

Article

The Burden of Yellow Fever on Migrating Humans through The Darién Gap, Adjacent Communities, and Primates' Biodiversity

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Abstract: Given the ongoing migratory crisis in Latin America, we aimed to assess the relationship between human mobility and the spread of yellow fever (YF) in the Darién Gap forest. We investigated how the time taken to cross the forest affects the burden of a potential YF outbreak on people migrating through the forest, the burden on adjacent communities, and the risk to primate biodiversity. Using an SEIR-SEI deterministic compartmental model for humans, monkeys, and vectors, and numerical simulations, we considered the time taken to cross the forest as a measure of exposure. If an outbreak occurs, over 23,000 human cases are projected, with approximately 19,000 infected individuals leaving the forest. Monkeys would also be significantly affected, with the number of human deaths being determined by monkey-related parameters. The pace of crossing the forest is strongly related to the number of exposed and active cases leaving the forest. Panamanian communities must receive support to prepare themselves to protect residents and thousands of people arriving in their territory daily. It would also impact the non-human primate community within the forest, preventing a YF outbreak. This reinforces the importance of a planetary health perspective which reinforces the mutual benefits and connections between efforts to protect human health and conserve biodiversity.

Keywords: epizootic diseases; infectious diseases; re-emerging diseases; migration; mathematical modeling



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1. Introduction

Infectious diseases know no borders, and in the context of humanitarian crises, they represent an additional layer of complexity to interventions. With climate change, the spread of climate-sensitive, vector-borne diseases increases in frequency, intensity, and geographic expansion [1–5]. These concerns challenge organizations as the five faces of humanitarian crises—migration, famine, epidemics, disasters, and conflict—are altered by weather patterns and whose interactions can have unpredictable effects [6].

One of the climate-sensitive infectious diseases with a neglect epidemic potential is yellow fever (YF), an epizootic vector-borne disease that circulates endemically in 13 Latin American countries [7]. Although recent trends do not position YF as one of the most pressing public health concerns compared to dengue or malaria, there are several reasons to remain vigilant about it: even with an effective and low-cost vaccine, the vaccination coverage in most South American countries is often below the recommended levels [8–12]. Other than Panama, Central American forests do not yet have evidence of YF as a circulating epizootic.

However, the presence of competent vectors and non-human primate hosts in abundance, associated with other environmental factors that affect the dynamics of climate-sensitive infectious diseases, creates a condition of risk [13]. Still, it is known that YF circulates endemically among non-human primates in the forest of the Darién National

Park, a world heritage that forms a bridge between the South and Central American continent [14,15].

The Darién National Park is surrounded by a continuous forest environment that forms the Darién Gap. This wild and remote roadless region covers the Panama Isthmus and has come to the public attention for being the scenario of one of the most dangerous and impressive phenomena of the recent history of the Latin American migration crisis. The access to the region is hindered by large rivers and mountains, the last 100 km unfinished of the Pan-American Highway built in the 1930s. However, more than 100 thousand people cross the entire forest on foot every year toward Central America [16,17].

By foot, the journey can take seven to more than ten days, and it is considered one of the most dangerous migratory routes in the world due to assault, physical and sexual violence, death by drowning, and homicides. However, those who can pay for a boat ride can reduce the journey to two days [17–19]. In 2022, up to 2400 people daily arrived in the Panamanian side from the Darién forest. It was estimated that 180,000 people would have crossed the gap that year, including 30,000 children, half of them below the age of five [19–21]. It means that, in case of a YF outbreak, the impact on adjacent Panamanian communities could reach great proportions. Moreover, as an epizootic disease, YF also threatens the primate biodiversity of the Darién Forest, which can bring implications for planetary health on unknown scales.

In this context, we aimed to establish a foundational model that serves as a starting point for further exploration. Our study aimed to explore the impact of human mobility on the spread of YF in the Darién Gap, with a focus on a potential outbreak among migrating populations, the implications for adjacent communities, and the risks to primate biodiversity. Using the Darién Gap forest as a scenario, our goal was to assess how the time taken to cross the forest (pace) can represent a risk exposure to YF. Unfolding goals were as follows: (1) explore how the pace affects the burden of a potential YF outbreak on people migrating through the forest in terms of cases and fatalities; (2) explore how it represents an additional burden on adjacent communities by counting the number of exposed or infected individuals leaving the forest; and finally, (3) explore in what way it represents a risk for the primate biodiversity in the Darién Gap.

2. Materials and Methods

2.1. Context and Initial Conditions

We evaluated the impacts of people crossing the Darién Forest from the perspective of both migrating humans and non-human primates living in the forest, as well as the burden of the disease on them by the continuous entry of new susceptible human hosts.

As the flow continuous in the forest, we considered that there were already 1000 susceptible humans inside the forest when the simulation started, where non-human primates already deal with the sylvatic circulation of YF. Then, based on the numbers and reports mentioned in the introduction section, we included 500 new people entering daily, summing up 180 thousand a year. Among these, we considered that one infected human host enters the forest at $t = 1$. For a population of 1000 monkeys, the number of mosquito vectors is 1.5 times higher ($N_v = 1500$). The selection of 1000 host individuals is arbitrary and chosen for simplicity. The proportion of mosquitoes being 1.5 times higher is based on Ronald Ross's malaria studies, specifically as the minimum number of vectors required to surpass the epidemic threshold. This convention has gained widespread adoption as a common practice in epidemiological modeling studies.

The time of exposure represented the time taken to cross the forest, leading to a certain number of infective individuals leaving the forest, which represents a burden for the Panamanian communities regarding YF outbreak risk.

2.2. Equations

We applied a deterministic compartmental model SEIR-SEI based on the classical Ross-Macdonald model for vector-borne diseases. The model contains three distinct

populations: human hosts, monkey hosts, and mosquito vectors. Each population contains compartments related to the stages of the epidemic. At the beginning, all individuals were considered to be susceptible (S), and when they first came into contact with the virus, they moved to the exposed (E, or latent) compartment. After becoming infected, the individuals moved to the infected compartment (I). Finally, humans and monkeys can recover (R) when they have survived the infection and are no longer transmitting the virus. Given the short lifespan of mosquitoes compared to the primate hosts and considering that they do not die from the infection, the recovered compartment was not applied to the population of vectors. The speed at which individuals move from one compartment to another was determined by the rates presented in Table 1.

System 1 for human hosts:

$$\frac{dSh}{dt} = \delta_h \cdot S_h - a \cdot b_1 \cdot I_v \cdot \left(\frac{Sh}{Nh} \right) - \mu_h \cdot S_h - \chi_h \cdot S_h \quad (1)$$

$$\frac{dEh}{dt} = a \cdot b_1 \cdot I_v \cdot \left(\frac{Sh}{Nh} \right) - (\varepsilon_h + \mu_h + \chi_h) \cdot E_h \quad (2)$$

$$\frac{dIh}{dt} = \varepsilon_h \cdot E_h - (\gamma_h + \alpha_h + \mu_h + \chi_h) \cdot I_h \quad (3)$$

$$\frac{dRh}{dt} = \gamma_h \cdot I_h - \mu_h \cdot R_h - \chi_h \cdot R_h, \quad (4)$$

System 2 for monkey hosts:

$$\frac{dSm}{dt} = -a \cdot b_2 \cdot I_v \cdot \left(\frac{Sm}{Nm} \right) - \mu_m \cdot (E_m + I_m + R_m) \quad (5)$$

$$\frac{dEm}{dt} = a \cdot b_2 \cdot I_v \cdot \left(\frac{Sm}{Nm} \right) - (\varepsilon_m + \mu_m) \cdot E_m \quad (6)$$

$$\frac{dIm}{dt} = \varepsilon_m \cdot E_m - (\gamma_m + \alpha_m + \mu_m) \cdot I_m \quad (7)$$

$$\frac{dRm}{dt} = \gamma_m \cdot I_m - \mu_m \cdot R_m, \quad (8)$$

System 3 for mosquito vectors:

$$\frac{dSv}{dt} = -a \cdot c \cdot S_v \cdot \left(\frac{Iv}{Nv} \right) + \mu_v \cdot (E_v + I_v) \quad (9)$$

$$\frac{dEv}{dt} = a \cdot c \cdot S_v \cdot \left(\frac{Iv}{Nv} \right) - (\varepsilon_v + \mu_v) \cdot E_v \quad (10)$$

$$\frac{dIv}{dt} = \varepsilon_v \cdot E_v - \mu_v \cdot I_v, \quad (11)$$

where the systems coupling is described following the parameters section.

2.3. Parameters

The parameters applied to the model, drawn from scientific literature and key organizational reports, are outlined in Table 1.

Table 1. Parameters and their respective meanings and assigned values.

Variables	Biological Meaning	Initial Value	Unit
S	Susceptible individuals	Variable	Individuals
E	Exposed or latent individuals	Variable	Individuals
I	Infected (or infective) individuals	Variable	Individuals
R	Recovered individuals	Variable	Individuals
Parameters	Biological meaning	Daily rates	Source
a	Average biting rate	0.33 day^{-1}	[22]
b_1	Fraction of infective bites from vector to human	0.25	[23]
b_2	Fraction of infective bites from vector to monkey	0.4	[23]
c	Susceptibility of <i>Haemagogus</i> mosquito to the virus	0.4	[23]
μ_h	Natural mortality rate of humans	$3.77 \times 10^{-5} \text{ day}^{-1}$	[24]
μ_m	Natural mortality rate of monkeys	0.00016 day^{-1}	[23]
μ_v	Natural mortality rate of <i>Haemagogus</i> mosquitoes	0.0153 day^{-1}	[25]
γ_h	Human recovery rate	0.1428 day^{-1}	[26]
γ_m	Recovery rate in monkeys	0.1 day^{-1}	[23]
ϵ_h	Latency rate in humans	0.167 day^{-1}	[26]
ϵ_m	Latency rate in monkeys	0.167 day^{-1}	[23]
ϵ_v	Latency rate in mosquitoes	0.111 day^{-1}	[26]
α_h	Disease-induced mortality rate in humans	$8.0 \times 10^{-4} \text{ day}^{-1}$	[22]
α_m	Disease-induced mortality rate in monkeys (average)	0.0083 day^{-1}	[23]
δ_h	Migration rate or entry rate	0.49 day^{-1}	[20]
χ_h	Pace: time taken to cross the forest	2 to 10	Variable

2.4. Systems Coupling

Each system of equations represents a population where the compartments are sub-scribed by h in the case of humans (S_h, E_h, I_h, R_h), m indicating monkeys (S_m, E_m, I_m, R_m), and v for vectors (S_v, E_v, I_v). The two host populations are connected to the vector population by the term of transmission based on the parameters of transmission from vector to host (b) and from host to vector (c) multiplied by the biting rate (a). The results of this equation mean that as the number of infected human hosts increases, the number of infected mosquitoes increases, raising the number of cases among monkeys or the other way around. If the first case happens in the vector population, both host populations will have new cases according to their rates.

Humans enter the system (representing the forest) according to the entry rate or migration rate (δ_h) and leave the system according to the number of days to cross the forest (pace). All humans enter the system in the susceptible compartment (S_h) since we assume all humans migrating are naive for YF. However, the leave rate was applied to all of the compartments indicating the time of exposure, since the time taken to cross the forest determines at what stage each individual leaves the system. This way, we counted how many people left the forest as exposed or infected, being able to carry the virus to the adjacent communities.

Assumptions

Assumptions are integral to modeling studies, aiming for feasibility, practicality, and clarity, and helping focus on essential elements and key factors without overwhelming complexity. When it is impractical or impossible to account for every detail in a system, assumptions allow us to create models that are feasible to develop, analyze, and interpret within the given resources and constraints.

- Our models involve parameters that are challenging to measure precisely, such as the YF immunization prevalence among migrants. For example, assuming that all migrants are naive helps to simplify the approach, making the model more practical. All of the assumptions listed below help focus on specific questions and can be incorporated into new versions of the model when they align with the objectives. However,

since they do not directly contribute to our primary goal, we have chosen to establish them as follows: all three population densities are assumed to be homogeneous with constant spatial distributions;

- There is no vaccination nor another control measure in the model;
- There is no seasonality in the dynamics of the disease;
- Vectors and monkeys do not migrate.

Simulations were performed in the R environment version 4.1.3 using the “*lsoda*” (Ordinary Differential Equations) function of the *deSolve* package version 1.33 [27].

2.5. Sensitivity Analysis

Sensitivity analyses provide means to assess model adequacy and identify factors influencing model outputs. Using the *epiR* 2.0.53 package, we employed the partial rank correlation coefficient (PRCC) analysis to examine the association between the number of cases generated and model parameters. Utilizing a sampling-based method, the PRCC generated 1000 parameter combinations, with each parameter uniformly distributed within its range. Calculating the PRCC allows for the determination of statistical relationships between each input parameter and the outcome variable while holding other parameters constant at their expected values. This approach unveils the independent effects of each parameter, even when correlated. The sign of the PRCC indicates the qualitative relationship, while its magnitude reflects the importance of input variable uncertainty in predicting the outcome variable. Parameters with PRCC > 0 exhibit a positive correlation with the number of cases, while those with PRCC < 0 show a negative correlation, signifying a decrease in cases with parameter increase. A substantial PRCC signifies a robust influence of the model parameter on the results. Direct evaluation of input variable importance is feasible by comparing PRCC values [28].

3. Results

3.1. Sensitivity Analysis

The partial rank correlation coefficient analysis shows the relative importance of parameters and variables to two outputs: the number of human cases (Figure 1A) and the number of human deaths (Figure 1B). Although the first elements have a similar effect on the number of cases and deaths, two components have different roles among the outcomes: the recovery rates in monkeys (γ_m) and the disease-induced mortality rates in monkeys (α_m).

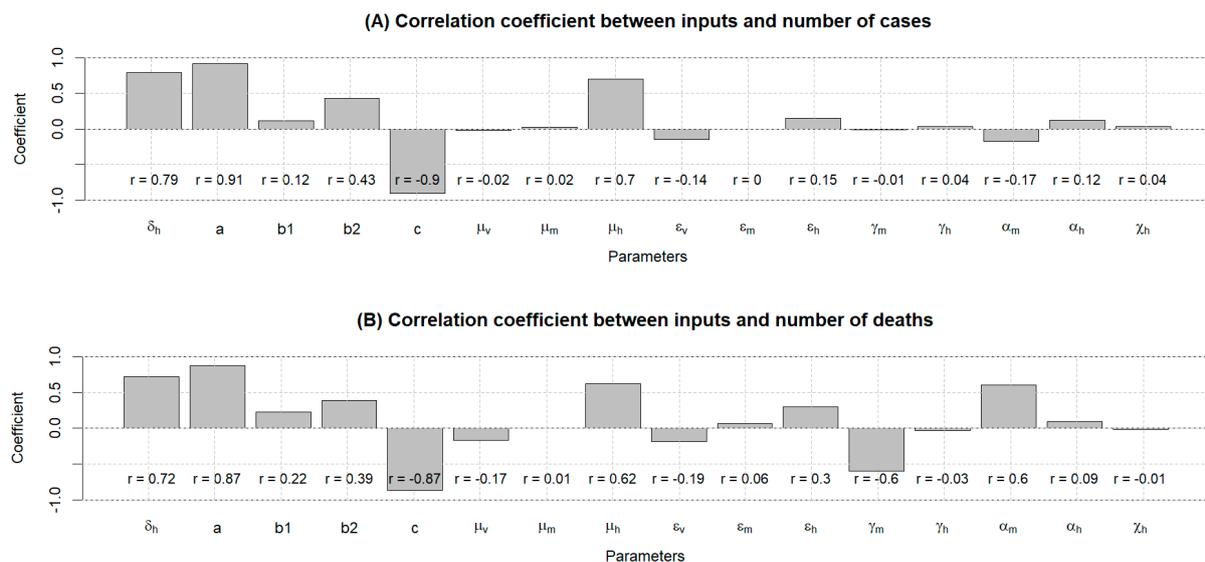


Figure 1. Partial rank correlation coefficients for the number of cumulative cases (A) and cumulative deaths (B) among humans crossing the Darién Forest as the output variable.

3.2. Burden on Migrants in the Darién Forest and Panamanian Communities throughout the Time of Exposure (χ_h)

With the continuous entry of new people into the forest, the system remains stable, balanced by the exit rate represented by the number of days people take to leave the forest. One exception is the pace of two days, which is too high to be compensated by the number of people entering every day. The disease dies out after 38 days due to the depletion of those susceptible, since this exceptionally rapid exit rate surpasses the compensatory capacity of daily entries (see Table 2).

Table 2. Output of the simulations.

Pace (Days)	Human Cases	Human Deaths	Exposed People Leaving
10	23,907	51	15,105
7	23,904	37	17,440
5	23,900	26	19,332
2	894	0	847

As depicted in Table 2, the time taken to traverse the forest exhibits an inverse relationship with the number of individuals exiting the forest in an exposed (E_h) or infected state (I_h). This relationship is most pronounced when the crossing duration is five days. Concurrently, Figure 2 illustrates that the outbreak dynamics remain similar across all three scenarios. Once initiated, the outbreak tends to persist with the continuous influx of migrating humans into the forest, without displaying the typical descending phase of the curve when susceptible individuals become scarce, due to the continuous entry of susceptible migrants.

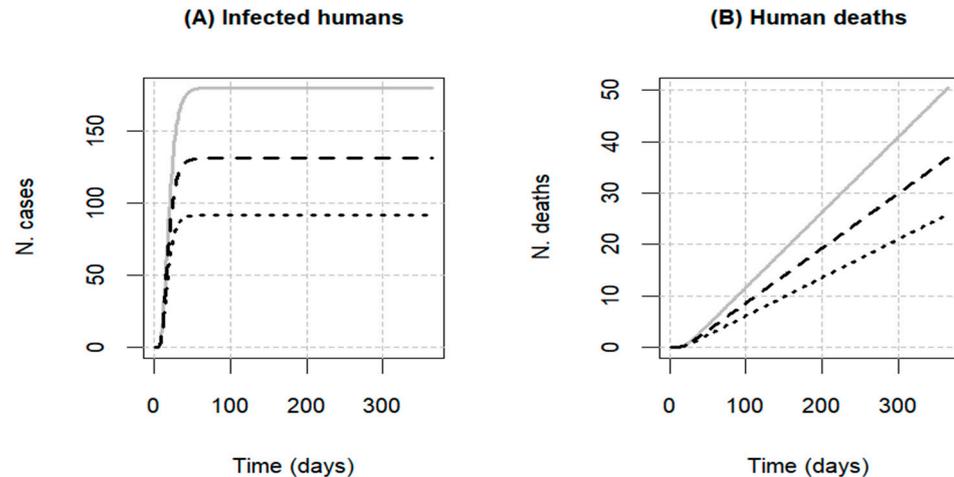


Figure 2. (A) Epidemic curve of human cases and (B) deaths according to the three paces tested: five days (dotted black line), seven days (dashed black line), and ten days (gray line). The pace of two days is not shown in the graphs since the disease dies out at such speed. Simulations are based on groups of 1000 people.

3.3. Burden on Primates' Community in the Darién Forest

Regardless of the conditions created in the simulations, the impact on the non-human primate population remains stable even with human groups crossing the forest in 5 or 10 days; in a year, there will be 1141 cases and 87 deaths among monkeys. In the case of people being able to cross the forest in 2 days, the number of infected monkeys would be 958 and 47 deaths, but as previously mentioned, with this condition, the epidemic dies out after 38 days. Still, if there were not a single human in the system and an infected mosquito introduced the YF instead, the outcome over the non-human primate community would be similar to the first results. Under the applied parameters, non-human primate populations

face significant vulnerability, reaffirming their status as the most affected group in the proximity of human populations experiencing YF outbreaks.

4. Discussion

One infected human with YF can initiate an outbreak of grand proportions, regardless of whether the individual is a migrant, a traveler, or a resident. The findings presented in this study are not, in any scenario, an excuse to impose barriers to migration which would increase the suffering of the migrant without solving the problem. Walls do not contain diseases, particularly vector-borne diseases, and in fact, there is evidence that migration may even decrease the disease burden between endemic communities by diluting cases and slowing down the transmission rate [29]. For simplicity, one of our assumptions is that vectors do not migrate. However, as the geographical distribution of vectors is predicted to expand with the changing climate, this spread may be a lot more significant to introducing diseases in new disease-free territories shortly.

Concerning the influence of the time taken to cross the forest, the sensitivity analysis results in Figure 1 align with the data in Table 2, indicating that the pace does not affect the number of cases, and has only a minor impact on deaths. The speed of forest crossing seems to be a confounding factor, running in parallel with the time it takes for the infection to naturally progress within the population. However, the pace does play a critical role in reducing the number of exposed individuals leaving the forest as their stay duration increases by determining how many people will become infected in or out of the forest limits. In other words, the less time people take to leave the forest, the greater the number of active cases entering adjacent Panamanian communities.

In addressing this concern, the hypothesis proposing that a higher proportion of small children crossing the forest would impede the group's progress, potentially leading to an increase in the number of cases, has been refuted. Nevertheless, this topic warrants thorough examination in future studies, particularly considering the notable surge in the number of small children traversing the Darién Gap in recent times. Young, unimmunized children represent the most vulnerable demographic to the disease, and in the event of a YF outbreak, it is plausible that they might constitute a significant proportion of the fatalities. [20,21].

It is essential to highlight that only people taking a boat in the first part of the journey can cross the forest in 2 days since the distance to be crossed is significantly reduced. However, in all of the other cases, which represent the majority of people crossing the Darién Gap, the figures on how a potential YF pandemic would affect such a large number of individuals are impressive. It is also expected that part of the group will be vaccinated against YF or immune due to previous contact with the disease, since many come from or have spent time in South American endemic countries. However, there are two reasons for not taking this into account: First, as most of them come from Venezuela and the national health system collapsed years ago, there are no data regarding YF immunization coming from the country, and the proportion of immunized people is hard to estimate [30]. Secondly, there are migrants from many other nations coming to South America to cross the border through the Darién Gap where the immunization rates can be hard to deduce.

The proportion of people leaving the forest either exposed or infected may bring an additional challenge for the adjacent Panamanian communities. Although Panama is one of the few yellow fever-endemic countries to reach recommended vaccination coverage in recent years, the widespread reduction in vaccination efforts in the surrounding countries is cause for concern. It is not debatable how much the maintenance of vaccination routines against climate-sensitive diseases works as a form of climate adaptation for endemic and at-risk communities [31]. Furthermore, vaccination works as a protective filter for Central America's human and non-human primate communities: humans vaccinated before the crossing help protect primate biodiversity and preserve lives along the way and in the adjacent Panamanian communities [10,26]. Moreover, in the case of YF, vaccination is the best cost-benefit solution.

As expected, the parameters related to specific mortality significantly impact the number of human deaths. However, the impact of monkey-related parameters on human deaths is remarkable. This finding suggests that the YF dynamics among humans and non-human primates and their impacts on biological diversity are worthy of further exploration in the context of planetary health studies. Although the geographic distribution of primate richness drastically reduces from the Amazon to Central America, the occurrence of *Alouatta* monkeys, the most susceptible genera to YF, overlaps with the geographic distribution of *Haemagogus*, the most competent vector for YF in the Americas. At the same time, these occurrences coincide with important migratory routes, one of them being the Darién Gap [32,33].

In addition, the disease-induced mortality rate for monkeys is an estimated average value and does not reflect the impact on particular species. For example, the YF fatality rate among howler monkeys can reach 60% or 80% [34–36]. This death rate means that, despite having a reasonable impact on the primate community, some species are strongly more affected than others, with a high risk of local extinction which will lower the regional ecological biodiversity and may bring consequences not explored in this paper. We have chosen to use an average fatality rate, since group-specific rates would strongly increase the complexity of the model and shift from its purpose, requiring a different system of equations for each taxonomic group. However, using an average value underestimates the real impact of YF on the primates' biodiversity, and exploring the impacts with more accurate and genera-specific numbers is an opportunity to be pursued in future studies.

Exploring further developments in the impacts of yellow fever can be achieved through a multi-host coupled system that takes into account various monkey species, each characterized by its distinct rates.

The high mortality of howler monkeys due to YF is probably one of the most relevant aspects of its spatiotemporal dynamics in South America. The disease displays spatially scattered and fairly regular episodes of epizootics outbreaks every 6 to 8 years, but those episodes occur in different regions, hardly hitting twice the same region 8 years later. The intense population decline in non-human primates due to the high lethality of YF may be responsible for the depletion of susceptible individuals, and the biological features of some primate species, such as a long gestational period and low reproductive rate, aggravate it. The low turnover for population restoration makes the maintenance of YF unlikely in populations that experience epizootic events [37]. That said, preventing yellow fever outbreaks is not just a matter of public health but of biodiversity conservation: a key component of planetary health.

In addition to the limitation imposed by the average death rate for monkeys mentioned above, future versions of the model could be age-structured to assess the impact of migrating children, since this is a concerning trend in the migration crisis and is mainly related to the risk of infectious diseases. The significance of this proposal is rooted in the potential of modeling tools to assess the distinct burden within each age group, facilitating the design and implementation of targeted interventions to address specific issues affecting vulnerable groups. Modeling studies serve as valuable tools for pattern deciphering and solution design, yet caution is necessary due to their inherent simplification of complex realities. Striking a balance is crucial, as overly complex models may have limited feasibility, while overly simplistic ones may produce poor predictions. Reformulation of the assumptions made in this study for their integration into more complex model versions supports ongoing refinement to accurately portray the complex reality. Additionally, recognizing that parameters from the literature may lack precision, the inclusion of fitting parameters from updated databases enhances the model's accuracy. This approach ensures modeling studies contribute insights into complex phenomena while being mindful of limitations and the need for continual improvement.

5. Conclusions

Current conditions of migration routes traversing forested landscapes are of deep concern, posing a significant threat to both human and non-human primate populations susceptible to yellow fever. Contrary to expectations, the time taken to cross the forest does not serve as a reliable proxy for exposure, as it does not amplify the number of cases. However, it does manifest in the count of active cases leaving the forest and entering neighboring Panamanian communities, thereby imposing an additional strain on local health systems. In the event of an outbreak initiated by the virus introduction into the forest, the primate community faces severe consequences. Under any scenario, virtually all non-human primates are susceptible to contracting the virus, and the imminent risk of ecosystem collapse arises due to the potential local extinction of certain species. In this context, this study's findings contribute valuable insights into the interplay between infectious diseases, migration, and biodiversity conservation, underscoring the necessity of adopting a holistic approach to public health through a planetary lens.

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