural uncertainty (due to inevitable variability or unpredictability); structural uncertainty (due to approximations and simplifications in model formulation); and parametric uncertainty (due to discrepancies over input parameters because of the lack of accurate data) [30]. With the last two, we explore how the structure of the model may influence model predictions, and the sensitivity of the initial disease transmission to model parameters. We describe the methods and results of the single patch age-structured model, followed by the methods and results of the meta-population

model.

Methods I: age-structured model

Model description

The deterministic compartmental model is subdivided into animal and human components. The animal component aggregates populations from all species that can carry monkeypox. The size of the animal reservoir at time t denoted by $N_M(t)$, and the animal reservoir consists of susceptible $S_M(t)$, infective $I_M(t)$ and removed $R_M(t)$ classes. Thus,

$$N_M(t) = S_M(t) + I_M(t) + R_M(t).$$

Monkeypox is a self-limiting infection that probably exhibits long-term natural immunity in most relevant animal species. Therefore once their infectious period ends, infective animals enter the removed/recovered class. Infection which can be acquired following effective contact with infected animals at a rate

$$\lambda_M = \beta_M \frac{I_M}{N_M},$$

where β_M is the transmission probability per contact. Culling has been a common method for pest control and ecosystem management [13, 31, 32]. Thus, the population is further reduced by natural death at a rate μ_M as well as culling at a rate μ_C. We also assume that the animal population follows a logistic growth rule with carrying capacity K_M and intrinsic growth rate r_M [25]. Infective animals are not likely to reproduce, however, we expect that the number of infective animals at any given time is small relative to the number of susceptible and recovered animals. Therefore, using $S_M + R_M \approx N_M$, the susceptible equation becomes

$$\frac{dS_M}{dt} = r_M N_M \left(1 - \frac{N_M}{K_M}\right) - \lambda_M S_M - (\mu_C + \mu_M) S_M.$$

The population of infectious animals is generated following the development of the disease in susceptible animals at a rate λ_M. This class is reduced by natural death (at a rate μ_M), culling (rate μ_C), disease-induced death (at a rate d_M), and progression to the removal class (at a rate τ_M), so that the rate of change of the population of infected animals is given by

$$\frac{dI_M}{dt} = \lambda_M S_M - (\tau_M + d_M + \mu_C + \mu_M) I_M.$$

The population of removed animals is generated following recovery of infectious animals (at a rate τ_M) and reduced due to natural mortality (at a rate μ_M) and culling (rate μ_C). Therefore,

$$\frac{dR_M}{dt} = \tau_M I_M - (\mu_C + \mu_M) R_M.$$

Hence, recalling that $\lambda_M = \beta_M I_M/N_M$, the following sub-model describing the dynamics of the epizootic disease in the animal population:

$$\begin{aligned}
\frac{dS_M}{dt} &= r_M S_M \left(1 - \frac{S_M}{K_M}\right) - \lambda_M S_M - (\mu_C + \mu_M) S_M, \\
\frac{dI_M}{dt} &= \lambda_M S_M - (\tau_M + d_M + \mu_C + \mu_M) I_M, \\
\frac{dR_M}{dt} &= \tau_M I_M - (\mu_C + \mu_M) R_M.
\end{aligned}$$

These equations assume transmission through direct contact, although monkeypox may also be transmissible through indirect contact. However, if the survival time of the virus in the environment is less than or equal to the duration of infectiousness, then it is possible to reduce a model with an additional equation representing virus in the environment to the above equations since the abundance of virus will scale linearly with the number of infective animals.

The severity of monkeypox disease and transmission patterns in humans is age-dependent. Also, residual immunity from previous smallpox vaccination programs will be stronger in adult than in juvenile populations. Hence, for the human component, we divide the population into juvenile and adult classes. Juveniles consist of susceptible juvenile $S_J(t)$, susceptible juvenile vaccinated (i.e. susceptible individuals who have previously been vaccinated against variola) $S_{JV}(t)$, (this compartment is empty when describing the current state of no ongoing variola vaccination), infected juvenile $I_J(t)$ and recovered juvenile $R_J(t)$. Adults consist of susceptible adults $S_A(t)$, susceptible adult vaccinated $S_{AV}(t)$, infected adult $I_A(t)$ and recovered adult $R_A(t)$.

We retrospectively account for a continuous vaccination program where a fraction of susceptible individuals were vaccinated per unit time (as opposed to cohort vaccination where a fraction of the newly-recruited members of the community were vaccinated or a combined continuous and cohort vaccination program) because smallpox vaccination was halted in the 80's as the disease was eradicated worldwide. Once vaccine based immunity has waned off completely, no individuals are protected and hence one could set $S_{JV} = S_{AV} = 0$.

Infection is acquired through effective contact with infectious animals at a rate λ_S where

$$\lambda_S = \sigma\lambda_M = \sigma\beta_M \frac{I_M}{N_M}.$$

The factor $\sigma < 1$ represents the fact that animals have more contact with one another than they do with humans, in general. Juveniles acquire infection through effective contact with other infectious humans at a rate λ_J, where

$$\lambda_J = \beta_{JJ} \frac{I_J}{N_J} + \beta_{JA} \frac{I_A}{N_A},$$

and where β_{JJ} (respectively, β_{JA}) is the transmission rate at which infectious juveniles (respectively, adults) infect juveniles. Similarly, adults acquire infection through effective contact with other infectious humans at a rate λ_A, where

$$\lambda_A = \beta_{AJ}\frac{I_J}{N_J} + \beta_{AA}\frac{I_A}{N_A},$$

and where β_{AJ} (respectively, β_{AA}) is the transmission rate at which infectious juveniles (respectively, adults) infect adults. Thus, the total force of infection for juveniles is

$$\lambda_J + \lambda_S = \beta_{JJ}\frac{I_J}{N_J} + \beta_{JA}\frac{I_A}{N_A} + \sigma\beta_M\frac{I_M}{N_M}$$

and for adults is

$$\lambda_A + \lambda_S = \beta_{AJ}\frac{I_J}{N_J} + \beta_{AA}\frac{I_A}{N_A} + \sigma\beta_M\frac{I_M}{N_M}.$$

The population of susceptible juvenile is generated through births at a constant rate Λ_J. This class is reduced by natural death at rate μ_H, by vaccination at a rate ν_J (this is included for a retrospective analysis for the time when smallpox vaccination was occurring; for the current situation, one could simply assume $\nu_J = 0$). Juveniles age at rate e, entering the adult classes. Therefore, the equation governing dynamics of the susceptible juveniles is given by

$$\frac{dS_J}{dt} = \Lambda_J - (\lambda_J + \lambda_S)S_J - (e + \nu_J + \mu_H)S_J.$$

The dynamics of the remaining classes are similarly described. Hence, from the schematic diagram of the model depicted in Figure 1, the proposed person-to-person and animal-to-humans monkeypox transmission model is given by the following deterministic systems of nonlinear ordinary differential equations which captures some of the realistic dynamics of the disease:

$$\text{Juvenile}\begin{cases} \dfrac{dS_J}{dt} &= \Lambda_J - (\lambda_S + \lambda_J)S_J - (e + \nu_J + \mu_H)S_J, \\ \dfrac{dS_{JV}}{dt} &= \nu_J S_J - \sigma_J(\lambda_S + \lambda_J)S_{JV} - (e + \mu_H)S_{JV}, \\ \dfrac{dI_J}{dt} &= (\lambda_S + \lambda_J)(S_J + \sigma_J S_{JV}) - (e + \tau_J + d_J + \mu_H)I_J, \\ \dfrac{dR_J}{dt} &= \tau_J I_J - (e + \mu_H)R_J, \end{cases} \tag{0.1}$$

$$\text{Adult}\begin{cases} \dfrac{dS_A}{dt} &= eS_J - (\lambda_S + \lambda_A)S_A - (\nu_A + \mu_H)S_A, \\ \dfrac{dS_{AV}}{dt} &= eS_{JV} + \nu_A S_A - \sigma_A(\lambda_S + \lambda_A)S_{AV} - \mu_H S_{AV}, \\ \dfrac{dI_A}{dt} &= (\lambda_S + \lambda_A)(S_A + \sigma_A S_{AV}) + eI_J - (\tau_A + d_A + \mu_H)I_A, \\ \dfrac{dR_A}{dt} &= \tau_A I_A + eR_J - \mu_H R_A, \end{cases} \tag{0.2}$$

$$\text{Animal}\begin{cases} \dfrac{dS_M}{dt} &= r_M N_M \left(1 - \dfrac{N_M}{K_M}\right) - \lambda_M S_M - (\mu_C + \mu_M)S_M, \\ \dfrac{dI_M}{dt} &= \lambda_M S_M - (\tau_M + d_M + \mu_C + \mu_M)I_M, \\ \dfrac{dR_M}{dt} &= \tau_M I_M - (\mu_C + \mu_M)R_M \end{cases} \tag{0.3}$$

where d_A is the death rate due to monkeypox in adults, d_J is the death rate due to monkeypox in juveniles, μ_H is the death rate due to other causes in adults and juveniles, τ_A is the recovery rate in adults, τ_J is the recovery rate in juveniles, σ_J is the degree to which susceptibility is reduced in vaccinated juveniles, σ_A is the degree to which susceptibility is reduced in vaccinated adults, and other parameters are as defined previously. The region where the above model makes biological sense appears in the Appendix.

Parameter estimation

Here we describe the baseline parameter values obtained from the published literature that were used in simulations. Due to uncertainties in monkeypox natural history and transmission, especially in animal populations, some parameter values had to be set arbitrarily. However, our primary goal in numerical simulation was to illustrate typical dynamics of the model rather than produce plausible quantitative projections for monkeypox epidemiology in specific human populations. Sensitivity analysis was conducted to evaluate the effect of parameter uncertainty on model predictions [13]. For data sources we focus on the Democratic Republic of the Congo (DRC), since 92% of cases in recent decades have occurred there [8]. All parameter estimates are given in Table A-0.1.

Studies of monkeypox outbreaks in the African setting report varying secondary attack rates, ranging from 3.3% to 8.0% [12]. However, the secondary attack rate among unvaccinated individuals is greater than that of individuals who had been vaccinated with the smallpox vaccine [1, 23]. A study of monkeypox outbreaks in the DRC from 1980 to 1984 reported that 130 primary monkeypox cases gave rise to

62 secondary cases [1, 23]. The data from these studies suggest that the R_0 value (the average number of secondary infections produced by a single infectious individual in a purely susceptible population [33]) for monkeypox in humans in the DRC during this time period was less than unity, and this has been confirmed by previous calculations of R_0 [24].

The great majority of monkeypox cases in these outbreaks occurred in children. Although this probably reflected the lower vaccination rate in that age group, transmission tends to be elevated in younger age groups for many infections. Hence, in line with standard assumptions for Who Acquires Infection From Who matrices that dictate the rate at which individuals from one age class infect individuals from another age class, we make the simplifying assumption $\beta_{JJ} \equiv \beta_1$ and $\beta_{AA} = \beta_{AJ} = \beta_{JA} \equiv \beta_2$. Due to uncertainties in monkeypox epidemiology in humans, for numerical results we will simply assume values $\beta_1 = 0.08$ per day and $\beta_2 = 0.04$ per day. We will see that this yields $R_0 < 1$ in humans, and does not lead to large epidemic outbreaks in simulations. Also, individuals remain infectious for approximately 7 days [12] and we assume this does not vary between juveniles and adults. This yields a recovery rate of $\tau_J = \tau_A \equiv \tau = 0.14$ per day.

Smallpox vaccine has an estimated efficacy of 95% [34], hence we assume $\sigma_J = \sigma_A = 0.05$ for the percent reduction in infection risk in vaccinated individuals. The case fatality rate of monkeypox in humans in the DRC during this period was approximately 15% [12]. About 80% of case fatalities occurring in juveniles, which may just reflect the higher incidence in those age groups [10, 12, 17]. Since $\tau_J = \tau_A = 0.14$ per day and $e \ll \tau_J$ and $\mu_H \ll \tau_J$, we take $d_J = d_A = 0.14/0.85 * 0.15 = 0.025$ per day such that 15% of all infected humans die from monkeypox and the remaining 85% recover. Since smallpox vaccination was discontinued after its eradication in 1980, we take $\nu_J = \nu_A = 0$.

The mortality rate $\mu_H = 1/55 = 0.018$ per year is estimated as the reciprocal of the average life span (about 55 years in Central and West African regions). Defining the juvenile age class as those aged 15 years and under, we have $e = 1/15 \approx 0.07$ per year. The DRC yearly growth rate was 4.9% per year in the 1980s [35]. With a total population of approximately 27 million in that country during the 1980s [35], the recruitment rate is approximately $\Lambda_J = 0.049 \times 27$ million $= 1.3$ million per year. Approximately 52% of the population of 27 million were adults in the DRC during the 1980s [35] and if $p_J = 0.1$ and $p_A = 0.93$ as above, then the initial population estimates of each class are as given in Table A-0.1. Finally, we assume for our initial conditions $I_J(0) = 10$ and $I_A(0) = 1$.

Less is known about the epidemiology of monkeypox in animal populations. For illustrative purposes we will assume an endemic infection with $R_0 = 5$ and $\tau_M = 0.14$ per day, hence $\beta_M \approx R_0\tau_M \approx 5{\times}0.14 = 0.7$ per day. Little is also known about how the animal-animal transmission rate differs from the animal-to-human transmission rate, but for illustration we assume $\sigma = 0.1$.

For the baseline parameter values we will take the culling rate $\mu_C = 0$ and we will increase this parameter in simulations to study the effect of culling. The natural history parameters for the animal populations are less important since the transmission for both animals and humans is governed by standard incidence (it depends on the proportion of infectious individuals, not the absolute number). It is only important that the values give qualitatively reasonable outputs. Hence, we assume a carrying capacity of $K_M = 5000$, a natural death rate of $\mu_M = 0.2$ per year, a disease-induced death rate of $d_M = 0.1$ per day, and a reproduction rate of $r_M = 0.5$ per year [36, 37].

Results I: age-structured model

Eradication Threshold

For epidemiological models, a disease threshold quantity, often referred to as the reproduction number, is derived to assess the asymptotic stability of the disease-free equilibrium E_0 given by

$$\begin{aligned} E_0 &= (S_J^0, S_{JV}^0, 0, 0, S_A^0, S_{AV}^0, 0, 0, S_M^0, 0, 0) \\ &= \left(\frac{\Lambda_J}{e+\nu_J+\mu_H}, \frac{\nu_J}{e+\mu_H}S_J^0\ 0,\ 0,\ \frac{e}{\nu_A+\mu_H}S_J^0,\ \frac{1}{\mu_H}\left\{eS_{JV}^0+\nu_A S_A^0\right\},\ 0,\ 0, K_M\left\{1-\frac{\mu_M}{r_M}\right\},\ 0,\ 0\right). \end{aligned} \tag{0.4}$$

Using the next generation operator method and the notation in [33], we have

$$F_i = \begin{pmatrix} \beta_{JJ}(\frac{I_J}{N_J}+\beta_{JA}\frac{I_A}{N_A}+\sigma\beta_M\frac{I_M}{N_M})(S_J+\sigma_J S_{JV}) \\ \beta_{AJ}(\frac{I_J}{N_J}+\beta_{AA}\frac{I_A}{N_A}+\sigma\beta_M\frac{I_M}{N_M})(S_A+\sigma_A S_{AV}) \\ \beta_M\frac{I_M}{N_M}S_M \end{pmatrix}, \quad V_i = \begin{pmatrix} (e+\tau_J+d_J+\mu_H)I_J \\ (\tau_A+d_A+\mu_H)I_A - eI_J \\ (\tau_M+d_M+\mu_C+\mu_M)I_M \end{pmatrix}.$$

Then, taking partial derivatives of F_i and V_i evaluated at the disease-free equilibrium yields

$$F = \begin{pmatrix} \frac{\beta_{JJ}}{N_J^0}(S_J^0+\sigma_J S_{JV}^0) & \frac{\beta_{JA}}{N_A^0}(S_J^0+\sigma_J S_{JV}^0) & \frac{\sigma\beta_M}{N_M^0}(S_J^0+\sigma_J S_{JV}^0) \\ \frac{\beta_{AJ}}{N_J^0}(S_A^0+\sigma_A S_{AV}^0) & \frac{\beta_{AA}}{N_A^0}(S_A^0+\sigma_A S_{AV}^0) & \frac{\sigma\beta_M}{N_M^0}(S_A^0+\sigma_A S_{AV}^0) \\ 0 & 0 & \frac{\beta_M}{N_M^0}S_M^0 \end{pmatrix},$$

$$V = \begin{pmatrix} (e+\tau_J+d_J+\mu_H) & 0 & 0 \\ -e & (\tau_A+d_A+\mu_H) & 0 \\ 0 & 0 & (\tau_M+d_M+\mu_C+\mu_M) \end{pmatrix}.$$

The resulting largest eigenvalue or spectral radius of $\rho(FV^{1})$ is

$$\begin{aligned} R_0 &= \frac{sa + xb + ye + \sqrt{s^2a^2 - 2saxb + 2saye + x^2b^2 + 2xbye + y^2e^2 + 4abry}}{2ab} \\ &= \frac{sa + xb + ye + \sqrt{(sa - xb - ye)^2 + 4a(sey + bry)}}{2ab} \end{aligned} \tag{0.5}$$

where

$$\begin{gathered} a = e + \tau_J + d_J + \mu_H, \quad b = \tau_A + d_A + \mu_H, \qquad x = \tfrac{\beta_{JJ}}{N_J^0}(S_J^0 + \sigma_J S_{JV}^0) \\ y = \tfrac{\beta_{JA}}{N_A^0}(S_J^0 + \sigma_J S_{JV}^0), \quad r = \tfrac{\beta_{AJ}}{N_J^0}(S_A^0 + \sigma_A S_{AV}^0), \quad s = \tfrac{\beta_{AA}}{N_A^0}(S_A^0 + \sigma_A S_{AV}^0) \end{gathered} \tag{0.6}$$

If e is very small, then ye is negligible and therefore

$$R_0 = \frac{s}{2b} + \frac{x}{2a} + \sqrt{\frac{1}{4}\left(\frac{s}{a} - \frac{x}{b}\right)^2 + \frac{ry}{ab}}. \tag{0.7}$$

The disease-free equilibrium of the model system (0.1-0.3) is locally asymptotically stable if $R_0 < 1$, and unstable otherwise (cf. Theorem 2 in [33]). This result means that there are insufficient new cases per case and the disease cannot invade the population [38].

The parameter values of Table A-0.1 lead to $R_0 = 0.24$, which is far less than unity. However, this value of R_0 is based on the arbitrary parameter values of Table A-0.1. It is possible to obtain an estimate of R using a simpler stochastic model as follows. (R is the average number of secondary infections produced by a single infectious individual in a population with some background immunity; R is related to R_0 in a vaccinated population via $R = (1-p)R_0 + pR_v$ where R_v is the reproduction ratio in the fully vaccinated population.) From the data on the outbreak in the DRC, with 130 primary cases and 63 secondary cases, each of which is linked to a single primary case, we estimate the probability q that a primary infection gives rise to a secondary infection as $q \approx 63/130 = 0.48$. Transmission took place mainly in households [23]. If we let N denote the number of individuals in the household, then we assume there are $N-1$ individuals still susceptible in a household with one index case. We consider the general stochastic model with infection and recovery of the index case as follows:

$$(S, I) \to (S-1, I+1) \qquad \text{with probability } \beta_s \tfrac{SI}{N} \tag{0.8}$$

$$(S, I) \to (S, I-1) \qquad \text{with probability } \alpha_s I \tag{0.9}$$

where β_s is the transmission rate and α_s is the recovery rate. Thus, because infection and recovery are competing risks, the probability q that a primary case infects a secondary case among $S = N-1$ susceptible individuals in the household before recovering is:

$$q = \frac{\beta \frac{SI}{N}}{\beta \frac{SI}{N} + \alpha I} = \frac{RS}{RS + N} = \frac{R(N-1)}{R(N-1) + N} \tag{0.10}$$

where we used $R \approx \beta/\alpha$. Solving this for R yields

$$R = \frac{Nq}{(1-q)(N-1)} \tag{0.11}$$

and thus with $q \approx 0.48$ we have $R = 1.84$ for $N = 2$, $R = 1.38$ for $N = 3$, and $R = 0.92$ as $N \to \infty$. Also, we note $R > 1$ when $N < 13$, and that whenever the observed $q > 0.5$ it follows that $R > 1$. Given the inherent uncertainty regarding the contact group size N (which might be estimated by household size) and the estimated q (which might be > 0.5), according to these arguments it is therefore uncertain whether $R < 1$ for monkeypox in humans. We note that this is only the start of the chain of infection events and it does not take into account that all other susceptible individuals do not get infected (neither by the index case nor by the subsequent secondary cases), or other factors such as heterogeneity in household size or in susceptibility and infectivity among individuals. We also note that none of the secondary cases created further cases in this outbreak, which may be due to behavioural changes or preventive measures implemented after finding the primary cases, that our calculation does not account for.

In animals, the case reproduction number is $R_M = 2.9$. Our parameterizations capture how the disease has the capability to spread in animal species [12], where it seems to have established a reservoir while only sporadically causing human disease. Because the disease persists in wild animals with a wide range of host, this would make global eradication difficult, and due to this impediment, sporadic cases in humans may be expected from time to time.

Impact of culling and changes in animal-human contact rates on monkeypox prevalence

While the elasticity index gives an idea of model sensitivity in the neighborhood of a fixed set of parameter values, it does not tell us how monkeypox prevalence varies when changes in parameter values are large. To investigate this, we ran a series of numerical simulations of the model. We projected the equilibrium monkeypox prevalence in human juveniles (Figure 2a) and adults (Figure 2b) as a function of the culling rate μ_C, for four different values of the animal-human contact rate σ. We also projected the equilibrium monkeypox prevalence in human juveniles (Figure 3a) and adults (Figure 3b) as a function of the animal-human contact rate σ, for four different values of the culling rate μ_C. All other parameter values were taken from Table A-0.1.

Since an increase in the culling rate should protect humans, we might expect that monkeypox prevalence in both juveniles and adults decreases as the culling rate μ_C increases. Likewise, we might expect that monkeypox prevalence in both juveniles and adults increases as the animal-human contact rate σ increases. However, this is not always the case. In adults, monkeypox prevalence decreases as the

culling rate increases (Figure 2b), but in juveniles, surprisingly, it actually increases as the culling rate increases (Figure 2a). This occurs because the recruitment of susceptible animals occurs through a density-dependent process according to $r_M N_M(1 - N_M/K_M)$. Both healthy and infected animals are culled. Density-dependent fecundity means that the birth rate of susceptible animals goes up as the overall population density goes down. Hence, as animals with natural immunity are culled, the birth rate of susceptible animals goes up, with the net effect that prevalence in animals goes up, and thus also prevalence in human juveniles, who are more susceptible than human adults. To confirm this mechanism, we also simulated the model by replacing density-dependent fecundity with a constant birth rate (results not shown). We found that increasing culling always decreased monkeypox prevalence in both juveniles and adults, which is to be expected in a situation where fecundity does not respond to culling when the birth rate is constant. Hence, for some parameter values, non-discriminate culling of animal reservoirs could actually increase the prevalence of monkeypox in human juveniles, who are the most vulnerable part of the human population.

The dependence of monkeypox prevalence in humans on changes in the animal-human contact rate σ also contains some surprises (Figures 3a, 3b). In juvenile humans, prevalence increases as σ increases as expected (Figure 3a). But in adults, it actually decreases as σ increases, when the culling rate μ_C is nonzero (Figure 3b). This occurs because increasing σ results in more infected juveniles and hence more recovered/naturally immune juveniles. This large cohort of more immune juveniles becomes a cohort of more immune adults, and thus monkeypox prevalence is less in the adult years, at least at equilibrium. Therefore, the impact of culling can depend sensitively both on assumptions about how the natural population rebounds from culling efforts as well as specific assumptions about how much contact there is between humans and animals.

Predicted dynamics in absence of smallpox-derived immunity

We can evaluate hypothetical scenarios, such as monkeypox prevalence in the same population without smallpox-derived vaccine protective immunity; this might apply in the future when the last birth cohorts that were immunized by smallpox or infected by smallpox vaccine have disappeared from the population. This corresponds to the current disease state and the basic reproduction number is $R_{01} = 0.45$. Thus, if there were to be an outbreak with the same strain, we should expect almost a 88% increase in transmission in the early stages of the outbreak. This expectation is consistent with the small rise in secondary cases in the 1997 outbreak (78% in 1997 versus 9-28% in 1970-86) [12], which was attributed to an attenuation in immunity after the cessation of smallpox vaccination in the early 1980s [42], and supports the major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns ceased in the Democratic Republic of Congo [7].

Impact of age structure in humans

Next, we explore how neglecting age structure in humans may influence model predictions. If the population is not stratified into age classes, then we have

$$R_{0H} = \frac{\beta_H}{\tau_H + d_H + \mu_H}, \tag{0.12}$$

with a value of $R_{0H} = 0.36$. The value in the presence of age structure was $R_0 = 0.24$. Hence, assuming homogeneous mixing across the entire population and ignoring age classes leads to an overestimate of the secondary attack rate by approximately 25%. Despite this, the threshold quantity (R_0 or R_{0H}) for the disease control which defines the number of secondary infections produced by a single infected individual in a completely susceptible population remains below 1, precluding an outbreak in humans. However, even when $R_0 < 1$, higher values of R_0 cause more secondary infections in the sporadic outbreaks that do occur. Indeed, Gaff et al., [38] pointed out that unlike values of R_0 for directly-transmitted diseases, the magnitude of the reproduction number does not necessarily scale in proportion to the intensity of the epidemic/epizootic transmission.

Some model parameters were estimated from information at our disposal as found in the literature, while other parameter values cannot be known exactly. In the latter case, parameter values can be set within biologically realistic bounds and we can check how sensitive the predicted disease transmission dynamics are to changes in the input parameters [39, 13]. In particular, a deterministic sensitivity analysis involving computation of an 'elasticity' index, which governs how sensitive model output is to a given input parameter, can be computed [40]. Sensitivity analysis also allows us to determine the relative importance of the different factors controlling monkeypox transmission and prevalence [41].

Given that culling can be a controversial strategy since locating infected wild animals may be daunting task (hence our assumption that both healthy and infected animals are culled), we nevertheless focus on this parameter to assess how sensitive the model outcome is with respect to culling. The elasticity of the culling factor μ_C with respect to the animal only reproduction number $\Re_M$ is -0.446. Thus, at baseline parameter values, increasing culling is expected to reduce secondary transmission. That is, a 10% increase of the culling rate leads to a 4.46% decrease in initial disease spread in animals. We note however that numerical simulations reveal that for some parameter values, if animal reproduction is a density-dependent process, culling can actually have the counter-productive outcome of increasing monkeypox infection in children.

Methods II: meta-population model

The broad host range of monkeypox and sero-prevalence studies suggest that several animal species act as reservoirs for monkeypox in nature [3]. Many species are infected with monkeypox virus under natural conditions, including squirrels, non-human primates, and rats. This has important public health implications for the transmission to exotic animals and the subsequent risk of human outbreak because the reservoir potential of these species is not known. It also has implications for how monkeypox is modeled, since several different populations consisting of different species can be responsible for sustaining transmission between animal reservoirs as well as between animals and humans.

The dynamics of disease spread between populations living in distinct 'patches' can vary substantially from dynamics in single populations, and the resulting differences in dynamics have implications for disease control [43, 13, 44, 25, 45]. Here, we formulate a meta-population monkeypox transmission model with n regions for the animal species. Dispersion among patches is represented by migration with constant proportions of migrants [46]. Let the subscript i denote the region i $(1 \leq i \leq n)$, let n_{ij} be the migration rate of susceptible animals from the j^{th} region to the i^{th} region, and m_{ij} is similarly defined for the infective animals. We assume $i \neq j$ always. The foregoing approach is adapted from [25, 45]. Thus, the animal meta-population model with culling is given by

$$\begin{aligned} \frac{dS_i}{dt} &= r_i N_i \left(1 - \frac{N_i}{K_i}\right) - \lambda_i S_i - (\mu_i + \mu_{ci}) S_i + n_{ij} S_j - n_{ji} S_i, \\ \frac{dI_i}{dt} &= \lambda_i S_i - (\tau_i + d_i + \mu_i + \mu_{ci}) I_i + m_{ij} I_j - m_{ji} I_i. \end{aligned} \tag{0.13}$$

where we dropped the subscript M for easy readability. Each population is bounded above by

$$S_i \leq K_i. \tag{0.14}$$

When $n = 2$, the disease control threshold is given by

$$\mathcal{R}_M = \frac{1}{2s}\left(P + Q + \sqrt{(P-Q)^2 + 4\beta_1\beta_2 m_{12} m_{21}}\right), \tag{0.15}$$

where

$$\begin{aligned} P &= \beta_1[(\mu_1 + d_1 + \mu_{c1}) + m_{21}], \qquad Q = \beta_2[(\mu_2 + d_2 + \mu_{c2}) + m_{12}], \\ s &= [(\mu_1 + d_1 + \mu_{c1}) + m_{21}][(\mu_2 + d_2 + \mu_{c2}) + m_{12}] - m_{12} m_{21}. \end{aligned} \tag{0.16}$$

Additional analytical details on the metapopulation model is provided in the Appendix. It is important to note that the expression in (0.15) is closely related to that in (0.7) since in the latter, the human population is subdivided into two classes. To study the impact of meta-populations, we can also assume that one or both of these patches are connected to the human population as through Equations 0.3.

Results II: meta-population model

We use the meta-population model to explore the impact of spatial structure on the potential success of culling strategies. We assume $n = 2$ (two patches). Except where noted, we assume the parameter values given in Table A-0.1. We furthermore assume that the human population is only in contact with patch 1. We consider three cases:

Case 1: Culling is applied only to patch 1, and there is no migration between patches 1 and 2. In this case, the migration rates are $m_{ij} = n_{ij} = 0$, the culling rate $\mu_C = 0$ for patch 2 and we explore a range of values for μ_C in patch 1. The case $m_{ij} = n_{ij} = 0$ corresponds to isolated populations and hence the disease dynamics of patch 2 have no impact on disease dynamics in patch 1 or in humans (however, disease dynamics in patch 1 do influence what happens in humans). This case reduces to the previous (single patch, age-structured) model, since there is no migration between patches 1 and 2. As for the single patch case, we observe that increasing the culling rate increases the prevalence of monkeypox infection in juvenile humans and decreases the prevalence of monkeypox infection in adult humans (Figure 4a,b).

Case 2: Culling is applied only to patch 1, and there is migration between patches 1 and 2. In this case, for migration rates we assume fairly well-connected patches with relatively high migration rates: $m_{12} = m_{21} = 0.05$ per day and $n_{12} = n_{21} = 0.1$ per day (m values are lower than n values since infected animals are less likely to travel between patches). $\mu_C = 0$ for patch 2 and we explore a range of values for μ_C in patch 1. Intuitively, one might expect a strong effect relative to Case 1, since the culled patch is receiving imports from the non-culled patch. However, the actual effect is very slight and applies mostly to adult humans (Figure 4a,b). This could be because culling rates are the same in healthy versus infected animals.

Case 3: Culling is applied to both patch 1 and patch 2, and there is migration between patches 1 and 2. In this case, for migration rates we assume fairly well-connected patches with $m_{12} = m_{21} = 0.05$ per day and $n_{12} = n_{21} = 0.1$ per day, as in Case 2. We assume the same value of μ_C is applied in both patches and we explore a range of values in μ_C. Intuitively, one might expect differences from Cases 1 and 2 since now culling is being applied in both patches. However, the results are the same as in Case 1 (Figure 4a,b).

Taken together, these results suggest that disease dynamics in animal reservoirs within which humans are not in direct contact do not necessarily have a significant impact on monkeypox in humans. However, a more adequate exploration of meta-population effects would require an exploration of greater regions of parameter space, a study of transient solutions as well as equilibrium solutions, and more realistic model

features such as greater population heterogeneity, stochasticity and rescue effects between patches.

Discussion

Human monkeypox is a zoonosis that occurs sporadically in the tropical rain forests of western and central Africa, and only occasionally infects humans [23]. Historical data from a variety of locations show occasional small outbreaks of monkeypox in humans separated by long disease-free periods. Here, we developed an age-structured model of monkeypox transmission in humans, and coupled it to a simple model of monkeypox transmission in animal populations. Recruitment in the animal population occurred through density-dependent fecundity. We explored the effect of culling interventions and the sensitivity of model predictions to changes in the animal-human contact rate.

On account of the assumption of density-dependent fecundity, we found that culling can produce counter-productive outcomes, in some cases actually increasing the equilibrium prevalence of monkeypox in children. We concluded this based on an analysis of model equilibria, but the answer may change if transient solutions were considered instead. Intuitively, the mechanism by which culling causes increased prevalence in children (removing mature, immune animals who are then replaced by juvenile, susceptible animals that fuel further outbreaks) depends on the timescale associated with culling versus the timescale associated with animal reproduction. In the very short term, culling should not increase monkeypox incidence since it takes time for a pool of susceptible animals to be built up again. However, in the longer term, the resulting build-up of susceptible animals may be responsible for heightened monkeypox incidence in humans in future outbreaks.

We also found that adding meta-population structure did not necessarily change the predicted impact of culling strategies. These findings suggest that the predict impact of culling depends to a significant degree on model assumptions, and therefore culling should not be implemented without a thorough understanding of disease transmission and demographic processes in the animal reservoirs that sustain monkeypox. We also found that removing age structure from the model increased the estimated basic reproduction number in humans, which again suggests that model structure should be carefully considered when using models to evaluate the impact of monkeypox interventions such as culling. Culling is also controversial on other grounds. For instance, it may be counterproductive in that it may actually require an increase in contacts during the culling process, especially in poor settings where barrier precautions are too expensive. Additionally, many animals are members of protected species. For instance, many primates are protected under national and international legislation (e.g., the Convention on International Trade in Endangered Species of Wild Fauna and Flora). By comparison, focusing on contact reduction can provide similar or better results than culling.

Sensitivity analysis indicated that culling can contribute in reducing initial disease transmission in the animal reservoir, but this may not be without consequences as numerical simulations reveal that this could be a counterproductive strategy that may contribute to increasing monkeypox infection in children if animal reproduction is a density-dependent process. Results illustrated how diminishing immunity derived from smallpox vaccination or infection could cause an increase in the number of cases, as noted in [7] where a large increase in human monkeypox incidence was observed 30 years after smallpox vaccination campaigns ceased in the Democratic Republic of Congo.

For mathematical tractability and convenience, several assumptions were made in the formulation and model analysis on which the results are based. These simplifying assumptions enabled analysis of the model and particularly, estimation of a basic reproduction number. However, simplifying assumptions can also introduces biases. In this case, important model limitations included (1) lack of explicit spatial structure, (2) lack of stochasticity, (3) lack of data with which to parameterize the model, especially in the animal reservoir, and (4) relative lack of population heterogeneity in both humans and animals. Model extension could deal with some of these limitations, however, empirical studies of monkeypox epidemiology in animal populations and the human-animal contact interface are required to populate the significant increase in the number of model parameters that would accompany development of a more sophisticated model structure.

Our models suggest that the impact of interventions can sometimes be different from expected. In particular, interventions such as culling might even have counter-productive consequences. Model predictions also depend sensitively and qualitatively on assumptions about age structure, spatial structure, degree of contact between humans and animals, and demographic processes in the animal reservoir. Better data on monkeypox epidemiology in animal populations and transmission routes between animals and humans is required to parameterized more sophisticated and realistic models. As a future trend, we anticipate an increasing partnership between theoretical and field researchers that will facilitate the development of such data-driven models for the control of monkeypox that could be used to inform control policy.

Summary

Monkeypox is a neglected but emerging disease that did not seem to pose a global threat until accidentally introduced into the United States in 2003. It is a viral zoonosis (occurring through animal-to-human transmission) that is endemic to central and western Africa, and is caused by a member of the orthopoxvirus genus. Although it has been known for decades that the virus seems to be poorly adapted to spread among humans, its transmissibility in humans has been rising slightly due to waning of immunity associated with past smallpox vaccination. The absence of effective therapeutic measures

furthermore raises concern about its potential use as a bioterrorism agent. Based on the spread mechanisms of monkeypox, deterministic models (age-structured and metapopulation) are formulated for humans and animals to study its transmission dynamics. We derive an expression which tells us how many secondary cases are produced per initial human monkeypox case, and we also evaluate the effectiveness of culling strategies by demonstrating how culling and age-structure influence the spread of monkeypox in human. The results indicate that the influence of culling depends on whether animal reproduction is a density-dependent process and the ignorance of age class leads to an overestimate of the secondary attack rate. Under certain conditions, culling of animals could actually have the counterproductive outcome of increasing monkeypox infections in children. Hence, more empirical studies of the demography and epidemiology of animal reservoirs of monkeypox infection are required before we can understand whether control strategies such as culling are likely to work. Numerical simulations are provided to illustrate the results, but there is a limitation to have real data to fit the epidemiological models.

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Competing Interests

The authors declared that no competing interests exist.

APPENDIX A

Model invariant region

For the model to be epidemiologically meaningful, all solutions must be non-negative and bounded. Let N_J, N_A and N_M denote the total number of juvenile, adults and monkeys, respectively. Then, the

feasible region for each sub-model is given by:

$$\mathcal{D}_J = \left\{(S_{JV}, S_J, I_J, R_J) \in \mathbb{R}^4_+ : \ N_J \leq \frac{\Lambda_J}{e+\mu_H}\right\},$$

$$\mathcal{D}_A = \left\{(S_{AV}, S_A, I_A, R_A) \in \mathbb{R}^4_+ : \ N_A \leq \frac{e\Lambda_J}{\mu_H(e+\mu_H)}\right\},$$

$$\mathcal{D}_M = \left\{(S_M, I_M, R_M) \in \mathbb{R}^3_+ : \ N_M \leq K_M\right\}.$$

Thus, the feasible region for the model is given by

$$\mathcal{D} = \mathcal{D}_J \times \mathcal{D}_A \times \mathcal{D}_M \subset \mathbb{R}^4_+ \times \mathbb{R}^4_+ \times \mathbb{R}^3_+, \tag{A-1}$$

which is positively invariant (with non-negative solutions) and attracting, so that solutions in $\mathcal{D}$ remain in there $\forall\ t \geq 0$.

A-0.1 The disease-free equilibrium and its stability

We focus only on the the disease-free equilibrium (disease-free equilibrium) because monkeypox infection has never reach epidemic proportion, at least at the human level. The disease-free equilibrium E_0 corresponds to the absence of infection in the population. The dynamics at the disease-free equilibrium consist of two types of flows: the demographic renewal flow and the vaccination flow. Since vaccination programs have been halted ($\nu_J = 0 = \nu_A \Rightarrow S_{JV} = 0 = S_{AV}$), and a present day model will have as disease-free equilibrium

$$E_{00} = \left(\frac{\Lambda_J}{e+\mu_H},\ 0\ 0,\ 0,\ \frac{e\Lambda_J}{\mu_H(e+\mu_H)},\ 0,\ 0,\ 0, K_M\left\{1-\frac{\mu_M}{r_M}\right\},\ 0,\ 0\right).$$

The impact of ν_J and ν_A on the disease threshold parameter have been investigated above. The linear stability of E_0 is governed by the reproduction number $\mathcal{R}_0$ given by eq. (0.7), and from Theorem 2 in [33], the following results holds.

Lemma A-1 *The disease-free equilibrium of the model is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable otherwise.*

Details on the metapopulation model

Case 1. The two regions are isolated
In this case,

$$\mathcal{R}_{0i} = \frac{\beta_i S_i^0}{\mu_i + \tau_i + d_i + \mu_{ci}}.$$

Thus,

$$\mathcal{R}_M = \sum_{i}^{2} \mathcal{R}_{0i}. \tag{A-2}$$

Case 2. Only susceptible monkeys are allow to travel

It is assumed here that proper screening before transportation to other countries/continent ($m_{ij} = 0$). This case is important in its own right. The disease threshold reduces to

$$\begin{aligned} \mathcal{R}_{01} &= \frac{\beta_1 S_1^0}{\mu_1 + \tau_1 + d_1 + \mu_{c1}}, \qquad \mathcal{R}_{02} = \frac{\beta_2 S_2^0}{\mu_2 + \tau_2 + d_2 + \mu_{c2}}, \\ \mathcal{R}_0 &= \max(\mathcal{R}_{01}, \mathcal{R}_{02}) \end{aligned} \tag{A-3}$$

where

$$S_1^0 = \left[\left(1 - \frac{\mu_1 + n_{21} + \mu_c}{r_1} \right) + \frac{n_{12} n_{21}}{\mu_1(\mu_2 + n_{12} + \mu_{c2})} \right] K_1, \quad S_2^0 = K_2.$$

$r_1 > \mu_1 + n_{21} + \mu_c$ and (S_1^0, S_2^0) is the biologically feasible solution of $S_1(r_1 a_2 - a_1 a_2 + n_{12} n_{21} - a_2 b_1 S_1) + n_{12} S_2(r_2 - b_2 S_2) = 0$ where $a_1 = \mu_1 + n_{21} + \mu_{c1},\ a_2 = \mu_2 + n_{12} + \mu_{c2},\ b_1 = r_1/K_1,\ b_2 = r_2/K_2$.

Case 3. Travel between the two patches is unidirectional

The disease may show up in other parts of the world [2], e.g. from Africa to any other continent (the obvious example here is the 2003 US outbreak). If animals only travel from region one to region two, then

$$\mathcal{R}_0 = \max\left(\frac{\beta_1 S_1^0}{\mu_1 + \tau_1 + d_1 + \mu_{c1}},\ \frac{\beta_2 S_2^0}{\mu_2 + \tau_2 + d_2 + \mu_{c2} + m_{12}} \right), \tag{A-4}$$

where for this case $S_2^0 = \left(1 - \dfrac{\mu_2 + n_{12}}{r_2} \right) K_2$, with $r_2 > \mu_2 + n_{12}$ and S_1^0 being the positive solution of the equation $b_1 S_1^2 - (r_1 - \mu_1) S_1 - n_{12} S_2^0 K_2 = 0$.

We note that in case 1, the disease is driven by the population with the largest disease threshold. If all the parameters are equal in the second case, then the disease will be driven by the population with the greatest initial number of individuals. Again, with all parameters equal as well as $S_1^0 = S_2^0$ in case 3, the disease will be driven by population 2 since in this case, $\mathcal{R}_{01} < \mathcal{R}_{02}$.

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Variable	Description	Initial value	Reference
S_J	Susceptible juveniles	11.6 million	Estimated [35, 23, 1]
S_{JV}	Susceptible juveniles previously vaccinated	1.3 million	Estimated [35, 23, 1]
I_J	Infected juveniles	10	Assumption
S_A	Susceptible adults	1.0 million	Estimated [35, 23, 1]
S_{AV}	Susceptible adults previously vaccinated	13.1 million	Estimated [35, 23, 1]
I_A	Infectious adults	1	Assumption

Parameter	Description	Baseline value	Reference
Λ_J	Human recruitment rate	1.3 million per year	[35]
β_{JJ}	Juvenile-Juvenile transmission rate	0.08 per day	Assumed; [23, 1]
$\beta_{JA}, \beta_{AJ}, \beta_{AA}$	Juvenile-Adult, Adult-Juvenile, Adult-Adult transmission rates	0.04 per day	Assumed; [23, 1]
σ_J, σ_A	Reduction in infection risk due to smallpox vaccine	0.05	[34]
ν_J, ν_A	Vaccination rate (for variola)	0	n/a
e	Aging parameter	0.07 per year	Assumed
τ_J, τ_A	Human recovery rates	0.14 per day	[12]
d_J, d_A	Disease-induced human death rates	0.025 per day	[12]
μ_H	Human natural death rate	0.018 per year	[35]
σ	Percent reduction in animal-human transmission, compared to animal-animal	0.1	Assumed
β_M	Effective animal transmission rate	0.7 per day	Assumed
r_M	Animal intrinsic growth rate	0.5	[36]
K_M	Animal carrying capacity	5000	Assumed
μ_C	Animal constant culling rate	0	n/a
μ_M	Animal natural death rate	0.2 per year	Assumed
d_M	Disease-induced death rate for animals	0.1 per day	Assumed
τ_M	Recovery rate in animals	0.14 per day	Assumed

Table A-0.1: Variable and parameter description. All parameters are per capita except where otherwise stated.

Figure Legends

Figure 1: Schematic model flowchart depicting the compartmental model described by the system of equations 0.1-0.3.

Figure 2: Disease prevalence in (a) juveniles and (b) adults at the model equilibrium for four different σ values $0, 0.05, 0.1, 0.2$, versus the culling rate μ_C ranging from 0 to 0.1 per day.

Figure 3: Disease prevalence in (a) juveniles and (b) adults at the model equilibrium for four different culling rate μ_C values $0, 0.01, 0.05, 0.1$ per day, versus σ ranging from 0 to 0.2.

Figure 4: Disease prevalence in (a) juveniles and (b) adults at the metapopulation model equilibrium for three different cases (see text) versus culling rate μ_C.