Supplemental Information

Assessing the Risk of International Spread of Yellow Fever Virus: A Mathematical Analysis of an Urban Outbreak in Asunción, 2008

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MODEL STRUCTURE

Overview. Each city is separated into two distinct human populations: travelers from other cities, T, and long-term residents of the city, R. Travelers are subdivided into compartments by their city of residence (because they may return there) and infection state. Residents are subdivided only by infection state. Each city also contains a single mosquito population. There are three independent types of transition events that take place: travel, infection progression, and birth/death. Because these processes are independent, we treat them in discrete steps. For each time step, we first calculate the number of travelers traveling between each city in each infection state. We then update each compartment accordingly. Next, we calculate updates to infection status (exposure, becoming infectious, and recovery) and, lastly, the population dynamics.

Travel. The first step is to calculate the number of travelers who move between each city pair. We assume that one-half of the outgoing travelers, Y, between locations i and j will be outgoing residents (and the other one-half will be travelers from j returning to j). The probability of outgoing resident travel, $p_{i,j}$, is, thus, one-half the number of expected outgoing travelers divided by the total resident population, R (including each compartment, c) currently in i:

$$p_{i,j} = (Y_{i,j}/2)/(\sum_c R_{i,c}).$$

For each resident compartment, $R_{i,c}$, the number of outgoing travelers, Ω^R, to each other city is sampled from a multinomial distribution:

$$\Omega^R_{i,\cdot,c} = \text{Multinomial}(R_{i,c}, p_{i,\bullet}).$$

For travelers who are residents of j but currently in i, the number returning to j in a time step is sampled from a binomial distribution for each traveler compartment, $T_{i,j,c}$, with a constant probability of return, ρ:

$$\Omega^T_{i,j,c} = \text{Binomial}(T_{i,j,c}, \rho).$$

After calculating all Ω, resident compartments are updated by adding the compartment-specific total number of returning travelers from each other city less the number of outgoing travelers:

$$R_{i,c} \Leftarrow R_{i,c} + \sum_{j \neq i}^{N} (\Omega^T_{i,j,c} - \Omega^R_{i,j,c}).$$

Each traveler compartment is also specific to the city of origin, and therefore, the change in one time step is the number of incoming compartment-specific travelers from the other city minus the number returning to that city:

$$T_{i,j,c} \Leftarrow T_{i,j,c} + \Omega^R_{i,j,c} - \Omega^T_{i,j,c}.$$

Infection states. Humans can be classified into four principal states relative to yellow fever infection: susceptible, exposed/incubating, infectious, and recovered/immune (H_S, H_E, H_I, and H_R, respectively). The H_E and H_I compartments are subdivided into temporal states to give more flexibility to the classification of these transient periods[1] and carry an additional subscript representing the time within that state. Subscripts for location and travelers versus residents are omitted for simplicity in presentation and because both residents and travelers are subject to the same local transmission dynamics. Nonetheless, to preserve the travel dynamics, in the code, there are explicit compartments and subcompartments for each resident and traveler group. Because we do not track changes in all compartments over time, all of the change components (h) are calculated before updating the compartments (H) themselves. Human infection in each city is dependent on the number of susceptible humans, H_S, and the force of infection for humans, λ_{VH}, the product of the vector density, φ, the daily biting rate, α, the efficiency of vector to human transmission, β_{VH}, and the proportion of vectors currently infectious, the total number of infectious vectors, V_I, divided by the total number of vectors from all compartments, ΣV:

$$\lambda_{VH} = \varphi\alpha\beta_{VH}(V_I/\textstyle\sum V).$$

Newly exposed humans are then sampled from a binomial distribution:

$$h_{S\rightarrow E_0} = Binomial(H_S, \lambda_{VH})$$

Humans become infectious with a time step-dependent probability, $p_{IIP}(\tau)$, determined by the cumulative distribution of the intrinsic incubation period, F_{IIP} (described in Parameterization):

$$h_{E_\tau \rightarrow I_0} = Binomial(H_{E_\tau}, p_{IIP}(\tau)),$$

for

$$\tau = 1, 2, \ldots \tau_{IIP}.$$

They may also become infectious the same day that they are infected:

$$h_{S\rightarrow E_0 \rightarrow I_0} = Binomial(h_{S\rightarrow E_0}, p_{IIP}(0)).$$

The human infectious period is expressed as a time-dependent cumulative distribution function, F_{IP}, with time step-specific probabilities of recovery, $p_{IP}(\tau)$:

$$h_{I_\tau \to R} = Binomial(H_{I_\tau}, p_{IP}(\tau))$$

for

$$\tau = 1, 2, \ldots \tau_{IP}.$$

Individuals may also recover the same day that they become infectious:

$$h_{E_\tau \to I_0 \to R} = Binomial(h_{E_\tau \to I_0}, p_{IP}(0)),$$

for

$$\tau = 1, 2, \ldots \tau_{IP,}$$

and

$$h_{S \to E_0 \to I_0 \to R} = Binomial(h_{S \to E_0 \to I_0}, p_{IP}(0)).$$

Vector mosquito populations are divided into three states relative to infection: susceptible, exposed/incubating, and infectious (V_S, V_E, and V_I, respectively). Only the V_E compartment includes subcompartments, because infectious mosquitoes are assumed to remain infectious until their death (mosquito mortality is discussed in the next section). In each city, the force of infection for vectors, λ_{VH}, is the product of the biting rate, α, the efficiency of human to vector transmission, β_{HV}, and the proportion of humans currently infectious, the total number of humans from all infectious subcompartments, ΣH_I, divided by the total number of humans from all compartments, ΣH:

$$\lambda_{HV} = \alpha \beta_{HV} \left(\sum H_I / \sum H \right).$$

This rate is used to sample a binomial distribution for newly exposed/incubating individuals:

$$v_{S \to E_0} = Binomial(V_S, \lambda_{HV}).$$

Progression from exposed/incubating subcompartments to the infectious state is dependent on completing the temperature-dependent extrinsic incubation period, F_{EIP}, with probabilities of progression $p_{EIP}(\tau, TEMP)$ (described in Parameterization):

$$v_{E_\tau \to I} = Binomial(V_{E_\tau}, p_{EIP}(\tau, TEMP))$$

for

$$\tau = 1, 2, \ldots \tau_{EIP}$$

and

$$v_{S \to E_0 \to I} = Binomial(v_{S \to E_0}, p_{EIP}(0, TEMP)).$$

Population dynamics. In addition to infection, populations are also susceptible to mortality. For the human population, we assume that there is no mortality. Although this assumption is clearly not realistic, human longevity greatly exceeds the complete course of a yellow fever virus (YFV) infection, and thus, human mortality may be ignored while modeling the short-term dynamics of YFV spread.

All vector compartments are susceptible to mortality, μ, which is dependent on mean daily local temperature, *TEMP*, and vapor pressure deficit, *VPD* (described in Parameterization). Each vector compartment, *c*, is exposed to the same spatio-temporally explicit mortality rate that we convert to a probability of survival:

$$v_{c \to survive} = Binomial(v_c, 1 - \mu(TEMP, VPD)).$$

New susceptible vectors are generated from a Poisson distribution. The mean of this distribution is the product of the parameterized nominal mean vector density (per human; described later), φ, the minimum daily mortality, $\mu_{\min}$, and the human population size, ΣH:

$$v_{emerge \to S} = Poisson\left(\varphi \mu_{\min} \sum H\right).$$

This parameterization results in a vector density of approximately φ under ideal environmental conditions (i.e., when mortality is minimal).

Model updates. After each vector and human change component is calculated, new values are calculated for each compartment:

$$H_S(t+1) = H_S(t) - h_{S \to E_0},$$

$$H_{E_1}(t+1) = h_{S \to E_0} - h_{S \to E_0 \to I_0},$$

and

$$H_{E_{\tau+1}}(t+1) = H_{E_\tau}(t) - h_{E_\tau \to I_0}$$

for

$$\tau = 1, 2, \ldots \tau_{IIP},$$

$$H_{I_1}(t+1) = h_{S \to E_0 \to I_0} - h_{S \to E_0 \to I_0 \to R} + \sum_{\tau=1}^{\tau_{IIP}} (h_{E_\tau \to I_0} - h_{E_\tau \to I_0 \to R})$$

and

$$H_{I_{\tau+1}}(t+1) = H_{I_\tau}(t) - h_{I_\tau \to R}$$

for

$$\tau = 1, 2, \ldots \tau_{IP},$$

$$H_R(t+1) = H_R(t) + h_{S \to E_0 \to I_0 \to R} + h_{E_0 \to I_0 \to R} + \sum_{\tau=1}^{\tau_{IP}} h_{I_\tau \to R},$$

$$V_S(t+1) = v_{emerge \to S} + Binomial(V_S(t) - v_{S \to E_0}, 1 - \mu(TEMP, VPD)),$$

$$V_{E_1}(t+1) = Binomial(v_{S \to E_0} - v_{S \to E_0 \to I}, 1 - \mu(TEMP, VPD)),$$

and

$$V_{E_{\tau+1}}(t+1) = Binomial(V_{E_\tau}(t) - v_{E_\tau \to I}, 1 - \mu(TEMP, VPD))$$

for

$$\tau = 1, 2, \ldots \tau_{EIP},$$

and

$$V_I(t+1) = Binomial\left(V_I(t) + v_{S \to E_0 \to I} + \sum_{\tau=1}^{\tau EIP} v_{E_\tau \to I}, 1 - \mu(TEMP, VPD) \right).$$

PARAMETERIZATION

Populations. A total of 141 cities were selected for the model based on their importance to international travel, proximity to yellow fever endemic areas, and involvement in the recent spread of chikungunya virus. Approximate human population sizes for each city were obtained from the United Nations Statistics Division (2005 Demographic Yearbook) and Population Division (World Urbanization Prospects: The 2007 Revision Population Database).

We first attempted to develop a complete *Aedes aegypti* life cycle model similar to the model of CIMSim.[2] However, modeling local populations in each city using standardized containers produced results that were not consistent with empirical data. For example, some cities only had adults seasonally, whereas ample empirical evidence suggests that adult vectors are present year round. Instead of modeling the complete lifecycle, we based the mosquito population on general habitat suitability and a maximum density of *Ae. aegypti* per person. First, we qualified each city as suitable if it experienced greater than 6 months in the average year with temperatures above 10°C and at least 1 mm of rainfall. Under those conditions, oviposition and survival of previously deposited eggs are unlikely.[3] For suitable cities, the initial vector population size is a random variable from a Poisson distribution with a mean of the product of this density, φ, the human population size, N_H, and the ratio of nominal mortality, $\mu_{\min}$, to actual mortality, $\mu(TEMP, VPD)$:

$$V_S = Poisson\left(\varphi N_H \frac{\mu_{\min}}{\mu(TEMP, VPD)}\right).$$

As described above, new susceptible mosquitoes were added daily to susceptible cities at a rate that would allow the population to reach the maximum density if weather conditions permitted minimum mortality. Three different maximum densities were assessed: one, two, and four female mosquitoes per person. These densities cover a spectrum of measured densities and exceed estimated dengue transmission thresholds.[4] Qualitatively, the populations showed expected patterns, with presence/absence and varying degrees of seasonality dependent on local climate.

Travel. Travel volumes between each city pair were estimated using a generalized linear regression model. The modeled outcome was the total number of itineraries originating and/or ending in a US airport included in the model from a 10% sample of all such flights (US Department of Transportation, www.transtats.bts.gov/Tables.asp?DB_ID=125). Itineraries were used rather than direct connection data, because direct travel only represents a proportion of travelers and connecting travelers are of particular importance when transmission efficiency is spatially heterogeneous.[5] To ensure that travel was directionally balanced, we used combined characteristics of the origin and destination cities and characteristics of the route between them as potential covariates. City characteristics included population size and airline network characteristics such as adjacency, strength, and betweenness centrality.[6] Route characteristics included physical distance, number of required connections, number of alternative routes, maximum daily passengers along the route, average connectivity of connecting cities, and whether the origin and destination are in the same country. The overall network was characterized using direct connection data (Official Airline Guide, www.oagaviation.com/Solutions/AnalysisTools/Traffic/t100inet.html).

Selecting the strongest correlates and eliminating potentially redundant measures, the final model used adjacency, strength, population size, and whether the origin and destination are in the same country. Although this model consistently overestimated infrequently traveled routes, it accounted for approximately 90.8% of the overall variation (R^2_{KL}).[7] This US-based model was then used to estimate daily travel volumes for each city pair within the complete set of global cities.

The duration of stay for travelers in locations other than their home city was parameterized as an exponential distribution, with mean duration of stay, d:

$$F_{RETURN} = 1 - e^{-t/d}.$$

The mean stay was estimated to be 18 days.[8] Because the exponential hazard is independent of time, the daily probability of return is equal to the cumulative distribution function over the first day:

$$\rho = 1 - e^{-1/18} \approx 0.054.$$

Vector activity. The rate of mosquito feeding, α, is difficult to measure directly. Although requiring one blood meal per gonotrophic cycle, *Ae. aegypti* often feed multiple times, either because of incomplete, interrupted feeding or metabolic necessity.[9] Variability also relates to the size of the mosquito[10] and the length of the gonotrophic cycle,[11] both dependent, in turn, on temperature. Rates of daily *Ae. aegypti* human biting ranging from 0.25 to 1.2 have been used for modeling.[12–14] The most comprehensive field study to date estimated rates of 0.63 and 0.76 human blood meals per mosquito per day in Puerto Rico and Thailand, respectively.[9] Here, we use three different values to capture the range of likely values: 0.5, 0.7, and 1.

Temperature- and humidity-dependent *Ae. aegypti* mortality was parameterized according to the CIMSim model by Focks and others[2]:

$$\phi_{TEMP}(TEMP) = \begin{cases} 0.05 & \text{if } TEMP \le 0 \\ 0.05 + (0.95/4)TEMP & \text{if } 0 < TEMP \le 4 \\ 1 & \text{if } 4 < TEMP \le 36 \\ 6.7 - (0.95/6)TEMP & \text{if } 36 < TEMP \le 42 \\ 0.05 & \text{if } 42 < TEMP \end{cases},$$

$$\phi_{VPD}(VPD) = \begin{cases} 1 & \text{if } VPD \le 10 \\ 1.2 - 0.02(VPD) & \text{if } 10 < VPD \le 30, \text{ and} \\ 0.6 & \text{if } 30 < VPD \end{cases}$$

$$\mu(TEMP, VPD) = 1 - 0.91(\phi_{TEMP}(TEMP))(\phi_{VPD}(VPD)).$$

Infection dynamics. The extrinsic and intrinsic incubation periods were assumed to follow Weibull and log-normal distributions, respectively, following previous work by Johansson and others[15]:

$$F_{EIP}(t, TEMP) = 1 - e^{-\lambda_{EIP} t^{\nu_{EIP}}},$$

where

$$\nu_{EIP} = 1.7$$

and

$$\lambda_{EIP} = e^{-7.6 + 0.11(TEMP),}$$

and

$$F_{IIP}(t) = -\Phi\left(\frac{\ln(t) - \mu_{IIP}}{1/\sqrt{\delta_{IIP}}}\right)$$

for $t > 0$, where $\mu_{IIP} = 1.46$ and $\delta_{IIP} = 8.0$. Using observations by Hindle[16] that human patients were only found to be infectious to mosquitoes during the first 3 days of fever, we conservatively assume that the infectious period was log-normally distributed with a mean of 3.0 days (log-mean, $\mu_{IP} \approx 0.97$) and a log-standard deviation of 0.5 (precision, $\delta_{IP} = 4.0$):

$$F_{IP}(t) = -\Phi\left(\frac{\ln(t) - \mu_{IP}}{1/\sqrt{\delta_{IP}}}\right)$$

for $t > 0$. Under this model, 75% of infected individuals are infectious between 2.3 and 7.1 days and 95% were infectious between 1.5 and 10.7 days. We used means of 3.0 and 4.0 days for the low and high transmissibility models, respectively, to test for sensitivity to this parameter, both with the same precision (4.0). Daily probabilities of progression, p_{EIP}, p_{IIP}, and p_{IP}, are calculated using the relevant cumulative distribution function, F_{EIP}, F_{IIP}, and F_{IP}, respectively (and the daily temperature covariate in the case of the extrinsic incubation period). Because we are converting from continuous to discrete distributions, we calculate the probabilities of progression based on half days to better maintain the underlying distributions. The probability of spending 0 days in state X is the cumulative probability of spending 0.5 days or less there:

$$p_X(0) = F_X(0.5).$$

For subsequent days, the probability of progression on day τ is the probability of progression between day $\tau - 0.5$ and day $\tau + 0.5$ given that progression has not occurred by day $\tau - 0.5$:

$$p_X(\tau) = (F_X(\tau + 0.5) - F_X(\tau - 0.5))/(1 - F_X(\tau - 0.5))$$

for

$$\tau = 1, 2, \ldots \tau_X - 1,$$

where τ_X is the maximum length of the respective period. To ensure progression of remaining individuals, the probability of progression in the final subcompartment of each state is set to one:

$$p_X(\tau_X) = 1.$$

The maximum extrinsic incubation period, τ_{EIP}, was set at 45 days, much longer than the average lifespan of a mosquito (11 days at the minimum mortality rate used here). The maximum intrinsic incubation and infectious periods, τ_{IIP} and τ_{IP}, respectively, were set at 15 days when greater than 99% of individuals will have already progressed to the next stage.

Transmissibility. The effective rate of human to vector transmission, β_{HV}, is also difficult to characterize. Comprehensive studies including *Ae. aegypti* from diverse locations found laboratory-controlled infection rates ranging from 0.07 to 0.57[17] and from 0 to 0.644.[18] More geographically focused studies have found probabilities of 0.4 to 1[19] and 0.12 to 0.28.[20] Previous models have assumed ranges of 0.1 to 0.5[12,14] or complete efficiency, $\beta_{HV} = 1$.[13] We use three values, including a low, moderate, and high estimate: 0.2, 0.5, and 1, respectively.

The effective rate of vector to human transmission, β_{VH}, is, for practical reasons, immeasurable, because performing the relevant experiments would put humans at unacceptable risk. One study found that the probability of an infected mosquito successfully transmitting YFV to a mouse was 0.3–0.7.[19] It is also clear that the range of this rate must be greater than zero (because transmission does occur) and less than or equal to one, equivalent to every bite being successful. With little information to go on, we use two values: 0.5 and 1 (0.5 is used for the low and moderate transmission models).

R_0 CALCULATION

We break R_0 into two components, the average number of infectious mosquitoes produced per infectious human, R_0^{HV}, and the average number of infectious humans produced per infectious mosquito, R_0^{VH}:

$$R_0 = R_0^{HV} R_0^{VH}.$$

R_0^{HV} is the product of the number of female mosquitoes per person, φ^*, the contact rate between humans and mosquitoes (bites per day), α, the effective rate of transmission from human to vector, β_{HV}, the average duration of the human infectious period (in days), D_{IP}, and the average proportion of vectors surviving the extrinsic incubation period, $p_{SurvEIP}$:

$$R_0^{HV} = \varphi^* \alpha \beta_{HV} D_{IP} p_{SurvEIP}.$$

The actual vector density, φ^*, reflects the stable vector density under relevant environmental conditions. The nominal density is multiplied by the ratio of nominal to actual (i.e., temperature- and humidity-dependent) mortality:

$$\varphi^* = \varphi(\mu_{\min}/\mu(TEMP, VPD)).$$

As parameterized here, the mean infectious period is:

$$D_{IP} = e^{\mu_{IP} + \frac{1}{2}\delta_{IP}^{-1}}.$$

The proportion of vectors surviving the extrinsic is calculated as the integral of the product of the probability density function for becoming infectious and the cumulative distribution function for survival, S_V:

$$p_{SurvEIP} = \int_0^\infty f_{EIP}(t) S_V(t) dt.$$

Here, these functions are

$$f_{EIP}(t, TEMP) = \nu_{EIP} \lambda_{EIP} t^{\nu_{EIP} - 1} e^{-\lambda_{EIP} t^{\nu_{EIP}}}$$

(as parameterized above) and

$$S_V(t) = e^{-\lambda_{SURV} t},$$

where

$$\lambda_{SURV} = -\log(1 - \mu(TEMP, VPD)).$$

The average number of humans infected per infectious mosquito is the product of the contact rate, α, the effective rate of

transmission from vector to human, β_{VH}, and the average vector longevity, L_V:

$$R_0^{VH} = \alpha\beta_{VH}L_V.$$

Given the continuous hazard assumed for climate-dependent mosquito survival,

$$L_V = 1/\lambda_{SURV}.$$

Together, the average number of humans newly infected per infectious human is

$$R_0 = \varphi^*\alpha^2\beta_{HV}\beta_{VH}L_V D_{IP}p_{SurvEIP}.$$

Lastly, we adjust for areas where *Ae. aegypti* populations are unlikely to persist. As detailed in Parameterization, Populations, persistence is unlikely in cities with monthly temperatures below 10°C or rainfall below 1 mm for at least 6 months of the year. For these cities, we assume $R_0 = 0$.

PROBABILITY OF INTRODUCTION

As above, the probability of an individual traveling from city i to city j can be written as $p_{i,j}$, with the probability that the individual does not travel to city j being $1 - p_{i,j}$. Thus, for any number of infected individuals in city i at time t, $N^I_{i,t}$, the probability of no infected travelers from city i to j is

$$(1 - p_{i,j})^{N^I_{i,t}},$$

where

$$N^I_{i,t} = \sum_{\tau=1}^{\tau_{IIP}} H_E(\tau,t) + \sum_{\tau=1}^{\tau_{IP}} H_I(\tau,t).$$

The probability of at least one infected traveler traveling from i to j at time t is

$$p_{INTRO^*}(i,j,t) = 1 - (1 - p_{i,j})^{N^I_{i,t}}.$$

The probability of infected individuals traveling is also dependent on other potential sources or sinks for infected people and the accumulation of risk over time. The cumulative probability of spread from city i' to any other city by time T can be written as one minus the cumulative probability of no infected individuals traveling to any city at any time up to time T:

$$p_{SPREAD}(i',T) \;=\; 1 - \prod_{t=0}^{T}\prod_{i\neq i'}^{I}(1 - p_{i',i})^{N^I_{i',t}},$$

where i is the city index for cities $I = 1, 2, \ldots, I$ and I is the total number of cities. The cumulative probability of introduction from any other city to city i' by time T can be written as

$$p_{INTRO}(i',T) = 1 - \prod_{t=0}^{T}\prod_{i\neq i'}^{I}(1 - p_{i,i'})^{N^I_{i,t}}.$$

PROBABILITY OF INTRODUCED AUTOCHTHONOUS TRANSMISSION

The probability of introduction leading to autochthonous transmission is approached as a branching process problem.[21] This approach caches the problem in terms of generations. In our case, a single infectious individual may generate a generation of infectious vectors, which may, in turn, generate a generation of infectious humans and so on. However, at each generational step, there is a chance for extinction. To analyze the branching process of interest here, probability generating functions, $g(s)$, where $0 \leq s \leq 1$, are assigned to each stochastic process within the model. The transmission components can be summarized as two Poisson distribution-generating functions based on R_0^{HV} and R_0^{VH}:

$$g_V(s) = e^{R_0^{HV}(s-1)}$$

and

$$g_H(s) = e^{R_0^{VH}(s-1)}.$$

Because both R_0^{HV} and R_0^{VH} are subject to spatiotemporal variation, we assign them subscripts (i for location and t for time):

$$g_V(s,i,t) = e^{R_{0i,t}^{HV}(s-1)}$$

and

$$g_H(s,i,t) = e^{R_{0i,t}^{VH}(s-1)}.$$

The composite function for autochthonous transmission given the introduction of an infectious human is

$$g_V(g_H(s,i,t)) = e^{R_{0i,t}^{HV}(e^{R_{0i,t}^{VH}(s-1)}-1)}.$$

(Note that, for the introduction of an infectious vector, this expression would be different—$g_H(g_V(s,i,t))$—but our interest is the introduction of infectious humans.)

We also need to incorporate the probability of infected travelers from city i arriving in another city, j. The generating function, using the notation presented above, is

$$g_{T_I}(s,i,j,t) = \left(1 - p_{i,j} + p_{i,j}s\right)^{N^I_{i,t}}.$$

The composite probability generating function for the complete process is

$$g_{T_I}(g_V(g_H(s,i,j,t))) = \left(1 - p_{i,j} \;+ p_{i,j}e^{R_{0j,t}^{HV}(e^{R_{0j,t}^{VH}(s-1)}-1)}\right)^{N^I_{i,t}}.$$

One useful property of probability generating function is that $g(0)$ is the probability of extinction at zero generations (i.e. no additional transmission events take place). Note that the probability of introduction presented in the previous section is

$$p_{INTRO^*}(i,j,t) = 1 - g_{T_I}(0,i,j,t) = 1 - \left(1 - p_{i,j}\right)^{N^I_{i,t}}.$$

Here, the interest is the probability of autochthonous transmission in city j resulting from an epidemic in city i, $p_{\mathrm{AUTO}\times}(i,j,t)$:

$$\begin{aligned} p_{AUTO^*}(i,j,t) &= 1 - g_{T_I}(g_V(g_H(0,i,j,t))) \\ &= 1 - \left(1 - p_{i,j} + p_{i,j}e^{R_{0j,t}^{HV}(e^{-R_{0j,t}^{VH}}-1)}\right)^{N^I_{i,t}}. \end{aligned}$$

The probability of spread from city i' resulting in local transmission in any other city by time T is

$$p_{SPREAD->AUTO}(i',T) = 1 - \prod_{t=0}^{T}\prod_{i\neq i'}^{I}(1 - p_{AUTO*}(i',i,t))$$

or

$$p_{SPREAD\rightarrow AUTO}(i',T) = 1 - \prod_{t=0}^{T}\prod_{i\neq i'}^{I}\left(1 - p_{i',i} + p_{i',i}e^{R^{HV}_{0i,t}(e^{-R^{VH}_{0i,t}}-1)}\right)^{N^{I}_{i,t}}.$$

The probability that novel autochthonous transmission occurs in city i' by time T is dependent on all potential source cities:

$$p_{AUTO}(i',T) = 1 - \prod_{t=0}^{T}\prod_{i\neq i'}^{I}(1 - p_{AUTO*}(i,i',t))$$

or

$$p_{AUTO}(i',T) = 1 - \prod_{t=0}^{T}\prod_{i\neq i'}^{I}\left(1 - p_{i,i'} + p_{i,i'}e^{R^{HV}_{0i',t}(e^{-R^{VH}_{0i',t}}-1)}\right)^{N^{I}_{i,t}}.$$

Vaccination can have an impact on this process. In the case of vaccination, the entire human population is no longer susceptible, meaning that some infectious vectors will feed on immune humans, increasing the probability of YFV extinction. This finding can be adjusted by using the effective reproductive number, R^{VH}_{E}, adjusted for the proportion of the population that is vaccinated, p_{VAX}, instead of R^{VH}_{0}:

$$R^{VH}_{E} = R^{VH}_{0}(1 - p_{VAX}).$$

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