A game-theoretic model of Monkeypox to assess vaccination strategies

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ABSTRACT

Monkeypox (MPX) is a zoonotic disease similar to smallpox. Its fatality rate is about 11% and it is endemic to the Central and West African countries. In this paper, we analyze a compartmental model of MPX dynamics. Our goal is to see whether MPX can be controlled and eradicated by voluntary vaccinations. We show that there are three equilibria - disease free, fully endemic and previously neglected semi-endemic (with disease existing only among humans). The existence of semi-endemic equilibrium has severe implications should the MPX virus mutate to increased viral fitness in humans. We find that MPX is controllable and can be eradicated in a semi-endemic equilibrium by vaccination. However, in a fully endemic equilibrium, MPX cannot be eradicated by vaccination alone.

1 INTRODUCTION

Monkeypox (MPX) is a zoonotic disease that has the potential to develop into one of the most threatening human *Orthopoxvirus* infections since the eradication of smallpox (Durski et al., 2018). The causative agent of MPX is monkeypox virus (MPXV), found in the same genus as the variola virus (smallpox), vaccinia virus, and cowpox virus (Shchelkunov et al., 2006; Sklenovská and Van Ranst, 2018). Common symptoms of MPX, though relatively milder than smallpox, include fever, severe headaches, skin lesions, and myalgia (CDC, 2003). Prevention of the disease has remained a challenge for poverty-stricken rural areas with poor infrastructure that lack necessary sanitary supervision (Sklenovská and Van Ranst, 2018).

MPX is endemic to Central Africa and West Africa (Weinstein et al., 2005; Yinka-Ogunleye et al., 2018). West African and Central African strains of MPXV exist, the latter of which is more virulent and symptomatically severe (Likos et al., 2005; Mwamba et al., 2014). In the Democratic Republic of the Congo (DRC) the mortality rate of the Central African strain is 11% (Ježek et al., 1987). Since the first case of human infection in 1970, there have been numerous outbreaks in the DRC (Eteng et al., 2018). Annually, the DRC reports over 2,000 cases of suspected infections (Mwamba et al., 2014). This estimate may be modest, as MPX is often misdiagnosed as chickenpox or other diseases that cause rashes (Ježek et al., 1988). Additionally, modern and robust surveillance of MPX is neglected as a consequence of limited funds and resources (Rimoin et al., 2010), and countries other than the DRC are not required to report all cases of MPX (Durski et al., 2018). Thus, the disease may be more severe than previously estimated.

In 2003, 47 cases of MPX were reported across 5 states in the U.S., originating from a shipment of animals from Ghana imported to Texas (CDC, 2003). In 2018, 3 cases of MPX were reported in the

United Kingdom, making it the first time since the 2003 United States outbreak that the disease had reached a country outside of Africa (Eteng et al., 2018).

The clinical presentation of MPX can be found in Di Giulio and Eckburg (2004). The incubation period for the virus ranges from 5 to 21 days. MPX infection is split into 2 distinct phases: the invasion period and the skin eruption period. The invasion period starts between 0-5 days and is characterized by fever, lymphadenopathy, intense asthenia, severe headaches, and myalgia. The skin eruption period occurs 1-3 days after the appearance of a fever or lymphadenopathy, and it is characterized by rash formation, which often begins on the face and spreads to the rest of the body. The rash first appears as maculopapules (lesions with flat bases) and progresses to fluid filled blisters called vesicles. The vesicles then burst, forming pustules, and a crust forms over the affected area within 10 days. The number of lesions formed can vary from a few to thousands across the body, with children reportedly experiencing more severe symptoms than adults.

The predominant mode of MPX transmission is through human-animal interaction. Direct contact with an infected animal's blood, bodily fluids, or lesions can lead to infection. Documented cases of MPX in Central and West Africa show that transmission can occur via the handling of wild animals (Reynolds et al., 2017). Cultural influences, such as consumption of "bush meat," can be a potential source of transmission. Additionally, direct contact with an infected person's bodily fluids and skin lesions can lead to the transmission of the disease (McCollum and Damon, 2013).

Despite MPX's high case fatality rate (Ježek et al., 1987) there are no known cures (Eteng et al., 2018). Until recently, there were no disease-specific preventative measures such as vaccines, though existing smallpox vaccines have historically been around 85% successful (Eteng et al., 2018). However, administration of the smallpox vaccine has ceased since the disease's eradication in 1980, resulting in lowered immunity against *Orthopoxviruses* in general. This has led to a supposed increase in population susceptibility to MPXV (Sklenovská and Van Ranst, 2018). In 2019, the vaccine termed Jynneos® was approved by the US FDA for protection against VARV and MPXV (Meyer et al., 2020).

It is possible that this lack of preventative measures is partially explained by a matching lack of literature on the potential dangers of inter-human transmission of MPX (Rimoin et al., 2010; Mwamba et al., 2014; Doshi et al., 2018; Sklenovská and Van Ranst, 2018). The urgency of better understanding of MPX is exacerbated considering vaccination cessation and immunocompromised populations in Central Africa, so a need for comprehensive preventative strategies is apparent (WHO, 2017). The factors such as (1) a lack of an effective vaccination strategy from fixed bases, (2) a shortfall in the vaccine supply and (3) logistical and security problems associated with the distance from the health centers, all contribute to the challenges of vaccinating the whole population in Central and Western Africa (Herp et al., 2003).

The identity of MPXV reservoir host(s) remains unknown (Di Giulio and Eckburg, 2004; Falendysz et al., 2017). The seroprevalence of MPXV was found highest in a population of moribund rope squirrel (*Funisciurus anerythrus*) in Zaire (now DRC), and it was also found in sun squirrels (*Heliosciurus rufobrachium*) and non-human primates in DRC (Khodakevich et al., 1987, 1988) as well as in Gambian pouched rats (*Cricetomys gambianus*) (Doty et al., 2017; Doshi et al., 2019). In West Africa, African dormice (*Graphiurus sp.*), and ground squirrels (*Xerus sp.*) were identified as additional hosts (Reynolds et al., 2010). The majority of reported human cases originate from an interaction with an infected animal (Arita et al., 1985). The transmission of MPX among animals can be affected by environmental conditions (Brown and Leggat, 2016). Deforestation and flooding could potentially increase or decrease the MPX reservoirs, depending on how the animal population is affected by these conditions (Brown and Leggat, 2016). Long-distance transportation of potential MPX carriers may result in the expansion of the geographical range of the MPX reservoir, as exemplified by the 2003 U.S. outbreak.

Currently, MPXV likely needs the animal reservoir as the human-to-human transmission chains of MPX are relatively short; the maximum number of generations reported in literature is seven (Learned et al., 2005). Nevertheless, as demonstrated by the case of H1N1 influenza (swine flu), some virus mutations can increase viral fitness in humans (Elderfield et al., 2014). We note that poxviruses have linear, double-stranded DNA genomes that vary from 130 to 230 kbp (Moss, 2013) and as such are evolving much slower than H1N1. Nevertheless, they can still adapt rapidly (Elde et al., 2012) and genetic engineering and modern molecular biology already turned a mousepox virus into unusually lethal strain (Jackson et al., 2001; Di Giulio and Eckburg, 2004).

Epidemiologic compartmental models have been used to better understand the potential implications of disease transmission and infection (Blackwood and Childs, 2018; Bidari and Goldwyn, 2019). For

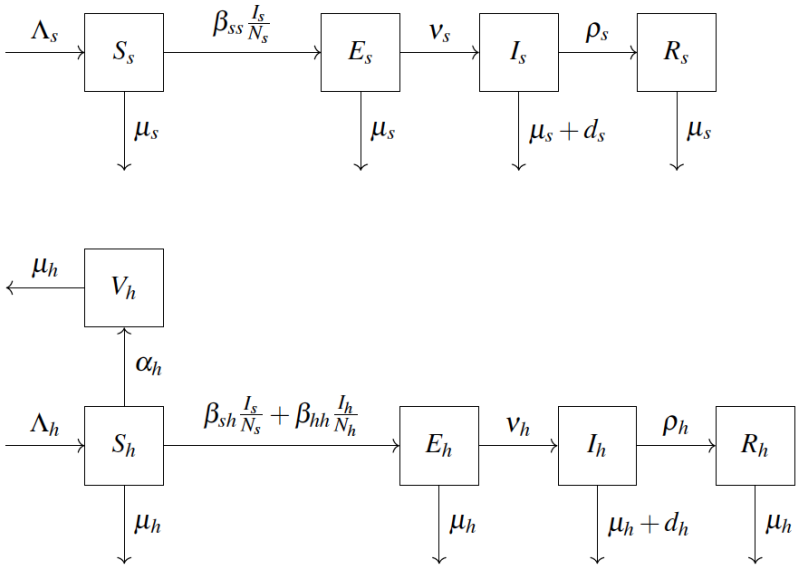

Figure 1. Scheme of mathematical model for humans and squirrels, adapted from Usman and Adamu (2017).

MPX, the framework for a mathematical model has been tentatively set, but existing iterations have had shortcomings, failing to address some of the aforementioned aspects of the disease in their entirety. Bhunu and Mushayabasa (2011) introduced a basic SIR vector-borne compartmental model between humans and primates, yet deem an endemic state solely in humans as trivial. Usman and Adamu (2017) build upon this framework by introducing an SVEIR compartmental model to account for the disease's incubation period and potential vaccine.

Game theoretical models attempt to study complex scenarios in which self-interested individuals will take an action based on the decisions of the rest of the population (Bauch and Earn, 2004). The model is a predictive tool in populations for extracting an optimum decision-making strategy (Chang et al., 2020). Game theory has been applied to protection strategies to control diseases such as smallpox (Bauch et al., 2003), toxoplasmosis (Sykes and Rychtář, 2015), cholera (Kobe et al., 2018), measles (Shim et al., 2012), rubella (Shim et al., 2009), influenza (Galvani et al., 2007), African sleeping sickness (Crawford et al., 2015), malaria (Orwa et al., 2018; Broom et al., 2016), zika (Padmanabhan et al., 2017; Bañuelos et al., 2019), polio (Cheng et al., 2020), Ebola (Brettin et al., 2018), chikungunya (Klein et al., 2019), meningitis (Martinez et al., 2019), typhoid (Acosta-Alonzo et al., 2020), Hepatitis C (Scheckelhoff et al., 2019) or Hepatitis B (Chouhan et al., 2019) among others. In this paper, we apply a similar approach to MPX to investigate a scenario in which individuals have the option of vaccinating to reduce the chance of contracting the virus. We further evaluate vaccination strategies on an individual and population-wide level by discussing the vaccination rates required to achieve herd immunity and Nash equilibrium.

In the present paper, we build on the work of Usman and Adamu (2017), see also Lauko et al. (2018) for a simplified SIR version of the model. The mathematical model of the MPX dynamics is shown in Section 2. In Section 3.1, we provide closed-form formulas for equilibrium states of MPX dynamics; the formulas provided in Usman and Adamu (2017) do not allow for direct calculations of the equilibria. We also show the existence of a "semi-endemic" equilibrium. This was not previously discussed in Usman and Adamu (2017), although it appears in Lauko et al. (2018). In Section 3.2, we apply a game-theoretic approach to evaluate individual and population-wide vaccination strategies on the basis of cost and probabilistic disease acquisition. In Section 3.3 we perform sensitivity analysis. We conclude the paper by a discussion in Section 4.

2 MATHEMATICAL MODEL

We adopt the compartmental epidemiological model introduced in Usman and Adamu (2017) and shown in Figure 1. We consider squirrels to be the primary reservoir hosts. The population is divided into

Table 1. Model parameters. The human MPX related death rate was taken as a solution to $d_h/(d_h+\rho_h) = 0.1$ where 10% is the MPX fatality (Ježek et al., 1987). Similarly, squirrel MPX related death rate was taken as a solution to $d_s/(d_s+\rho_s) = 0.6$ where 60% is an estimate for the MPX fatality found between 50-75% (Falendysz et al., 2017). We estimated the effective squirrel-to-squirrel transmission rate as $\beta_{ss} = 40$; this yields about 24% of seropositive squirrels in the population, a number that agrees with estimates from Khodakevich et al. (1988). The effective transmission rates between humans was estimated as $\beta_{hh} = 32.85$ as follows. Arita et al. (1985) provide transmission risk $p = 0.15$ amongst household contacts and $p = 0.03$ amongst other contacts. We assumed human-to-human contact rate $\gamma = 365$ (i.e. once a day) and obtained $\beta_{hh} = 365 \cdot \frac{0.15+0.03}{2} = 32.85$. The effective squirrel-to-human transmission rate was estimated to be $\beta_{sh} = 0.05$ as this yields about 1% of seropositive humans (Khodakevich et al., 1988). The actual cost of vaccine is \$4.85 (Lambert de Rouvroit and Heegaard, 2016). While the vaccine is provided for free, there are many other direct and indirect costs associated with vaccination (need to travel to the health center, associated security risk, loss of income etc., see for example Herp et al. (2003)) and we estimated the cost of vaccination to be \$4. We note that the previously approved smallpox vaccines such as ACAM2000 could cause severe side effects (Wollenberg and Engler, 2004; Nalca and Zumbrun, 2010). It is not clear if the new vaccine, JYNNEOS, is more effective to protect against MPXV infections in humans than ACAM2000 and what the potential side effects are.

Symbol	Meaning	Value	Source
Λ_h	Human birth rate	0.0328	CIA (2019)
Λ_s	Squirrel birth rate	2	Hayssen (2008)
μ_h	Human natural death rate	$1/60$	World Bank (2019)
μ_s	Squirrel natural death rate	0.5	Khodakevich et al. (1988)
d_h	Human MPX related death rate	3.12	Ježek et al. (1987)
d_s	Squirrel MPX related death rate	17.5	Falendysz et al. (2017)
ρ_h	Human recovery rate	28.08	Di Giulio and Eckburg (2004)
ρ_s	Squirrel recovery rate	12	Falendysz et al. (2017)
ν_h	Human infection rate	30.42	Di Giulio and Eckburg (2004)
ν_s	Squirrel infection rate	120	Falendysz et al. (2017)
α_h	Vaccination rate	variable	
β_{ss}	Squirrel-to-squirrel transmission rate	40	Assumed based on Khodakevich et al. (1988)
β_{sh}	Squirrel-to-human transmission rate	0.05	Assumed based on Khodakevich et al. (1988)
β_{hh}	Human-to-human transmission rate	32.85	Arita et al. (1985)
C_V	Cost of vaccination	\$4	Herp et al. (2003)
C_{MPX}	Cost of MPX infection	\$100	Adam et al. (2003)

squirrels and humans, denoted by s and h subscripts, respectively. Individuals are born as Susceptible (S) at rate Λ. Susceptible humans vaccinate (move to V_h) at rate α_h. Vaccinated humans are assumed to never contract the disease in the remainder of their lifetime. Susceptible squirrels become Exposed (E_s) by coming into contact with infected squirrels with effective transmission rate β_{ss}. Susceptible humans become exposed by coming into contact with either infected squirrels (with effective transmission rate β_{sh}) or infected humans (with effective transmission rate β_{hh}). After an incubation period ν^{-1}, the exposed individuals become Infected (I). Infected individuals are infectious. They Recover (R) at rate ρ. Any individual may die due to natural causes at rate μ. Infected individuals can also die from the disease at rate d. The notation is summarized in Table 1. The model yields the following differential equations, see for example Blackwood and Childs (2018).

$$\frac{dS_s}{dt} = \Lambda_s - \left(\mu_s + \beta_{ss}\frac{I_s}{N_s}\right) S_s \tag{1}$$

$$\frac{dE_s}{dt} = \beta_{ss}\frac{I_s}{N_s} S_s - (\mu_s + \nu_s)\, E_s \tag{2}$$

$$\frac{dI_s}{dt} = \nu_s E_s - (\mu_s + d_s + \rho_s) I_s \tag{3}$$

$$\frac{dR_s}{dt} = \rho_s I_s - \mu_s R_s \tag{4}$$

$$\frac{dS_h}{dt} = \Lambda_h - \left(\mu_h + \left(\beta_{sh}\frac{I_s}{N_s} + \beta_{hh}\frac{I_h}{N_h}\right) + \alpha_h\right) S_h \tag{5}$$

$$\frac{dV_h}{dt} = \alpha_h S_h - \mu_h V_h \tag{6}$$

$$\frac{dE_h}{dt} = \left(\beta_{sh}\frac{I_s}{N_s} + \beta_{hh}\frac{I_h}{N_h}\right) S_h - (\mu_h + \nu_h) E_h \tag{7}$$

$$\frac{dI_h}{dt} = \nu_h E_h - (\mu_h + d_h + \rho_h) I_h \tag{8}$$

$$\frac{dR_h}{dt} = \rho_h I_h - \mu_h R_h \tag{9}$$

3 RESULTS

3.1 Equilibrium states of the MPX dynamics

The basic reproduction numbers were derived by Usman and Adamu (2017) and are given by

$$R_{0ss} = \beta_{ss} \cdot \frac{1}{\mu_s + d_s + \rho_s} \cdot \frac{\nu_s}{\mu_s + \nu_s} \tag{10}$$

$$R_{0hh} = \beta_{hh} \cdot \frac{\mu_h}{\alpha_h + \mu_h} \cdot \frac{1}{\mu_h + d_h + \rho_h} \cdot \frac{\nu_h}{\mu_h + \nu_h}. \tag{11}$$

As shown in Appendix A1, R_{0ss} corresponds to a number of secondary squirrel infections caused by a single infected squirrel in an otherwise healthy population. The meaning of R_{0hh} is similar.

There are three qualitatively distinct equilibria of the dynamics (1) - (9). First, ε^0 is the disease free equilibrium. It occurs when $R_{0ss} < 1$ and $R_{0hh} < 1$. Second, ε^* is the fully endemic equilibrium with disease occurring amongst humans as well as squirrels. The equilibrium is stable when $R_{0ss} > 1$. Finally, $\varepsilon^\dagger$ is a semi-endemic equilibrium with disease prevalent only amongst human population. It is stable when $R_{0ss} < 1$ and $R_{0hh} > 1$.

The closed form formulas are given in the Table 2. Step-by-step derivation can be found in Appendix A1.

3.2 Herd immunity and Nash equilibrium vaccination rates

The average cost of not vaccinating when the population vaccination rate is α_h is denoted $C_{notV}(\alpha_h)$ and it is given as a product of the cost of the MPX infection (C_{MPX}) and the probability of moving from the S_h

Table 2. Different equilibria of the MPX dynamics. The formulas for N_h^* and $N_h^\dagger$ are too long for the table and are given in Appendix A1.

	Disease-free (ε^0)	**Fully Endemic (ε^*)**	**Semi-endemic ($\varepsilon^\dagger$)**
N_s	$\frac{\Lambda_s}{\mu_s}$	$\frac{\Lambda_s \cdot \left(\frac{\mu_s+d_s+\rho_s}{\nu_s}+1+\frac{\rho_s}{\mu_s}\right)}{\mu_s \cdot \left(\frac{\mu_s+d_s+\rho_s}{\nu_s}\right)+d_s \cdot \left(1-\frac{1}{R_{0ss}}\right)+\mu_s+\rho_s}$	$\frac{\Lambda_s}{\mu_s}$
S_s	N_s^0	$N_s^* \cdot \frac{1}{R_{0ss}}$	$N_s^\dagger$
E_s	0	$\left(\frac{\mu_s+d_s+\rho_s}{\nu_s}\right) \cdot I_s^*$	0
I_s	0	$\frac{\Lambda_s-\mu_s N_s^*}{d_s}$	0
R_s	0	$\frac{\rho_s}{\mu_s} \cdot I_s^*$	0
N_h	$\frac{\Lambda_h}{\mu_h}$	(45)	(59)
S_h	$\frac{\mu_h}{\mu_h+\alpha_h} \cdot N_h^0$	$\frac{(\mu_h+\nu_h)\left(\frac{\mu_h+d_h+\rho_h}{\nu_h}\right) \cdot I_h^*}{\beta_{sh}\left(\frac{I_s^*}{N_s^*}\right)+\beta_{hh}\left(\frac{I_h^*}{N_h^*}\right)}$	$\frac{(\mu_h+d_h+\rho_h)(\mu_h+\nu_h)}{\nu_h \beta_{hh}} \cdot N_h^\dagger$
V_h	$\frac{\alpha_h}{\mu_h+\alpha_h} \cdot N_h^0$	$\frac{\alpha_h}{\mu_h} \cdot S_h^*$	$\left(\frac{\alpha_h}{\mu_h}\right) \cdot S_h^\dagger$
E_h	0	$\left(\frac{\mu_h+d_h+\rho_h}{\nu_h}\right) \cdot I_h^*$	$\left(\frac{\mu_h+d_h+\rho_h}{\nu_h}\right) \cdot I_h^\dagger$
I_h	0	$\frac{\Lambda_h-\mu_h N_h^*}{d_h}$	$\frac{\Lambda_h-\mu_h N_h^\dagger}{d_h}$
R_h	0	$\frac{\rho_h}{\mu_h} \cdot I_h^*$	$\frac{\rho_h}{\mu_h} \cdot I_h^\dagger$

compartment to the I_h compartment, i.e.

$$C_{notV}(\alpha_h) = C_{MPX} \cdot \left(\frac{\left(\beta_{sh}\frac{I_s}{N_s}+\beta_{hh}\frac{I_h}{N_h}\right)}{\left(\beta_{sh}\frac{I_s}{N_s}+\beta_{hh}\frac{I_h}{N_h}\right)+\mu_h} \right) \cdot \left(\frac{\nu_h}{\nu_h+\mu_h} \right). \tag{12}$$

As the vaccination rate α_h increases, R_{0hh} decreases by (11). Furthermore, the fraction $\frac{I_h}{N_h}$ at the appropriate equilibrium also decreases. Consequently, the cost of not vaccinating decreases. In the semi-endemic equilibrium, the cost eventually becomes 0 when the vaccination rate reaches

$$\alpha_{HI} = \max\left\{0, \frac{\nu_h \beta_{hh} \mu_h}{(\mu_h+d_h+\rho_h)(\mu_h+\nu_h)} - \mu_h\right\}. \tag{13}$$

At that point the herd immunity is achieved and the disease is eradicated from the population. In the fully endemic equilibrium, there is always a reservoir of MPX in the squirrel population. This reservoir causes an influx of MPX infections amongst humans. Therefore the disease can never be fully eradicated and the cost of not vaccinating will never reach 0, see Figure 2.

When the vaccination rate is such that $C_{notV}(\alpha_h) = C_V$, the vaccination rate is at Nash equilibrium, α_{NE}. When $\alpha_h < \alpha_{NE}$, it is beneficial for the individual to vaccinate; when $\alpha_h > \alpha_{NE}$, it is beneficial for the individual not to vaccinate.

Figure 3 shows a scenario where $\beta_{hh} = 60$. While this value is unrealistically high, we investigated this hypothetical scenario to see what would happen if MPXV mutates as was the case of H1N1 influenza (swine flu) or is genetically engineered as was the case of mousepox (Jackson et al., 2001; Di Giulio and Eckburg, 2004). When β_{hh} is large enough, specifically when

$$\beta_{hh} > \frac{\alpha_h+\mu_h}{\alpha_h} \cdot (\mu_h+d_h+\rho_h) \cdot \frac{\mu_h+\nu_h}{\nu_h} \tag{14}$$

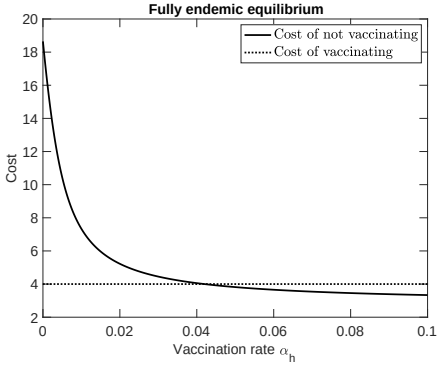

Figure 2. Cost versus vaccination rate. The vaccination rate (α_h) is varied while all other parameter values are as specified in Table 1.

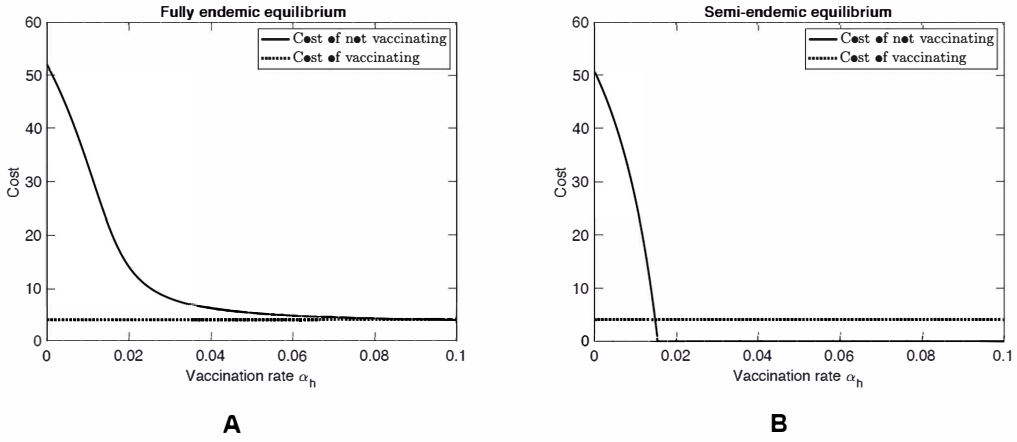

Figure 3. Costs vs. Vaccination rate when the effective human-to-human transmission rate is high, $\beta_{hh} = 60$. **A** the fully endemic state. **B** the semi-endemic state ($\beta_{ss} = 30 < (\mu_s + d_s + \rho_s) \cdot \frac{\mu_s + \nu_s}{\nu_s}$). The same scenario occurs when $\beta_{sh} = 0$ and β_{ss} is arbitrary. In both figures, the vaccination rate (α_h) is varied while all other parameter values are as specified in Table 1.

MPX no longer needs squirrels to persist in the human population. In particular, it can become endemic even in countries without natural squirrel population (i.e. even when $\beta_{sh} = 0$). At the same time, in the semi-endemic equilibrium, the disease can be controlled through vaccination. Note that there is almost no difference between the Nash equilibrium rate α_{NE} (a solution to $C_{notV}(\alpha_h) = C_V$) and the rate α_{HI} needed for the herd immunity (a solution to $C_{notV}(\alpha_h) = 0$).

3.3 Sensitivity analysis

As shown in Figure 2, as α_h increases, $C_{notV}(\alpha_h)$ approaches an asymptote. Consequently, the value of α_{NE}, a solution to $C_{notV}(\alpha_h) = C_V$ can be very sensitive to C_V when $C_V \approx 3$. Any small decrease of C_V can cause a significant increase of α_{NE}. The same sensitivity is demonstrated in Figure 3.

Figure 4 shows the sensitivity analysis and how α_{NE} depends on variation of different parameters. We can see the high sensitivity of α_{NE} on the squirrel-to-human transmission rate, β_{sh}, and on the cost of vaccination, C_V, for low values of C_V. Moreover, the figure demonstrates that α_{NE} can be quite sensitive on the effective transmission rate amongst squirrels, β_{ss} and the squirrels recovery rate, ρ_s. For $\beta_{ss} < (\mu_s + d_s + \rho_s) \cdot \frac{\mu_s + \nu_s}{\nu_s}$, there is a semi-endemic equilibrium and $\alpha_{NE} = 0$. However, as β_{ss} increases above that threshold value, α_{NE} rapidly increases and, when $\beta_{ss} > 45$, there is no Nash equilibrium vaccination rate. Similarly, when ρ_s is large enough to have a semi-endemic equilibrium, the optimal vaccination rate is 0. However, for small ρ_s, there is no Nash equilibrium and the change is relatively abrupt as in the case of β_{ss}.

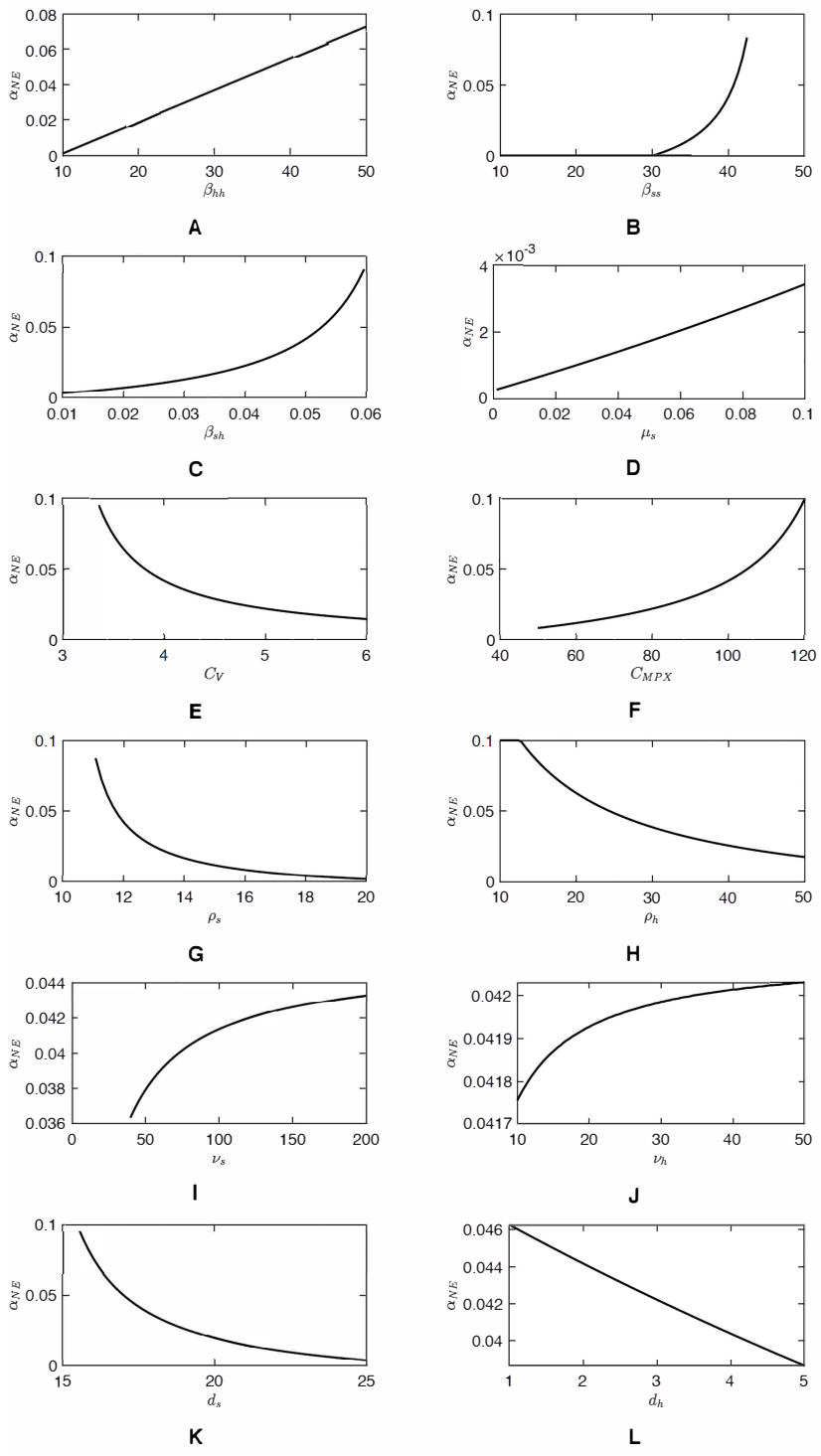

Figure 4. Dependence of α_{NE} on different parameter values. Unless varied, the parameter values are as specified in Table 1. For those parameters, $\alpha_{NE} = 0.0419$ and the sensitivity index, $SI_x = \left(\frac{x}{\alpha_{NE}}\right)\left(\frac{\partial \alpha_{NE}}{\partial x}\right)$ of α_{NE} with respect to parameters are as follows: $SI_{\beta_{hh}} = 1.415$, $SI_{\beta_{sh}} = 3.472$, $SI_{\beta_{ss}} = 10.911$, $SI_{\mu_s} = 0.932$, $SI_{\rho_s} = -7.120$, $SI_{\rho_h} = -1.258$, $SI_{\nu_s} = 0.077$, $SI_{\nu_h} = 0.004$, $SI_{d_s} = -5.917$, $SI_{d_h} = -0.141$, $SI_{C_V} = -3.518$, $SI_{C_{MPX}} = 3.603$.

3.4 Model validation

For the parameters in Table 1, the proportion of seropositive squirrels, given as $\frac{I_s+R_s}{N_s}$, is 24.44% which generally agrees with Khodakevich et al. (1988). Also, the proportion of seropositive people, $\frac{I_h+R_h}{N_h}$, is 1.06%, again agreeing with Khodakevich et al. (1988).

4 DISCUSSION

The phylogenetic relatedness between MPXV and variola virus grants the smallpox vaccine an 85% effectiveness in preventing MPX (Reynolds and Damon, 2012). Poxviruses from the *Orthopoxvirus* genus have cross-reactive antibodies, meaning that vaccinated individuals would have a much lower risk of infection and mortality compared to unvaccinated individuals (Louten, 2016). The imperfect prevention rate of the vaccine was omitted in the design of the mathematical model for the sake of simplicity. As noted in Wu et al. (2011), imperfect protection aggravates the dilemma of voluntary protective actions as lower vaccine effectiveness can lead to better vaccine coverage and smaller free-riding effects; however, the impact of the epidemic can be harder to mitigate.

It is of interest to identify and evaluate possible preventative measures in addition to vaccination that would have a measurable effect on the transmission of MPX. For instance, decreasing the animal-to-human contact and launching an education campaign about dangers of eating raw meat which seems to be the main culprit behind squirrel-to-human transmission Khodakevich et al. (1988) would significantly decrease the animal-to-human transmission rate. It could still come at a considerable individual cost (such as decrease of meat supply) but it would not require a complex or well-developed healthcare infrastructure needed for the vaccination, thus providing the general population with an easily accessible preventative measure. The mathematical model for such a measure would become more complex. The main idea would follow the spirit of Kobe et al. (2018) that investigated a situation for cholera prevention where individuals could either vaccinate or avoid drinking potentially contaminated water.

The reservoir host for monkeypox remains unclear (Di Giulio and Eckburg, 2004; Falendysz et al., 2017). We focused on a moribund rope squirrel, *Funisciurus anerythrus*, but we note that the disease has also been confirmed in other animals (Arita et al., 1985; Khodakevich et al., 1988; Reynolds et al., 2010). As noted in Falendysz et al. (2017), in a recent outbreak of MPXV in DRC, no association was found between contact with rope squirrels and human infection (Nolen et al., 2015). Additionally, a recent survey of 34 villages in the Tshuapa region of DRC did not detect contact with a rope squirrel carcass in the previous 30 days, although they reported contacts with red-legged sun squirrel, *Heliosciurus rufobrachium*, (Monroe et al., 2015) which was identified in Khodakevich et al. (1988) as another frequent host of monkeypox.

5 CONCLUSIONS

We modeled MPX dynamics using the compartmental model of Usman and Adamu (2017). As one of our major contributions, we provided closed form formulas of the equilibrium states of the dynamics. Moreover, we also showed a potential existence of the semi-endemic equilibrium, in which there is no infection in the squirrel population and the disease still persists in the human population. Currently, MPX does not seem to have the viral fitness to become endemic solely through human transmission. Yet, simple mutations in viral proteins could still occur and increase successive inter-human cases as seen in the H1N1 virus outbreak (Le et al., 2009). Should this mutation occur, a careful understanding of the semi-endemic equilibrium will be needed.

In addition, we applied a game-theoretical approach to assess vaccination decision-making developed by Bauch and Earn (2004). Individuals in any population susceptible to MPX have the choice to vaccinate against the disease or risk the possibility of contracting the disease. Naturally, it is in the individual's best interest to choose the option with the smaller expected cost. The model quantifies the costs and benefits of getting smallpox vaccine. We found that the optimal vaccination rate is about 0.04, i.e. individuals should vaccinate about once every 25 years.

We must note that the parameter values we used are only estimates based on available literature. In reality, the parameters may be quite different, in large part because the reservoir hosts are different as discussed above. The performed sensitivity analysis allows us to gain insight into how our results depend on the specific parameter values. We observed that the optimal vaccination rate, α_{NE}, is about 10 times more sensitive to parameters related to animal hosts than to a corresponding parameter related to humans.

It is therefore important to establish more accurate parameters. Consequently, greater efforts are needed to track the true prevalence and recurrent cases of MPX in all populations rather than relying on suspected cases.

Though not perfect in practice, mathematical modeling of diseases remains a powerful tool that grants a more profound understanding how MPX operates under certain conditions. The scope of epidemiological modeling and game-theoretic cost analysis is wide. As cases of MPX become increasingly reported among humans (Antwerpen et al., 2019), we hope that the models may serve as a predictive tool to better study the spread of MPX.

ACKNOWLEDGEMENTS

S.V.B., S.K., W.H., and P.M. worked on this manuscript as part of the course MATH/BIOL 380 - Introduction to mathematical biology. They wish to acknowledge the help and support of their classmates.

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APPENDIX A1 STEP-BY-STEP SOLUTIONS TO EQUILIBRIUM STATES

In this section we find the equilibrium states of the system (1) - (9). We will look for solutions of the following system.

$$0 = \Lambda_s - \left(\mu_s + \beta_{ss}\frac{I_s}{N_s}\right) S_s \tag{15}$$

$$0 = \beta_{ss}\frac{I_s}{N_s} S_s - (\mu_s + \nu_s) E_s \tag{16}$$

$$0 = \nu_s E_s - (\mu_s + d_s + \rho_s) I_s \tag{17}$$

$$0 = \rho_s I_s - \mu_s R_s \tag{18}$$

$$0 = \Lambda_h - \left(\mu_h + \left(\beta_{sh}\frac{I_s}{N_s} + \beta_{hh}\frac{I_h}{N_h}\right) + \alpha_h\right) S_h \tag{19}$$

$$0 = \alpha_h S_h - \mu_h V_h \tag{20}$$

$$0 = \left(\beta_{sh}\frac{I_s}{N_s} + \beta_{hh}\frac{I_h}{N_h}\right) S_h - (\mu_h + \nu_h) E_h \tag{21}$$

$$0 = \nu_h E_h - (\mu_h + d_h + \rho_h) I_h \tag{22}$$

$$0 = \rho_h I_h - \mu_h R_h \tag{23}$$

where (15) - (18) are equations for the squirrels and (19) - (23) are for the humans.

We will distinguish three equilibrium states ε^0, ε^* and $\varepsilon^\dagger$ depending on the existence of infection among squirrels and humans. However, by (16), (18), (20), (21) and (23), no matter which equilibrium

state, the following formulas will always be valid.

$$E_s = \frac{\mu_s + d_s + \rho_s}{\nu_s} I_s \tag{24}$$

$$R_s = \frac{\rho_s}{\mu_s} I_s \tag{25}$$

$$V_h = \frac{\alpha_h}{\mu_h} S_h \tag{26}$$

$$E_h = \frac{\mu_h + d_h + \rho_h}{\nu_h} I_h \tag{27}$$

$$R_h = \frac{\rho_h}{\mu_h} I_h \tag{28}$$

Disease-free equilibrium, ε^0

Assume $I_h^0 = I_s^0 = 0$. It follows from (24) that $E_s^0 = 0$, from (25) that $R_s^0 = 0$ and from (15) that $S_s^0 = \frac{\Lambda_s}{\mu_s}$. Also, by (27), $E_h^0 = 0$ and, by (28), $R_h^0 = 0$. It follows from (19) that

$$S_h^0 = \frac{\Lambda_h}{\alpha_h + \mu_h}. \tag{29}$$

and thus, by (26),

$$V_h^0 = \frac{\Lambda_h}{\mu_h} \cdot \frac{\alpha_h}{\alpha_h + \mu_h}. \tag{30}$$

The stability of ε^0 was discussed and the basic reproduction numbers were derived in Usman and Adamu (2017) using the next-generation matrix method of Van den Driessche and Watmough (2002). Here we present an alternative derivation of the basic reproduction numbers.

Assume there is an infected squirrel in an otherwise disease-free population. The squirrel stays infected for a period of $(\mu_s + d_s + \rho_s)^{-1}$ during which it exposes susceptible individuals at the rate $\beta_{ss} \frac{S_s^0}{N_s^0} = \beta_{ss}$. The newly exposed individuals end up in the I_s compartment with probability $\frac{\nu_s}{\mu_s + \nu_s}$. Consequently, the number of secondary infections from a single infected squirrel in an otherwise disease free equilibrium is given by

$$R_{0ss} = \beta_{ss} \cdot \left(\frac{1}{\mu_s + d_s + \rho_s} \right) \cdot \left(\frac{\nu_s}{\mu_s + \nu_s} \right). \tag{31}$$

Similarly, we can derive that the number of secondary infections caused by a single infected human in otherwise disease-free population is

$$R_{0hh} = \beta_{hh} \frac{S_h^0}{N_h^0} \cdot \left(\frac{1}{\mu_h + d_h + \rho_h} \right) \cdot \left(\frac{\nu_h}{\mu_h + \nu_h} \right) = \frac{\nu_h \beta_{hh} \mu_h}{(\mu_h + d_h + \rho_h)(\mu_h + \nu_h)(\alpha_h + \mu_h)}. \tag{32}$$

Case when $I_s > 0$.

By adding (15) - (18), we get $0 = \Lambda_s - \mu_s N_s^* - d_s I_s^*$ which yields

$$I_s^* = \frac{\Lambda_s - \mu_s N_s^*}{d_s}. \tag{33}$$

By (24), (16) becomes

$$0 = \frac{\beta_{ss} I_s^* S_s^*}{N_s^*} - (\mu_s + \nu_s) \cdot \frac{\mu_s + d_s + \rho_s}{\nu_s} \cdot I_s^* \tag{34}$$

and since we are assuming $I_s^* > 0$, we can divide by I_s and get

$$S_s^* = N_s^* \cdot \frac{(\mu_s + \nu_s)(\mu_s + d_s + \rho_s)}{\beta_{ss}\nu_s} = \frac{N_s^*}{R_{0ss}}. \tag{35}$$

Consequently,

$$\begin{aligned} N_s^* &= S_s^* + E_s^* + I_s^* + R_s^* \\ &= \frac{N_s^*}{R_{0ss}} + \left(\frac{\mu_s + d_s + \rho_s}{\nu_s} + 1 + \frac{\rho_s}{\mu_s}\right) \cdot \left(\frac{\Lambda_s - \mu_s N_s^*}{d_s}\right) \end{aligned} \tag{36}$$

which yields

$$N_s^* = \frac{\Lambda_s \cdot \left(\frac{\mu_s + d_s + \rho_s}{\nu_s} + 1 + \frac{\rho_s}{\mu_s}\right)}{\mu_s \cdot \left(\frac{\mu_s + d_s + \rho_s}{\nu_s}\right) + \mu_s + \rho_s + d_s\left(1 - \frac{1}{R_{0ss}}\right)}. \tag{37}$$

Fully endemic equilibrium, ε^*, human population

Adding (19) - (23) yields

$$0 = \Lambda_h - \mu_h N_h^* - d_h I_h^* \tag{38}$$

and consequently

$$I_h^* = \frac{\Lambda_h - \mu_h N_h^*}{d_h}. \tag{39}$$

Substituting (39) into (23), (21), (19), (20) we get

$$R_h^* = \frac{\rho_h}{\mu_h} \cdot \left(\frac{\Lambda_h - \mu_h N_h^*}{d_h}\right) \tag{40}$$

$$E_h^* = \left(\frac{\mu_h + d_h + \rho_h}{\nu_h}\right) \cdot \left(\frac{\Lambda_h - \mu_h N_h^*}{d_h}\right) \tag{41}$$

$$S_h^* = \frac{(\mu_h + \nu_h) \cdot \left(\frac{\mu_h + d_h + \rho_h}{\nu_h}\right) \cdot \left(\frac{\Lambda_h - \mu_h N_h^*}{d_h}\right)}{\beta_{sh}\left(\frac{I_s^*}{N_s^*}\right) + \beta_{hh}\frac{\frac{\Lambda_h - \mu_h N_h^*}{d_h}}{N_h^*}} \tag{42}$$

$$V_h^* = \frac{\alpha_h}{\mu_h} \cdot \left(\frac{(\mu_h + \nu_h) \cdot \left(\frac{\mu_h + d_h + \rho_h}{\nu_h}\right) \cdot \left(\frac{\Lambda_h - \mu_h N_h^*}{d_h}\right)}{\beta_{sh}\left(\frac{I_s^*}{N_s^*}\right) + \beta_{hh}\frac{\frac{\Lambda_h - \mu_h N_h^*}{d_h}}{N_h^*}}\right). \tag{43}$$

Since $N_h^* = S_h^* + V_h^* + E_h^* + I_h^* + R_h^*$, we get

$$N_h^* = \frac{\rho_h}{\mu_h}\left(\frac{\Lambda_h - \mu_h N_h^*}{d_h}\right) + \left(\frac{\mu_h + d_h + \rho_h}{\nu_h}\right)\cdot\left(\frac{\Lambda_h - \mu_h N_h^*}{d_h}\right)$$

$$+ \frac{\Lambda_h - \mu_h N_h^*}{d_h} + \frac{(\mu_h + \nu_h)\cdot\left(\frac{\mu_h + d_h + \rho_h}{\nu_h}\right)\cdot\left(\frac{\Lambda_h - \mu_h N_h^*}{d_h}\right)}{\beta_{sh}\left(\frac{I_s^*}{N_s^*}\right) + \beta_{hh}\frac{\frac{\Lambda_h - \mu_h N_h^*}{d_h}}{N_h^*}} \tag{44}$$

$$+ \frac{\alpha_h}{\mu_h}\cdot\left(\frac{(\mu_h + \nu_h)\cdot\left(\frac{\mu_h + d_h + \rho_h}{\nu_h}\right)\cdot\left(\frac{\Lambda_h - \mu_h N_h^*}{d_h}\right)}{\beta_{sh}\left(\frac{I_s^*}{N_s^*}\right) + \beta_{hh}\frac{\frac{\Lambda_h - \mu_h N_h^*}{d_h}}{N_h^*}}\right).$$

This yields that N_h^* is a positive root of the equation $AN_h^2 + BN_h + C = 0$, i.e.

$$N_h^* = \frac{-B + \sqrt{B^2 - 4AC}}{2A} \tag{45}$$

where

$$A = g\cdot d_h + k\cdot c\cdot d_h\cdot\mu_h\left(1 + \frac{\alpha_h}{\mu_h}\right) + g\cdot\mu_h(1 + z + k) \tag{46}$$

$$B = d_h\cdot\beta_{hh}\cdot\Lambda_h - (g\cdot\Lambda_h - \beta_{hh}\cdot\Lambda_h\cdot\mu_h)(1 + z + k) - k\cdot c\cdot d_h\cdot\Lambda_h\left(1 + \frac{\alpha_h}{\mu_h}\right) \tag{47}$$

$$C = -\Lambda_h^2\cdot\beta_{hh}(1 + z + k) \tag{48}$$

and

$$k = \frac{\mu_h + d_h + \rho_h}{\nu_h} \tag{49}$$

$$g = d_h\beta_{sh}\left(\frac{I_s^*}{N_s^*}\right) - \beta_{hh}\mu_h \tag{50}$$

$$c = \mu_h + \nu_h \tag{51}$$

$$z = \frac{\rho_h}{\mu_h}. \tag{52}$$

The positive solution for N_h^* from (45) can then be recursively substituted into (39), (40), (41), (42), and (43) to get closed-form formulas for equilibrium values.

Semi-endemic equilibrium

Here, $I_s = 0$. As above, by adding all equations (19) - (23) we get $0 = \Lambda_h - \mu_h N_h^\dagger - d_h I_h^\dagger$ which yields

$$I_h^\dagger = \frac{\Lambda_h - \mu_h N_h^\dagger}{d_h}. \tag{53}$$

Substituting (53) into (23), (21), (19) we get

$$R_h^\dagger = \frac{\rho_h}{\mu_h} \cdot \left(\frac{\Lambda_h - \mu_h N_h^\dagger}{d_h} \right) \tag{54}$$

$$E_h^\dagger = \left(\frac{\mu_h + d_h + \rho_h}{\nu_h} \right) \cdot \left(\frac{\Lambda_h - \mu_h N_h^\dagger}{d_h} \right) \tag{55}$$

$$S_h^\dagger = \frac{(\mu_h + \nu_h) \cdot \left(\frac{\mu_h + d_h + \rho_h}{\nu_h} \right) \cdot \left(\frac{\Lambda_h - \mu_h N_h^\dagger}{d_h} \right)}{\beta_{sh} \left(\frac{I_s^\dagger}{N_s^\dagger} \right) + \beta_{hh} \frac{\frac{\Lambda_h - \mu_h N_h^\dagger}{d_h}}{N_h^\dagger}}. \tag{56}$$

Since $I_s^\dagger = 0$, we get

$$S_h^\dagger = N_h^\dagger \cdot \frac{(\mu_h + d_h + \rho_h)(\mu_h + \nu_h)}{\nu_h \beta_{hh}} \tag{57}$$

and consequently, by (20),

$$V_h^\dagger = N_h^\dagger \cdot \left(\frac{\alpha_h}{\mu_h} \right) \cdot \frac{(\mu_h + d_h + \rho_h)(\mu_h + \nu_h)}{\nu_h \beta_{hh}}. \tag{58}$$

Finally, summing up (53) - (58), we obtain the closed-form formula

$$N_h^\dagger = \frac{\Lambda_h \cdot \left(\frac{\rho_h}{\mu_h} + \frac{\mu_h + d_h + \rho_h}{\nu_h} + 1 \right)}{d_h + \mu_h \cdot \left(\frac{\rho_h}{\mu_h} + \frac{\mu_h + d_h + \rho_h}{\nu_h} + 1 \right) - d_h \cdot \left(\frac{\mu_h + d_h + \rho_h}{\nu_h} \left(\frac{\mu_h + \nu_h}{\beta_{hh}} \right) + \frac{\alpha_h}{\mu_h} \left(\frac{\mu_h + d_h + \rho_h}{\nu_h} \right) \left(\frac{\mu_h + \nu_h}{\beta_{hh}} \right) \right)} \tag{59}$$

which can be used to calculate equilibrium values.