Modelling the Transmission Dynamics of Pox-like Infections

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***Abstract*—During the last two decades, reports on emerging human monkey pox outbreaks in Africa and North America have reminded us that beside the eradicated smallpox there are other poxviruses which have a great potential to cause harm to people. Here, a mathematical model for the transmission dynamics of monkey pox is presented as a system of non-linear differential equations. The conditions under which the disease-free equilibrium is globally asymptotically stable are shown when the both basic reproduction numbers (the human and non-human) are less than unity. The Lyapunov approach is employed to show the global stability of the animal (non-human) endemic equilibrium only when the basic reproduction number for the animal is greater than unity and the basic reproduction number for the humans is less than unity. Using the centre manifold theory the endemic equilibrium point where the infection exists in both the human and non-human population of the model is shown to be locally asymptotically stable when the basic reproduction number for the humans is greater than unity. Numerical simulations tend to suggest immune status of people tends to vary the way people recover following infection with the orthopox virus.**

***Index Terms*—Monkey pox, Centre Manifold Theory, Reproduction number.**

I. Introduction

POX viruses comprise of a group of long known pathogens including some zoonotic members affecting livestock animals and humans. Monkey pox virus which is closely related to variola virus, was first identified as the causal agent in two outbreaks of pox infection in cynomolgus monkeys that was then received from Singapore at Statens Serum institute, Coperhagen, Denmark [1], [2]. Monkey pox virus was first described as causes of pox like illnesses in monkeys in the late sixties of the last century [13]. In monkeys the disease is characterized by generalized skin eruptions, developing to papules on the trunk, face, palms and soles. Papules subsequently develop into vesicles and scabs which usually fall off after about 10 days after the rash developed [13]. The severity of the disease varies with regard to host species for example mild in cynomolgus monkeys, but more severe in orang utans [4], [20]. Epidemiological investigations have revealed that the monkey pox virus is endemic in squirrels in the tropical rainforest of Africa.

However, in the 1970s human monkey pox was reported for the first time in countries of Western and Central Africa [3]. It was discovered at a time when smallpox was already eradicated in those regions. Investigations into the rash causing illnesses by the World Health Organisation from 1970 to 1986 showed that was the monkey pox virus with a case fatality of 10-17%. The secondary attack rate (3%) was much lower than that of smallpox (upto 80% in non-immunized contacts). In 1996/1997 and 2001-2004 large human monkey pox outbreaks were reported in the Democratic Republic of Congo [15]. In 1996/1997 the mortality was low (1.5%), but secondary attack rate was high (upto 78%). This is explained by a reduced immunity due to the abolishment of mandatory smallpox vaccination [13]. This tends to suggest that mandatory smallpox vaccination was also contributing to the control of monkey pox. In 2005 the emergence of occasional human monkey pox virus infections were reported for the first time in Southern Sudan, an area ecological different from the tropical rainforest [14]. An investigation by World Health Organisation found sporadic cases of monkey pox cases in the area supporting the argument of recurrent carryover from local animal reservoirs [12]. The outbreak of monkey pox in the USA in 2003 through rodents (monkey pox virus infected) imported from Ghana [11] reveal that monkey pox may show up in other parts of the world.

Currently there is not much work on mathematical modelling of monkey pox. This paper provides possibly a first attempt to mathematically analyse the transmission dynamics of monkey pox and it is organised as follows. In the next section the monkey pox model is presented and conditions for the local and global stability of the disease-free equilibrium and endemic equilibrium are determined. Section 3 presents some numerical simulations. In Section 4, the discussion is presented.

II. Model description

The model divides non-human primates and some wild rodents into susceptibles (S_n), infectives (I_n) and the recovered with permanent immunity (R_n), so that the total non human population is given by

$$N_n(t) = S_n(t) + I_n(t) + R_n(t). \tag{1}$$

Susceptibles non-human primates and some wild rodents are recruited through births a rate Λ_n and are infected with the monkey pox virus, a virus that causes monkey pox a rate λ_n with

$$\lambda_n = \frac{\beta_{n_1} I_n}{N_n} \tag{2}$$

where β_{n_1} is the product of the effective contact rate and probability of the non-human animal getting infected per contact with an infectious case. Once infected, susceptibles (S_n) progress to the infectious state (I_n). Animals in the I_n are capable of infecting other animals they come in close contact with, die due to disease at a rate d_n and some recover with permanent immunity at a rate ρ_n into R_n class, the recovered class. All non-human animals experience natural death a rate μ_n which is proportional to the number of

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TABLE I
MODEL PARAMETERS.

Symbol	Value	Source
Λ_h	0.029yr^{-1}	CS0Z [7]
μ_h	0.02yr^{-1}	CSOZ[7]
ρ_h	0.83-0.9yr^{-1}	[13]
d_h	0.1-0.17yr^{-1}	[13]
Λ_n	2yr^{-1}	Assumed
μ_n	1.5yr^{-1}	Assumed
ρ_n	0.6yr^{-1}	Assumed
d_n	0.4yr^{-1}	Assumed
β_{n_1}, β_{n_2}, β_h	0.0027, 000252, 0.000063yr^{-1}	Assumed

animals in each class. The total human population is divided into three distinct subgroups that is the susceptibles (S_h), the infected (I_h) and the recovered with permanent immunity (R_h). Thus, the total human population is given by

$$N_h(t) = S_h(t) + I_h(t) + R_h(t) \tag{3}$$

Susceptibles are recruited through birth and migration at a rate Λ_h and are infected with the monkey pox virus at rate λ_h with

$$\lambda_h = \frac{\beta_{n_2} I_n}{N_n} + \frac{\beta_h I_h}{N_h}, \tag{4}$$

where β_{n_2} is the product of the effective contact rate and probability of the human being getting infected per contact with an infectious non-human animal possibly through eating the infected carcass and β_h is the product of the effective contact rate and probability of the human being getting infected per contact with an infectious human case. It is assumed here that mortality of monkeys due to being hunted by humans is negligible and can be safely ignored. Once infected susceptible humans (S_h) progress to the infectious state (I_h). Individuals in I_h class die due to the disease at a rate d_h and recover with permanent immunity at a rate ρ_h into R_h class, the recovered state. Individuals in each human subgroup experience natural death at a rate μ_h which is proportional to the number in each class. Parameters described will assume values in Table I. The structure of the model is presented in Figure 1. Based on these assumptions the following system of differential equations is obtained.

$$\begin{aligned}
S_n'(t) &= \Lambda_n - (\mu_n + \lambda_n)S_n, \\
I_n'(t) &= \lambda_n S_n - (\mu_n + \rho_n + d_n)I_n, \\
R_n'(t) &= \rho_n I_n - \mu_n R_n, \\
S_h'(t) &= \Lambda_h - (\mu_h + \lambda_h)S_h, \\
I_h'(t) &= \lambda_h S_h - (\mu_h + \rho_h + d_h)I_h, \\
R_h'(t) &= \rho_h I_h - \mu_h R_h.
\end{aligned} \tag{5}$$

All feasible solutions of model system (5) enter the region

$$\Omega = \left\{ \begin{array}{l} (S_n, I_n, R_n) \in \Re_+^3 : N_n \leq \dfrac{\Lambda_n}{\mu_n}, \\ \\ (S_h, I_h, R_h) \in \Re_+^3 : N_h \leq \dfrac{\Lambda_h}{\mu_h}, \end{array} \right. \tag{6}$$

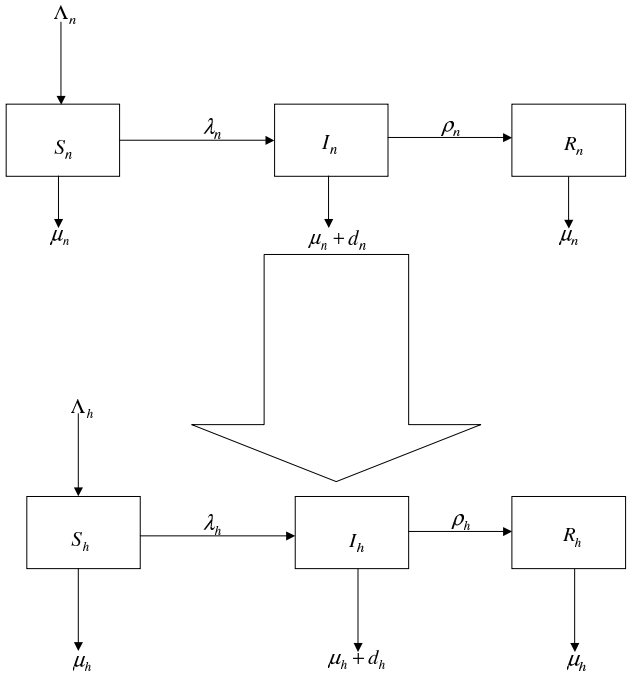

Fig. 1. Structure of model

which is positively invariant and attracting and it is sufficient to consider solutions in Ω. Existence, uniqueness and continuation results for system (5) hold in this region and all solutions starting in Ω remain in there for all $t \geq 0$. Hence, (5) is mathematically and epidemiologically well-posed and it is sufficient to consider the dynamics of the flow generated by the model system(5) in Ω. Also, all parameters and state variables for model system (5) are assumed to be non-negative since it monitors human, non-human primates and some rodent populations.

A. Disease-free equilibrium and stability analysis

The disease-free equilibrium of model system (5) is given by

$$\begin{aligned}
\mathcal{E}^0 &= \left(S_n^0, I_n^0, R_n^0, S_h^0, I_h^0, R_h^0\right) \\
&= \left(\frac{\Lambda_n}{\mu_n}, 0, 0, \frac{\Lambda_h}{\mu_h}, 0, 0\right).
\end{aligned} \tag{7}$$

Following van den Driessche and Watmough [19], the reproduction numbers of the model are

$$\{\mathcal{R}_{0_n}, \mathcal{R}_{0_h}\} \tag{8}$$

with $\mathcal{R}_{0_n}$ and $\mathcal{R}_{0_h}$ being the monkey pox induced reproduction numbers for humans and non-humans, respectively, which are given by

$$\begin{aligned}
\mathcal{R}_{0_n} &= \frac{\beta_{n_1}}{\mu_n + \rho_n + d_n}, \\
\mathcal{R}_{0_h} &= \frac{\beta_h}{\mu_h + \rho_h + d_h}.
\end{aligned} \tag{9}$$

The following Theorem 1 follows from Theorem 2 of van den Driessche and Watmough [19].

Theorem 1: The disease-free equilibrium $\mathcal{E}^0$ is locally asymptotically stable whenever $\mathcal{R}_{0_n} < 1$ and $\mathcal{R}_{0_h} < 1$, and unstable otherwise.

Following Castillo-Chavez et al. [10] we now list two conditions which if met guarantee the global asymptotic stability of $\mathcal{E}^0$. Rewriting model system (5) as

$$\begin{aligned} X'(t) &= F(X,Y) \\ Y'(t) &= G(X,Y),\ G(X,\mathbf{0}) = 0 \end{aligned} \tag{10}$$

where $X = (S_n, R_n, S_h, R_h)$ and $Y = (I_n, I_h)$ with $X \in \Re_+^4$ denoting the number of uninfected components (individuals) and $Y \in \Re_+^2$ denoting the number of infected components(individuals). The disease-free equilibrium is now denoted by $\mathcal{E}^0 = (X_0, \mathbf{0})$ where $X_0 = \left(\frac{\Lambda_n}{\mu_n}, 0, \frac{\Lambda_h}{\mu_h}, 0\right)$. The conditions (H1) and (H2) below must be met to guarantee global asymptotic stability of $\mathcal{E}^0$

$$\begin{aligned} &H1 \quad \text{For} \quad X'(t) = F(X^*, 0), \\ &\quad X^* \quad \text{is a globally asymptotically stable} \\ &H2 \quad G(X,Y) = AY - \widehat{G}(X,Y), \\ &\quad \widehat{G}(X,Y) \geq 0 \text{ for } (X,Y) \in \Omega. \end{aligned} \tag{11}$$

If (10) satisfies conditions in (11) then Theorem 2 holds provided $\beta_{n_2} = 0$

Theorem 2: The fixed point $\mathcal{E}^0$ is a globally asymptotically stable whenever $\beta_{n_2} = 0$, $\mathcal{R}_{0_n} < 1$ and $\mathcal{R}_{0_h} < 1$.

Proof: Consider $F(X,0) = \begin{bmatrix} \Lambda_n - \mu_n S_n \\ 0 \\ \Lambda_h - \mu_h S_h \\ 0 \end{bmatrix}$,

$$A = \begin{bmatrix} -(\mu_n + \rho_n + d_n) + \beta_{n_1} & 0 \\ \dfrac{\beta_{n_2}\Lambda_h\mu_n}{\mu_h\Lambda_n} & \beta_h - (\mu_h + \rho_h + d_h) \end{bmatrix}$$

and $\widehat{G}(X,Y) = \begin{bmatrix} \widehat{G_1}(X,Y) \\ \widehat{G_2}(X,Y) \end{bmatrix}$

$$= \begin{bmatrix} \dfrac{\beta_{n_1} I_n (N_n - S_n)}{N_n} \\ \dfrac{\beta_h I_h (N_h - S_h)}{N_h} + \dfrac{\beta_{n_2} I_n (\Lambda_h \mu_n N_n - S_h \mu_h \Lambda_n)}{\mu_h \Lambda_n N_n} \end{bmatrix}. \tag{12}$$

This means that where there is no transmission between non-humans and humans ($\beta_{n_2} = 0$), then $\widehat{G}(X,Y) \geq 0$, meaning that the disease-free equilibrium will be globally asymptotically stable. However when there is cross infection from non-humans to humans which is the case with monkey pox infections then the disease-free equilibrium is not necessarily globally asymptotically stable as this is not always true ($\widehat{G_2}(X,Y) \geq 0$) everywhere in Ω. This actually suggests the existence of multiple endemic equilibria. ■

B. Endemic equilibrium and stability analysis

They are basically three mathematically possible endemic equilibria states, the animal-only endemic equilibrium, the human-only endemic equilibrium and the equilibrium state where the disease co-exists. Basing on the fact that monkey-pox infections are mainly transmitted from animals to humans, this allows to leave the analysis of human-only endemic equilibrium as human to human monkey pox infections rarely lead to monkey pox outbreak and as such we take this equilibrium to be a trivial endemic equilibrium.

Animal-only endemic equilibrium: This occurs when there is only animal to animal infections and no human to human infection and no animal to human infections ($\beta_{n_2} = \beta_h = 0$). In this case the endemic equilibrium is given by $\mathcal{E}_1^* = (S_n^*, I_n^*, R_n^*, S_h^*, 0, 0),\ S_h^* = \dfrac{\Lambda_h}{\mu_h}$. The nature of S_h^* shows that $\mathcal{R}_{0_h} < 1$. We now carry out some manipulations to find the exact values of the remaining components of $\mathcal{E}_1^*$. The animal-only model is standard SIR model which at equilibrium we have

$$\begin{aligned} \Lambda_n &= (\mu_n + \lambda_n^*) S_n^*, \\ \lambda_n^* S_n^* &= (\mu_n + \rho_n + d_n) I_n^*, \\ \rho_n I_n^* &= \mu_n R_n^*,\ \lambda_n = \tfrac{\beta_{n_1} I_n}{N_n}. \end{aligned} \tag{13}$$

Adding the first two equations of system (13) one gets

$$\begin{aligned} &\Lambda_n = \mu_n S_n^* + (\mu_n + \rho_n + d_n) I_n^* \\ &\Rightarrow S_n^* = \frac{\Lambda_n}{\mu_n} - \frac{\mu_n + \rho_n + d_n}{\mu_n} I_n^* \end{aligned} \tag{14}$$

From the last equation in system (13) we have $R_n^* = \dfrac{\rho_n}{\mu_n} I_n^*$. Adding all the equations in system (13) we have

$$\Lambda_n = \mu_n N_n^* + d_n I_n^* \Rightarrow N_n^* = \frac{\Lambda_n}{\mu_n} - \frac{d_n}{\mu_n} I_n^* \tag{15}$$

then, the second equation in system (13) gives $I_n^* = 0$ or

$$\begin{aligned} &\beta_{n_1} S_n^* = (\mu_n + \rho_n + d_n) N_n^*, \\ &\Rightarrow \beta_{n_1} \left(\frac{\Lambda_n}{\mu_n} - \frac{\mu_n + \rho_n + d_n}{\mu_n} I_n^* \right) \\ &\quad = \frac{\mu_n + \rho_n + d_n}{\mu_n} (\Lambda_n - d_n I_n^*), \\ &\Rightarrow I_n^* = \frac{\Lambda_n (\beta_{n_1} - (\mu_n + \rho_n + d_n))}{(\beta_{n_1} - d_n)(\mu_n + \rho_n + d_n)}. \end{aligned} \tag{16}$$

Only solution with $S_n^*, I_n^*, N_n^* > 0$ is if $\beta_{n_1} > (\mu_n + \rho_n + d_n) \Rightarrow \mathcal{R}_{0_n} > 1$. This leads to Lemma 1.

Lemma 1: The endemic equilibrium $\mathcal{E}_1^*$ exists whenever $\mathcal{R}_{0_n} > 1$ and $\mathcal{R}_{0_h} < 1$.

Now we have to check onto the stability of this endemic equilibrium. In order to investigate the global stability of the endemic equilibrium, we adopt the approach by Korobeinikov [6]. Assume that $\mathcal{R}_{0_n} > 1$, then $\mathcal{E}_1^*$ exists for all $S_n;\ I_n;\ R_n;\ S_h > \epsilon$, for some $\epsilon > 0$. Let $\lambda_n S_n := g(S_n; I_n; R_n)$ be a positive and monotonic function, and

define the following continuous function in $\Re^3_+$ (for more details, see Korobeinikov, 2006). A function

$$\begin{aligned} V(S_n, I_n, R_n) &= S_n - \int_\epsilon^{S_n} \frac{g(S_n^*, I_n^*, R_n^*)}{g(\tau, I_n^*, R_n^*)} d\tau \\ &+ I_n - \int_\epsilon^{I_n} \frac{g(S_n^*, I_n^*, R_n^*)}{g(S_n^*, \tau, R_n^*)} d\tau \\ &+ R_n - \int_\epsilon^{R_n} \frac{g(S_n^*, I_n^*, R_n^*)}{g(S^*, I_n^*, \tau)} d\tau. \end{aligned} \tag{17}$$

If $g(S_n, I_n, R_n)$ is monotonic with respect to its variables, then the endemic state $\mathcal{E}_1^*$ is the only extremum and the global minimum of this function. Indeed

$$\begin{aligned} \frac{\partial V}{\partial S_n} &= 1 - \frac{g(S_n^*, I_n^*, R_n^*)}{g(S_n, I_n^*, R_n^*)}, \\ \frac{\partial V}{\partial I_n} &= 1 - \frac{g(S_n^*, I_n^*, R_n^*)}{g(S_n^*, I_n, R_n^*)}, \\ \frac{\partial V}{\partial R_n} &= 1 - \frac{g(S_n^*, I_n^*, R_n^*)}{g(S_n^*, I_n^*, R_n)}, \end{aligned} \tag{18}$$

grow monotonically, then the function $g(S_n, I_n, R_n)$ has only one stationary point. Furthermore, since

$$\begin{aligned} \frac{\partial^2 V}{\partial S_n^2} &= \frac{g(S_n^*, I_n^*, R_n^*)}{[g(S_n, I_n^*, R_n^*]^2} \cdot \frac{\partial g(S_n, I_n^*, R_n^*)}{\partial S_n}, \\ \frac{\partial^2 V}{\partial I_n^2} &= \frac{g(S_n^*, I_n^*, R_n^*)}{[g(S_n^*, I_n, R_n^*)]^2} \cdot \frac{\partial g(S_n^*, I_n, R_n^*)}{\partial I_n}, \\ \frac{\partial^2 V}{\partial R_n^2} &= \frac{g(S_n^*, I_n^*, R_n^*)}{[g(S_n^*, I_n^*, R_n)]^2} \cdot \frac{\partial g(S_n^*, I_n^*, R_n)}{\partial R_n}, \end{aligned} \tag{19}$$

are non-negative, then the point $\mathcal{E}_1^*$ is a minimum. That is, $V(S_n, I_n, R_n) \geq V(S_n^*, I_n^*, R_n^*)$ and hence, V is a Lyapunov function. In the case of our model system when $\beta_{n_2} = \beta_h = 0$ (animal to animal transmission only), then

$$\begin{aligned} \Lambda_n &= g(S_n^*, I_n^*, R_n^*) + \mu_n S_n^*, \\ (\mu_n + \rho_n + d_n) I_n^* &= g(S_n^*, I_n^*, R_n^*), \\ \rho_n I_n^* &= \mu_n R_n^*. \end{aligned} \tag{20}$$

The Lyapunov function (17) satisfies

$$\begin{aligned} \frac{dV}{dt} &= S_n' - S_n' \frac{g_n^*}{g_{s_n}} + I_n' - I_n' \frac{g_n^*}{g_{i_n}} \\ &\quad + R_n' - R_n' \frac{g_n^*}{g_{r_n}} \\ &= \Lambda_n - g_n - \mu_n S_n - \Lambda_n \frac{g_n^*}{g_{s_n}} + g_n \frac{g_n^*}{g_{s_n}} \\ &\quad + \mu_n S_n \frac{g_n^*}{g_{s_n}} + g_n \\ &\quad - (\mu_n + \rho_n + d_n) I_n - g_n \frac{g_n^*}{g_{i_n}} \\ &\quad + (\mu_n + \rho_n + d_n) I_n \frac{g_n^*}{g_{i_n}} + \rho_n I_n - \mu R_n \\ &= \mu_n S_n^* \left(1 - \frac{S_n}{S_n^*}\right) \left(1 - \frac{g_n^*}{g_{s_n}}\right) \\ &\quad + g_n^* \left(1 - \frac{g_n^*}{g_{s_n}} - \frac{g_n}{g_{s_n}}\right) \\ &\quad + g_n^* \left(-\frac{I_n}{I_n^*} + \frac{I_n}{I_n^*} \frac{g_n^*}{g_{i_n}} - \frac{g_n}{g_{i_n}}\right) \\ &\quad + \mu_n R_n^* \left(\frac{I_n}{I_n^*} - \frac{R_n}{R_n^*}\right) \left(1 - \frac{g_n^*}{g_{r_n}}\right) \\ &= \mu_n S_n^* \left(1 - \frac{S_n}{S_n^*}\right) \left(1 - \frac{g_n^*}{g_{s_n}}\right) \\ &\quad + g_n^* \left(1 - \frac{g_n^*}{g_{s_n}}\right) \left(1 - \frac{g_{s_n}}{g_{i_n}}\right) \\ &\quad + g_n^* \left(\frac{I_n}{I_n^*} - \frac{g_n}{g_{s_n}}\right) \left(\frac{g_n^*}{g_{i_n}} - 1\right) \\ &\quad + \mu_n R_n^* \left(\frac{I_n}{I_n^*} - \frac{R_n}{R_n^*}\right) \left(1 - \frac{g_n^*}{g_{r_n}}\right), \end{aligned} \tag{21}$$

with $g_n^* = g(S_n^*, I_n^*, R_n^*)$, $g_n = g(S_n, I_n, R_n)$, $g_{s_n} = g(S_n, I_n^*, R_n^*)$, $g_{i_n} = g(S_n^*, I_n, R_n^*)$, $g_{r_n} = g(S_n^*, I_n^*, R_n)$. Since $\mathcal{E}_1^* > 0$, the function $g(S_n, I_n, R_n)$ is concave with respect to I_n, and $\frac{\partial^2 g(S_n, I_n, R_n)}{\partial I_n^2} \leq 0$, then $\frac{dV}{dt} \leq 0$ for all $S_n,\ I_n, R_n > 0$. Also, the monotonicity of $g(S_n, I_n, R_n)$ with respect to S_n ensures that

$$\left(1 - \frac{S_n}{S_n^*}\right) \left(1 - \frac{g(S_n^*, I_n^*, R_n^*)}{g(S_n, I_n^*, R_n^*)}\right) \leq 0 \tag{22}$$

and

$$\left(1 - \frac{g(S_n^*, I_n^*, R_n^*)}{g(S_n, I_n^*, R_n^*)}\right) \left(1 - \frac{g(S_n, I_n, R_n)}{g(S_n^*, I_n, R_n^*)}\right) \leq 0 \tag{23}$$

holds for all $S_n, I_n, R_n > 0$. Furthermore,

$$\left(\frac{I_n}{I_n^*} - \frac{g(S_n, I_n, R_n)}{g(S_n, I_n^*, R_n^*)}\right) \left(\frac{g(S_n^*, I_n^*, R_n^*)}{g(S_n^*, I_n, R_n^*)} - 1\right) \leq 0$$

if

$$\frac{g(S_n,I_n,R_n)}{g(S_n,I_n^*,R_n^*)} \geq \frac{I_n}{I_n^*}$$

$$\text{when } \; g(S_n^*,I_n,R_n^*) \leq g(S_n^*,I_n^*,R_n^*) \;\text{ and} \tag{24}$$

$$\frac{g(S_n,I_n,R_n)}{g(S_n,I_n^*,R_n^*)} \leq \frac{I_n}{I_n^*}$$

$$\text{when } \; g(S^*,I_n,R_n^*) \geq g(S_n^*,I_n^*,R_n^*).$$

holds for all $S_n, I_n, R_n > 0$. Since $g(S_n, I_n, R_n)$ is monotonic $g(S_n*, I_n, R_n^*) \geq g(S_n*, I_n^*, R_n^*) \Rightarrow I_n \geq I_n^*$ and $g(S_n*, I_n, R_n^*) \leq g(S_n*, I_n^*, R_n^*) \Rightarrow I_n \leq I_n^*$. Also,

$$\left(\frac{I_n}{I_n^*} - \frac{R_n}{R_n^*}\right)\left(1 - \frac{g(S_n^*,I_n^*,R_n^*)}{g(S_n^*,I_n^*,R_n)}\right) \leq 0 \tag{25}$$

if

$$\frac{R_n}{R_n^*} \geq \frac{I_n}{I_n^*} \text{ when } g(S_n^*,I_n^*,R_n) \geq g(S_n^*,I_n^*,R_n^*) \text{ and}$$

$$\frac{R_n}{R_n^*} \leq \frac{I_n}{I_n^*} \text{ when } g(S_n^*,I_n^*,R_n) \leq g(S_n^*,I_n^*,R_n^*). \tag{26}$$

holds for all $S_n, I_n, R_n > 0$. Since $g(S_n, I_n, R_n)$ is a monotonic function $g(S_n^*, I_n^*, R_n) \geq g(S_n^*, I_n^*, R_n^*) \Rightarrow R_n \geq R_n^*$ and $g(S_n^*, I_n^*, R_n) \leq g(S_n^*, I_n^*, R_n^*) \Rightarrow R_n \leq R_n^*$. Inequalities (24) and (26) will hold for any concave function and are sufficient to ensure that $\frac{dV}{dt} \leq 0$.Thus, we have established the following result:

Theorem 3: The unique endemic equilibrium $\mathcal{E}_1^*$ is globally asymptotically stable whenever conditions (24) and (26) are satisfied.

Co-existence of monkey pox infections in both human and non-human endemic equilibrium: This occurs when there animal to animal, animal to human and human to human infections. This endemic equilibrium for the model is given by $\mathcal{E}_2^*$ where

$$\mathcal{E}_2^* = (S_n^*, I_n^*, R_n^*, S_h^*, I_h^*, R_h^*), \tag{27}$$

with S_n^*, I_n^* and R_n^* taking the same expressions as in $\mathcal{E}_1^*$ where they were shown to exist whenever $\mathcal{R}_{0_n} > 1$. To find the remaining components it is necessary to consider the human subsystem which is given by

$$\begin{aligned} \Lambda_h &= (\mu_h + \lambda_h^*)S_h^*, \\ \lambda_h^* S_h^* &= (\mu_h + \rho_h + d_h)I_h^*, \\ \rho_h I_h^* &= \mu_h R_h^*, \; \lambda_h = \frac{\beta_{n_2} I_n}{N_n} + \frac{\beta_h I_h}{N_h}. \end{aligned} \tag{28}$$

Adding the first two equations of system (28) the following is obtained

$$\begin{aligned} &\Lambda_h = \mu_h S_h^* + (\mu_h + \rho_h + d_h)I_h^* \\ &\Rightarrow S_h^* = \frac{\Lambda_h}{\mu_h} - \frac{\mu_h + \rho_h + d_h}{\mu_h} I_h^*. \end{aligned} \tag{29}$$

Adding all the equations of system (28) we obtain

$$\Lambda_h = \mu_h N_h^* - d_h^* I_h^* \Rightarrow N_h^* = \frac{\Lambda_h}{\mu_h} - \frac{d_h}{\mu_h} I_h^*, \tag{30}$$

then the second equation of system (28) gives

$$\begin{aligned} &\left(\frac{\beta_{n_2} I_n^*}{N_n^*} + \frac{\beta_h I_h^*}{N_h^*}\right)\left(\frac{\Lambda_h}{\mu_h} - \frac{m_h}{\mu_h} I_h^*\right) = m_h I_h^*, \\ &m_h = (\mu_h + \rho_h + d_h). \end{aligned} \tag{31}$$

Set $x^* = \frac{1}{\mu_h}\frac{\beta_{n_2} I_n^*}{N_n^*}$ then (31) becomes

$$\begin{aligned} &(\beta_h I_h^* + x^*(\Lambda_h - d_h I_h^*))\left(\frac{\Lambda_h}{\mu_h} - \frac{m_h}{\mu_h} I_h^*\right) \\ &= m_h\left(\frac{\Lambda_h}{\mu_h} - \frac{d_h}{\mu_h} I_h^*\right) I_h^* \\ &\Rightarrow (\beta_h - d_h(1+x^*))\,(I_h^*)^2 \\ &+\Lambda_h\left((1+x^*) - \frac{\beta_h - d_h x^*}{m_h}\right) I_h^* - \frac{\Lambda_h^2 x^*}{m_h} = 0, \\ &m_h = (\mu_h + \rho_h + d_h) \end{aligned} \tag{32}$$

and this has a single positive root if $\beta_h > d_h(1 + x^*)$. The permanence of the disease destabilizes the disease-free equilibrium $\mathcal{E}^0$ since $\mathcal{R}_{0_h} > 1$ and $\mathcal{R}_{0_n} > 1$, the endemic equilibrium $\mathcal{E}_2^*$ exists.

Lemma 2: System (5) is uniformly persistent on Ω.

Proof: Uniform persistence system of (5) implies there exists a constant $\zeta > 0$ such that any solution of (5) which starts in

$$\left(S_n^0, I_n^0, R_n^0, S_h^0, I_h^0, R_h^0\right) \in \overset{\circ}{\Omega}, \tag{33}$$

satisfies,

$$\begin{aligned} &\zeta \leq \liminf_{t\to\infty} S_n(t), \; \zeta \leq \liminf_{t\to\infty} I_n(t), \\ &\zeta \leq \liminf_{t\to\infty} R_n(t), \; \zeta \leq \liminf_{t\to\infty} S_h(t), \\ &\zeta \leq \liminf_{t\to\infty} I_h(t), \zeta \leq \liminf_{t\to\infty} R_h(t). \end{aligned} \tag{34}$$

Define the following Korobeinikov-Maini [17] type Lyapunov functional

$$\begin{aligned} V(S_n,I_n,R_n,S_h,I_h,R_h) &= (S_n - S_n^* \ln S_n) \\ &+ (I_n - I_n^* \ln I_n) + (R_n - R_n^* \ln R_n) \\ &+ (S_h - S_h^* \ln S_h) + (I_h - I_h^* \ln I_h) \\ &+ (R_h - R_h^* \ln R_h). \end{aligned} \tag{35}$$

which continuous for all $x_i > 0$ $(i = 1, 2, \cdots, 5)$ and satisfies $\frac{\partial V}{\partial x_i} = \left(1 - \frac{x_i^*}{x_i}\right)$ [16]. Consequently, the endemic equilibrium $\mathcal{E}^*$ is the only extremum and the global minimum of the function $V \in \Re_+^6$. Also, $V(S_n, I_n, R_n, S_h, I_h, R_h) > 0$ and $V'(S_n, I_n, R_n, S_h, I_h, R_h) = 0$ only at $\mathcal{E}^*$. Thus, $V(S_n, I_n, R_n, S_h, I_h, R_h)$ is a Lyapunov function. At equilibrium, $\Lambda_j = \lambda_j^* S_j^* + \mu_j S_j^*$ $(j = n, h)$, substituting this into the time derivative of V along the solution path of model

system (5), we have

$$V' = (S_n - S_n^*)\frac{S_n'}{S_n} + (I_n - I_n^*)\frac{I_n'}{I_n} + (R_n - R_n^*)\frac{R_n'}{R_n}$$
$$+(S_h - S_h^*)\frac{S_h'}{S_h} + (I_h - I_h^*)\frac{I_h'}{I_h} + (R_h - R_h^*)\frac{R_h'}{R_h}$$
$$\leq -\mu_h\frac{(S_h - S_h^*)^2}{S_h} + g(S_n, I_n, R_n, S_h, I_h, R_h). \tag{36}$$

g can be shown to be non-positive using Barbalat Lemma [5] or by following the approach of McCluskey [18]. Hence, $V'(S_n, I_n, R_n, S_h, I_h, R_h) \leq 0$ with equality only at $\mathcal{E}_2^*$. The only invariant set in $\overset{\circ}{\Omega}$, the interior of Ω is the set consisting of the endemic equilibrium $\mathcal{E}_2^*$. Thus, all solutions of (5) which intersect $\overset{\circ}{\Omega}$ limit to and invariant set, the singleton $\{\mathcal{E}_2^*\}$. Therefore, from Lyapunov-Lasalle invariance principle, system (5) is uniformly persistent. ■

To analyze the stability of this equilibrium point we make use of the Centre Manifold Theory [8] as described in Theorem 4.1 of Castillo-Chavez and Song [9], to establish the local asymptotic stability of the non smoking only endemic equilibrium. Let us make the following change of variables $S_n = x_1,\ I_n = x_2,\ R_n = x_3,\ S_h = x_4,\ I_h = x_5,\ R_h = x_6$, so that
$N_n(t) = \sum_{n=1}^{3} x_n$ and $N_h(t) = \sum_{m=1}^{3} x_{m+3}$. Using the vector notation $X = (x_1, x_2, x_3, x_4, x_5)^T$. Model system (5) under these conditions can be written in the form
$\frac{dX}{dt} = (f_1, f_2, f_3, f_4, f_5, f_6)$, such that

$$x_1'(t) = f_1 = \Lambda_n - \frac{\beta_{n_1} x_2 x_1}{\sum_{n=1}^{3} x_n} - \mu_n x_1,$$
$$x_2'(t) = f_2 = \frac{\beta_{n_1} x_2 x_1}{\sum_{n=1}^{3} x_n} - (\mu_n + \rho_n + d_n)x_2,$$
$$x_3'(t) = f_3 = \rho_n x_2 - \mu_n x_3,$$
$$x_4'(t) = f_4 = \Lambda_h - \frac{\beta_h x_5 x_4}{\sum_{m=1}^{3} x_{m+3}} - \frac{\beta_{n_2} x_2 x_4}{\sum_{m=1}^{3} x_m} - \mu_h x_4, \tag{37}$$
$$x_5'(t) = f_5 = \frac{\beta_h x_5 x_4}{\sum_{m=1}^{3} x_{m+3}} + \frac{\beta_{n_2} x_2 x_4}{\sum_{m=1}^{3} x_m} - (\mu_h + \rho_h + d_h)x_5,$$
$$x_6'(t) = f_6 = \rho_h x_5 - \mu_h x_6.$$

The Jacobian matrix of system (37) at $\mathcal{E}^0$ is given by $J(\mathcal{E}^0)$ expressed below

$$\begin{bmatrix} -\mu_n & -\beta_{n_1} & 0 & 0 & 0 & 0 \\ 0 & k_{n_1} & 0 & 0 & 0 & 0 \\ 0 & \rho_n & -\mu_n & 0 & 0 & 0 \\ 0 & -k_{n_2} & 0 & -\mu_h & -\beta_h & 0 \\ 0 & k_{n_2} & 0 & 0 & k_h & 0 \\ 0 & 0 & 0 & 0 & \rho_h & -\mu_h \end{bmatrix}, \tag{38}$$

$$k_{n_1} = \beta_{n_1} - (\mu_n + \rho_n + d_n),\ k_{n_2} = \frac{\beta_{n_2}\Lambda_h\mu_n}{\Lambda_n\mu_h},$$
$$k_h = \beta_h - (\mu_h + d_h + \rho_h).$$

From equation (38) it follows that the reproduction number are,

$$\{\mathcal{R}_{0_n}, \mathcal{R}_{0_h}\}, \tag{39}$$

as defined earlier. If β_h is taken as a bifurcation point and if we consider the case when $\mathcal{R}_{0_h} = 1$ and solve for β_h we obtain

$$\beta_h = \beta_h^* = \mu_h + \rho_h + d_h. \tag{40}$$

The linearized system of the transformed equation (37) with $\beta_h = \beta_h^*$ has a simple zero eigenvalue, hence the Centre Manifold Theory (1981), can be used to analyze the dynamics of (37) near $\beta_h = \beta_h^*$. It can be shown that the Jacobian of (37) at $\beta_h = \beta_h^*$ has a right eigenvector associated with the zero eigenvalue given by $w = [w_1, w_2, w_3, w_4, w_5, w_6]^T$ where,

$$w_1 = w_2 = w_3 = 0,\ w_4 = -\frac{\beta_h^* w_5}{\mu_h},$$
$$w_5 = w_5 > 0,\ w_6 = \frac{\rho_h w_5}{\mu_h}. \tag{41}$$

The left eigenvector of $J(\mathcal{E}^0)$ associated with the eigenvalue at $\beta = \beta^*$ is given by $z = [z_1, z_2, z_3, z_4, z_5, z_6]^T$ where,

$$z_1 = z_3 = z_4 = z_6 = 0,\ z_5 = z_5 > 0,$$
$$z_2 = -\frac{\beta_{n_2}^* \Lambda_h \mu_n z_5}{\Lambda_n \mu_h (\beta_{n_1}^* - \mu_n - \rho_n - d_n)}. \tag{42}$$

noindent In order to establish the conditions for the existence of backward bifurcations, we use Theorem 4 proven in Castillo-Chavez and Song [9].

Theorem 4: Consider the following general system of ordinary differential equations with a parameter ϕ

$$\frac{dx}{dt} = f(x, \phi),\ f : \Re^n \times \Re \to \Re \text{ and } f \in (\Re^n \times \Re), \tag{43}$$

where 0 is an equilibrium of the system that is $f(0, \phi) = 0$ for all ϕ and assume

A1: $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ is the linearisation of system (43) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;

A2: Matrix A has a right eigenvector u and a left eigenvector v corresponding to the zero eigenvalue.

Let f_k be the k^{th} component of f and

$$a = \sum_{k,i,j=1}^{n} z_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$
$$b = \sum_{k,i=1}^{n} z_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \tag{44}$$

The local dynamics of (43) around 0 are totally governed by a and b.

i. $a > 0,\ b > 0$. When $\phi < 0$ with $|\phi| << 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi << 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;

ii. $a < 0,\ b < 0$. When $\phi < 0$ with $|\phi| << 1$, 0 unstable; when $0 < \phi << 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;

iii. $a > 0,\ b < 0$. When $\phi < 0$ with $|\phi| << 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi << 1$, 0 is stable, and a positive unstable equilibrium appears;

iv. $a < 0,\ b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

Computations of a and b:

For system (37), the non-zero partial derivatives of F associated with b are,

$$\frac{\partial^2 f_2}{\partial x_2 \partial \beta_h^*} = D_1,\ \frac{\partial^2 f_5}{\partial x_4 \partial \beta_h^*} = \frac{\mathcal{D}_1 \Lambda_h \mu_n}{\mathcal{D}_2 \Lambda_n \mu_h},\ \frac{\partial^2 f_5}{\partial x_5 \partial \beta_h^*} = 1. \tag{45}$$

It follows from (45) that

$$b = z_5 w_5 > 0. \tag{46}$$

Since $w_1 = w_2 = w_3 = 0$ then for system (37), the non-zero partial derivatives of F associated with a at the disease-free equilibrium are

$$\frac{\partial^2 f_5}{\partial x_5^2} = -\frac{2\beta_h^* \mu_h}{\Lambda_h},\ \frac{\partial^2 f_5}{\partial x_5 \partial x_5} = -\frac{\beta_h^* \mu_h}{\Lambda_h}. \tag{47}$$

It follows from (47) that

$$a = -\frac{2(\mu_h + \rho_h)\beta_h^* \mu_h}{\mu_h \Lambda_h} z_5 w_5^2 < 0. \tag{48}$$

So, $a < 0$ and $b > 0$. Using Theorem 4 item (iv) we establish Theorem 5.

Theorem 5: The unique endemic equilibrium $\mathcal{E}_2^*$ is locally asymptotically stable for $\mathcal{R}_{0_h} > 1$ but close to 1 and $\mathcal{R}_{0_n} > 1$.

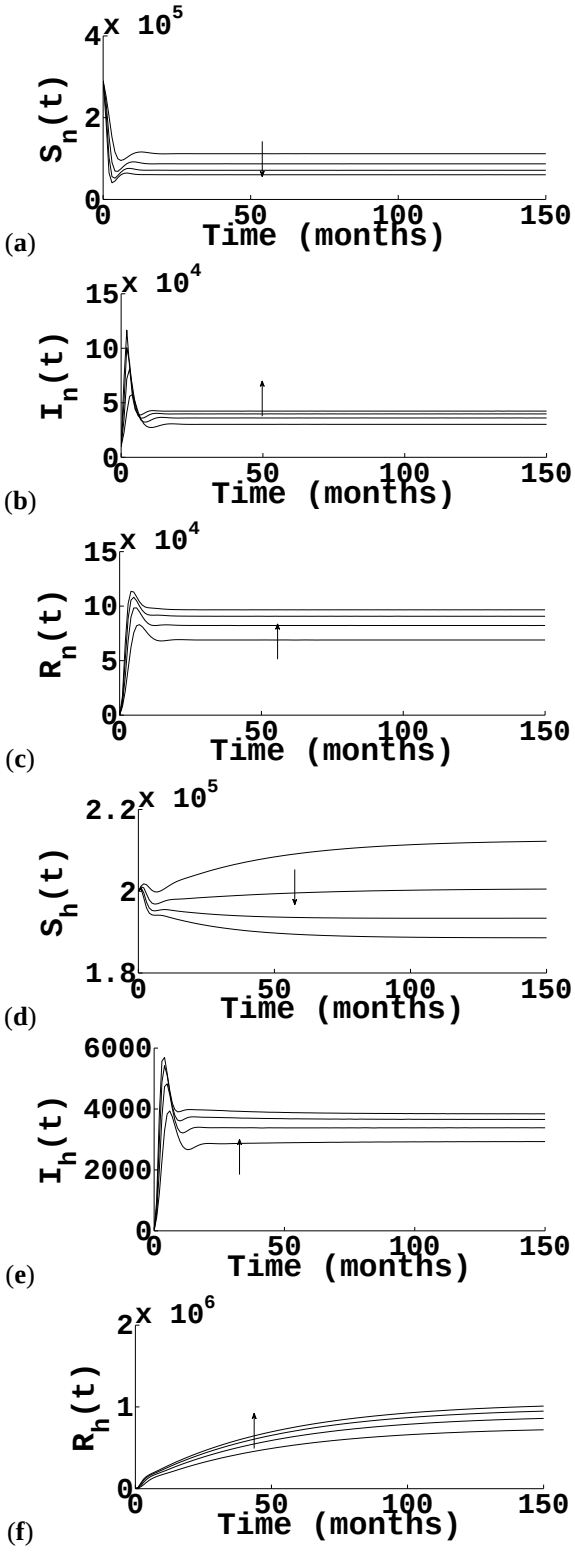

Fig. 2. Simulations of model system (5) showing plots of S_n, I_n, R_n, S_h, I_h and R_h with varying β_{n_1} among non human primates and rodents. The direction of the arrow shows an increase in β_{n_1} among non-humans from 2.0 with a step size of 0.5. Parameters values used are as in Table I.

III. Numerical simulations

The fourth-order Runge-Kutta numerical scheme coded in C++ programming language is used to approximate progression through the disease Complete data on monkeypox are almost unavailable and hard to obtain due to the remote geographical regions where outbreaks have occured in the past, but, for the purpose of illustration, we use a set of reasonable estimates. The model parameters and the values they assume are listed in Table I. Two of the parameter values are provided courtesy of the Central Statistics Office of Zimbabwe (CSOZ) as reported in [7]. Figure 2 is graphical representation showing the effect of varying the infection rate which are represented by β_{n_1}. Figures 2 (a), (b) and (c) show

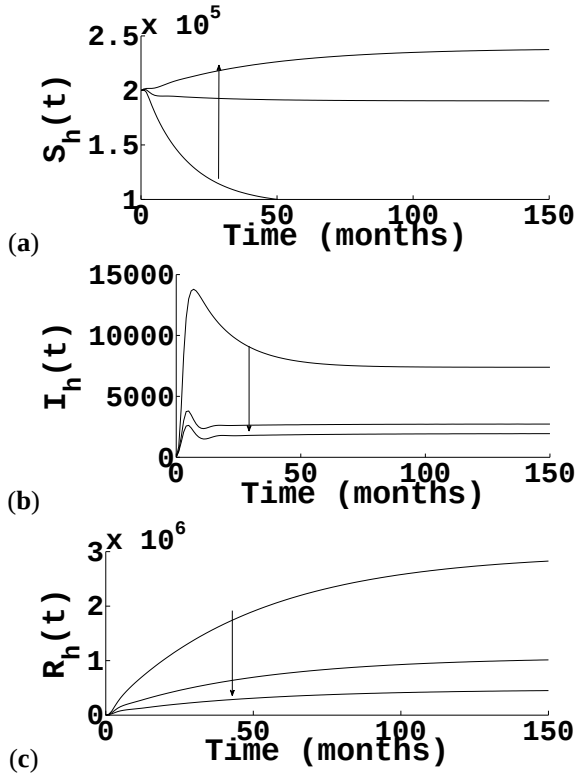

Fig. 3. Simulations of model system (5) showing plots of S_h, I_h and R_h with varying ρ_n among non human primates and rodents. The direction of the arrow shows an increase in ρ_n among non-humans from 0.25 with a step size of 0.25. Parameters values used are as in Table I.

as increase of transmission rate among monkeys result in the depletion of the susceptible monkey population, increase of the infected monkeys, and increase of the recovered monkeys as well, respectively. The increase in infected monkeys results also increase of humans getting infected with monkey pox as it results in increased chances of humans getting infected monkeys when they hunt. Thus, increase of infected humans result in a decrease of susceptible human population and increase of the recovered human population given the high levels of recovery for the monkey pox infected individuals. Here, it is worth noting deforestation and urbanisation turns to shrink the habitat of monkeys increasing the contact between infected monkeys and uninfected ones as making it easier for them to be hunted by humans. All this result in an increase monkey pox related infections among monkeys and humans. Figure 3 shows the effect of increasing the recovery rate among non humans, translate to increase in the human susceptibles and a corresponding decrease of human infectives. This tends to suggest decrease of deforestation and other human activities causing the shrinking of non humans shelter and foraging areas will be able to keep the infections at bay. Increasing ρ_n suggests a situation where the population (non-human) is well fed and as such its immune system will be competent to fend of some infections. This is typical in places where the forests are still virgin where animals have enough to eat. General poverty turns to force people in Africa to hunt and destroy habitats of monkeys and rodents for their meat leading to an increase in human-animal contact rate and consequently an increase in the number of monkeypox related sickness. If poverty can be alleviated, then less contact will likely be translated into less monkeypox infections in humans.

IV. Discussion

A mathematical model which looks into the transmission dynamics of the orthopox virus which causes monkey pox is presented and analyzed. Stability analysis of the endemic equilibria were carried using the Lyapunov functions and centre manifold theory. Using the Lyapunov function conditions where the animal-only endemic equilibrium is globally asymptotically stable were shown when $\mathcal{R}_{0_n} > 1$ and $\mathcal{R}_{0_h} < 1$. The endemic equilibrium where monkey pox infections exist in both the human and non-human populations was shown using the centre manifold theory to be locally asymptotically stable when $\mathcal{R}_{0_h} > 1$, but close to 1. Effects of poor nutrition and general human well being were captured using numerical simulations by varying the rate of recovery. General poverty turns to force people in Central and West Africa to hunt monkeys and rodents for their meat-resulting in an increase of monkey pox cases in people. Poor malnourished individuals recover at slower rate when suffering from monkey pox as their immune system will be weak. Perhaps it may be necessary to re-introduce chicken pox vaccination in monkey pox endemic regions as chicken pox vaccination was known to have some positive impact in curtailing the spread of monkey pox. Since in West and Central Africa non-human and rodents are taken as food source (relish) by humans-possibly the source of orhopox virus infection it may be best for the governments and non governmental organisations to intensively campaign to stop eating of rodents and monkeys as this spreads monkey pox infections from non-humans to humans.

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References

[1] Von Magnus P, Andersen EK, Petersen KB, Birch-Anderson A. A pox like disease in cynomolgus monkeys. *Acta Pathol Microbiol Scand* **46**: 156-176, 1959.

[2] Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. *Bull World Health Organ* **46**:593597, 1972.

[3] Jezek A, Marennikova SS, Mutumbo M, Nakano JH, Paluku KM, Szczeniowski M. Human monkeypox: a study of 2510 contacts of 214 patients. *Journal of Infectious Diseases* **154**:551-555, 1986.

[4] Arita I, Gispen R, Kalter SS, Wah LT, Marennikova SS, Netter R, Tagaya I. Outbreaks of monkey pox and serological surveys in non-human primates. *Bull. WHO* **46**: 625, 1972.

[5] Barbalat I, Système d'équation différentielle d'Oscillation, Nonlinéaires, *Rev. Roumain Math. Pures Appl.* **4**: 267-270, 1959.

[6] Korobeinikov A. Lyapunov functions and global stability for SIR and SIRS epidemiological models with non-linear transmission. *Bulletin of Mathematical Biology* **68**(3):615-626, 2006.

[7] Bhunu CP, Garira W and Magombedze G: Mathematical analysis of a two strain HIV/AIDS model with antiretroviral treatment. *Acta Biotheor* 2009, **57**:361-381.

[8] Carr J. Applications Centre Manifold theory. Springer-Verlag, New York, 1981.

[9] Castillo-Chavez C, Song B. Dynamical models of tuberculosis and their applications. *Math. Biosci. Engr.* **1**(2): 361-404, 2004.

[10] Castillo-Chavez C, Feng Z, Huang W. On the computation of R0 and its role on global stability. math.la.asu.edu/chavez/2002/JB276.pdf, 2002.

[11] Croft DR, Sotir MJ, Williams CJ, Kazmierczak JJ, Wegner MV, Rausch D, Graham MB, Foldy SL, Wolters M, Damon IK, Karem KL, Davis JP. Occupational risks during a monkey pox outbreak, Wisconsin, 2003. *Emerg. Infect. Dis* **13**(8): 1150-1157, 2007.
[12] Damon IK, Roth CE, Chowdhary V. Discovery of monkey pox in Sudan. *N. Engl. J. Med.* **355**(9): 962-963, 2006.
[13] Essbauer S, Pfeffer M, Meyer H. Zoonotic poxviruses. *Vet. Microbiol.* doi:10.1016/j.vetmic.2009.08.026, 2009.
[14] Formenty P, Muntasir MO, Damon I, Chowdhary V, Opoka ML, Monimart C, Mutasim EM, Manuguerra J, Davidson WB, Karem KL, Cabeza J, Wang S, Malik MR, Durand T, Khalid A, Rioton T, Kuong-Ruay A, Babiker AA, Karsani MEM, Abdall MS. Human monkeypox outbreak caused by novel virus belonging to Congo Basin Clade, Sudan, 2005. *Emerg. Infect. Dis.* **16**(10): 1539-1545, 2010.
[15] Rimoin AW, Kisalu N, Kebela-Ilungam B, Mukaba T, Wright LL, Formenty P, Wolfe ND, Shongo RL, Tshioko F, Okitolonda E, Muyembe JJ, Ryder RW, Meyer H. Endemic human monkey pox, Democratic Republic of Congo, 2001-2004. *Emerg. Infect. Dis* **13**(6): 934-936, 2007.
[16] Korobeinikov A. Wake G.C. Lyapunov functions and global stability for SIR, SIRS, and SIS epidemiological models, *Appl. Math. Lett.* **15**, 955-960, 2002.
[17] Korobeineikov A, Maini PK, A Lyapunov functional and global properties for SIR and SEIR epidemiological models with nonlinear incidence. *Math. Biosci. Engr.* **1**(1), 57-60, 2004..
[18] McCluskey CC. Lyapunov functions for tuberculosis models with fast and slow progression.*Math. Biosci. Eng.* **3**(4), 603-614, 2006.
[19] van den Driessche P, Watmough J. Reproduction numbers and sub-threshold endemic equilibria for the compartmental models of disease transmission. *Math. Biosci.* **180**, 29-48, 2002.
[20] Zaucha GM, Jahrling PB, Geisbert TW, Swearengen JR, Hensely L. The pathology of experimental aerosolized monkey pox virus infection in cynomolgus monkeys (*Macaca fascicularis). Lab. Invest.* **81***: 1581-1600, 2001*.