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A metapopulation approach to identify targets for *Wolbachia*-based dengue control

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Over the last decade, the release of *Wolbachia*-infected *Aedes aegypti* into the natural habitat of this mosquito species has become the most sustainable and long-lasting technique to prevent and control vector-borne diseases such as dengue, zika, or chikungunya. However, the limited resources to generate such mosquitoes and their effective distribution in large areas dominated by the *Aedes aegypti* vector represent a challenge for policymakers. Here we introduce a mathematical framework for the spread of dengue in which competition between wild and *Wolbachia*-infected mosquitoes, the cross-contagion patterns between humans and vectors, the heterogeneous distribution of the human population in different areas, and the mobility flows between them are combined. Our framework allows us to identify the most effective areas for the release of *Wolbachia*-infected mosquitoes to achieve a large decrease in the global dengue prevalence.

Dengue is an acute viral syndrome caused by the dengue virus (DENV) and its transmission between humans is mediated by the bites of female *Aedes aegypti* mosquitoes. To date, there is no medical treatment for dengue and therefore entomological surveillance has been the best ally in containing its spread. Recently, the use of mosquitoes infected with *Wolbachia* bacteria has emerged as a sustainable and long-lasting way to prevent and control dengue since this bacterium nullifies the ability of mosquitoes to transmit the dengue virus. However, the use of *Wolbachia* poses technical difficulties since its dissemination in a wild mosquito population requires to introduce laboratory manipulated eggs in which the bacterium has been previously inoculated. Here we propose a theoretical framework that offers policymakers an alternative to effectively release *Wolbachia*-infected mosquitoes by identifying the most epidemiologically vulnerable areas, thus concentrating the use of the limited resources available for better control of dengue transmission.

I. INTRODUCTION

In the last decades, dengue has turned into the most widespread vector-borne disease in the world. More than 3.9 billion people living in 129 countries are at risk of contracting dengue fever[1,2] and currently, 96 million cases are reported every year, a quantity that is estimated to represent around 25% of all real cases[3,4]. In addition, over the past two decades, reported cases of dengue fever have increased 8-fold as a result of rapid unplanned urbanization, globalization of travel and trade, and environmental changes that favor the proliferation of vectors[5].

The lack of effective therapeutics or vaccines lays emphasis on entomological surveillance and source reduction for the prevention and control of *Aedes aegypti* mosquito breeding, the primary vector carrying dengue. The suppression of mosquito populations by removal of urban breeding habitats and insecticide/larvicide treatments has been the most popular control response. However, mosquito populations can recover fast influenced by favorable weather conditions and, furthermore, acquiring insecticide resistance[6].

In 2009, it was discovered that an infection caused by *Wolbachia* bacteria in *Aedes aegypti* mosquitoes prevents them from transmitting viruses that cause dengue and other diseases such as zika and chikungunya[7]. However, *Aedes aegypti* do not acquire *Wolbachia* in their natural environment and the bacterium should be introduced into the mosquito eggs in a laboratory. *Wolbachia*-carrying mosquitoes are then released and consistently transmit *Wolbachia* infection to their offspring. The release of *Wolbachia*-carrying mosquitoes in dengue-endemic areas has shown positive and long-lasting results, reducing the frequency of transmissions. This success is due to the natural competition bias that favors the proliferation of *Wolbachia*-carrying mosquitoes over wild-type vectors[8]. This evolutionary advantage of *Wolbachia*-bearing vectors underlies the cytoplasmic incompatibility[9,10]. As a result, eggs resulting from the mating of an uninfected female mosquito and an infected male mosquito do not hatch, whereas the offspring of the mating of an infected female mosquito and any male mosquito (regardless of infection status) will carry *Wolbachia*.

Despite that *Wolbachia* is safe and self-sustaining at a high-level control method, introducing *Wolbachia* in all places where is needed is not an easy task and requires strategic planning to efficiently distribute the limited resources to protect the most people as possible. In this work, we develop an analytical method to help this strategic planning. In particular, our method allows us to classify the epidemic risk of different areas of a territory. We use this classification to identify the patches whose immunization with *Wolbachia* leads to the best result in terms of disease mitigation and confirm this hypothesis through numerical simulations.

II. MODEL EQUATIONS

In this section, we define the basic equations that allow us to study the evolution of three different co-evolving processes: the competition of *Wolbachia*-infected and wild mosquitoes, the recurrent mobility patterns of humans, and the cross-infection between humans and wild mosquitoes. To this end, we will use a discrete-time approach that is inspired in the metapopulation framework introduced in[11,12] and subsequently applied to vector-borne diseases[13].

A. Competition dynamics among vector populations

To elucidate the competition between wild and *Wolbachia*-infected mosquitoes, we first analyze their ecological growth in the same habitat (patch). To this aim, we make use of the iterative logistic growth of the invasion dynamics of *Wolbachia* presented in[18]. This model includes the shortening of the life cycle of *Wolbachia*-infected mosquitoes, reducing their birth probability (r) and increasing their death probability (α) compared to the wild species, i.e. $r_w < r_m$ and $\alpha_w > \alpha_m$ respectively. The two variables at work are $m_i(t)$ and $w_i(t)$, which are the populations of wild-type and *Wolbachia*-infected mosquitoes in patch i respectively. The time-discrete evolution equations for these two variables read:

$$m_i(t+1) = m_i(t)\left[1 + r_m \frac{m_i(t)}{m_i(t)+w_i(t)} - \alpha_m - \beta_m\left(m_i(t)+w_i(t)\right)\right], \quad (1)$$

$$w_i(t+1) = w_i(t)\left[1 + r_w - \alpha_w - \beta_w\left(m_i(t)+w_i(t)\right)\right]. \quad (2)$$

The second terms in the r.h.s of these equations represent the mosquitoes' renewal. Let us recall that female *Wolbachia*-carrying mosquitoes successfully reproduce by any mating interaction, however, the reproduction of wild mosquitoes is affected by *Wolbachia*-infected male mosquitoes since their offspring will not hatch, so the term $\frac{m_i(t)}{m_i(t)+w_i(t)}$ accounts for the probability of interacting with wild-type males. Respectively, the third and fourth terms in the r.h.s of the former equations represent the removal due to mortality and the competition between the two species respectively. Let us note that we assume that the competition parameters, β_m, and β_w, are given by the ability of each species to survive in the absence of the other. Under this premise, we fix their respective values so that the stationary state yields $m_i^* = w_i^* = \gamma_i n_i$ when the dynamics of each species takes place in isolation, being n_i the number of humans living in patch i and γ_i the reported ratio between vectors and humans populations in patch i.

In Figure 1.a we plot different trajectories in the phase portrait of the system that illustrates the ecological invasion of *Wolbachia*-infected mosquitoes over the wild-type population. It is clear that regardless of the initial amount of *Wolbachia*-infected mosquitoes, the wild-type population will eventually vanish so that $(m^* = 0,\ m_w^* = 1)$ is the only stable fixed point. Obviously, the more *Wolbachia*-infected mosquitoes are released the faster the population replacement takes place. In Figure 1.b we show the temporal evolution of an initial release of *Wolbachia*-carrying mosquitoes representing just 10% of the wild-type population. Notice that before *Wolbachia*-infected mosquitoes take over the habitat, the population of wild-type vectors is practically extinct.

B. Human recurrent mobility

Now we focus on the metapopulation model encapsulating the mobility of a human population that, in its turn, drives the interaction with mosquitoes. Considering that the estimated flight range of vectors is only about 200 m[19,20], we suppose that the mosquito does not move between the zones.

The metapopulation is composed of N_p subpopulations (or patches), each of which represents a geographic area (here an urban district). Each subpopulation $i \in 1,2,...,N_p$ has n_i habitats such that the overall human population size N is: $N = \sum_{i=1}^{N_p} n_i$. The set of N_p patches that compose the metapopulation are interconnected in the form a complex weighted and directed network $\mathscr{G}$ with N_p nodes (the patches) and L links. A link from node i to node j is weighted according to the volume, W_{ij}, of daily human trips that inhabitants of patch i make to j. Thus, the information needed to construct the metapopulation under study comprises the census of each urban area n_i and the Origin-Destination matrix $\mathbf{W}$ of urban flows between the former areas.

Equipped with the information encoded in $\mathscr{G}$ we construct a right stochastic matrix $\mathbf{R}$, whose elements R_{ij} are defined as:

$$R_{ij} = \frac{W_{ij}}{\sum_{l=1}^{N_p} W_{il}}, \quad (3)$$

thus accounting for the probability that a resident in patch i moves to patch j. Of course, not all residents of the patches move to other places to do their daily activities. To characterize the mobility of the whole population we define the active population as the fraction $p \in [0,1]$ of the whole population that moves to other patches.

In this work, we make use of both the census and the commuting mobility patterns of the city of Santiago de Cali (Colombia), an urban area in which dengue is endemic. According to this information[21], Santiago de Cali has an overall population of 2.2 millions of inhabitants and is divided into 22 administrative divisions (see Figure 1.c) that constitute the patches of our metapopulation, being the daily commuting flows between them available to build matrix $\mathbf{R}$.

C. Contagion dynamics

We round off this section by coupling the contagion dynamics at work with human mobility and competition dynamics between the two vector populations. Here we model the dissemination of DENV making use of the Ross-Macdonald

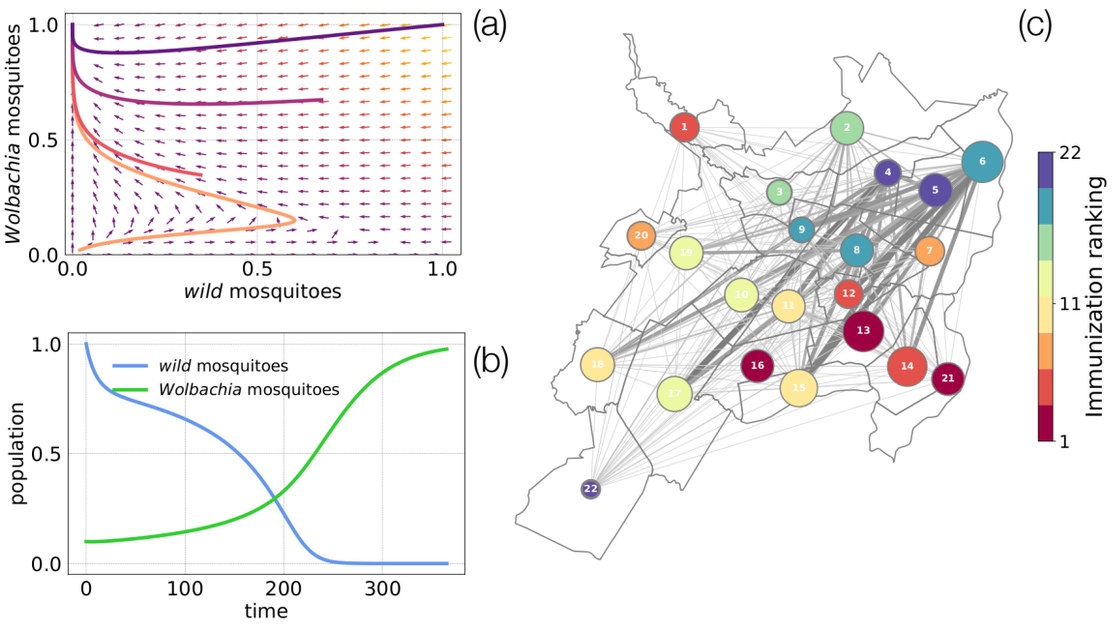

FIG. 1. (a) Phase plane of the competition dynamics between wild-type and *Wolbachia*-infected mosquitoes. Note that populations appear normalized to their maximum possible value. All the trajectories start with a similar population of the two types of vectors. The parameters used in Eqs. (1)-(2) are chosen according to current estimates: $r_m = 0.14$[14,15], $r_w = r_m/2$[16], $\alpha_m = 0.2 r_m$, $\alpha_w = 1.5\alpha_m$[17], $\beta_m = (r_m - \alpha_m)/n\gamma$, $\beta_w = (r_w - \alpha_w)/n\gamma$, and $n\gamma = 5 \cdot 10^4$. (b) Time evolution of the populations of wild-type and *Wolbachia*-infected mosquitoes when introducing a small initial population of the latter. (c) The map represents the metapopulation of Santiago de Cali as a network in which the size of the nodes is proportional to the human population of each district whereas the colors are set according to their importance. Links account for the structure of the Origin-Destination matrix $\mathbf{W}$.

(RM) model, a compartmental model that assumes that both vectors and individuals can adopt two epidemiological states: susceptible (S) to contracting the disease or infectious (I).

The cross contagion process proceeds as follows. First, susceptible humans contract the disease with probability λ^{MH} after being bitten by a dengue-infected mosquito and become again susceptible with probability μ^H. Likewise, susceptible mosquitoes can be dengue-infected after biting an infected human with probability λ^{HM}, while they are replaced by susceptible vectors according to their usual death probability α_M. In addition, the RM model assumes that each mosquito makes a number of β contacts (bites) with humans per day. It is worth recalling that neither direct human-to-human nor vector-to-vector transmission is allowed.

According to the former contagion rules let us start by capturing the contagion dynamics in the human population. To this aim, we assign to each patch i of the metapopulation one variable, $n_i^I(t)$, that accounts for the number of infectious residents of patch i at time t. Obviously, this single variable completely characterizes the epidemiological state of residents in patch i since the number of susceptible residents at time t is $n_i - n_i^I(t)$. Analogously, for the vector population in a patch i we define a set of three variables $\{m_i^S(t), m_i^I(t), w_i(t)\}$ that correspond to the total number of wild-type infectious mosquitoes, the number of susceptible wild-type mosquitoes, and the number of *Wolbachia*-infected mosquitoes respectively. Note that the sum of the first two variables correspond to the total number of wild-type mosquitoes in patch i, $m_i^S(t) + m_i^I(t) = m_i(t)$, whose evolution together with that of $w_i(t)$ is given by Eqs. (1)-(2).

The time-discrete evolution of the number of infectious residents of patch i, $n_i^I(t)$, obeys the following set of equations:

$$n_i^I(t+1) = n_i^I(t)(1-\mu^H) + (n_i - n_i^I(t))\Pi_i^H(t)\,, \qquad (4)$$

where the first term accounts for being infected at the residence patch i while the second term captures the probability that the infection occurs in any of the possible commuting destinations reached from patch i. Thus, in the former expression $\Pi_i^H(t)$ accounts for the probability that a healthy human with residence in patch i is infected at time t, and can be written as:

$$\Pi_i^H(t) = (1-p)P_i^H(t) + p\sum_{j=1}^{N} R_{ij} P_j^H(t)\,, \qquad (5)$$

where $P_i^H(t)$ is the probability that an agent placed in population i at time t is infected. This probability reads:

$$P_i^H(t) = 1 - \left(1 - \lambda^{MH}\frac{1}{n_i^{\text{eff}}(t)}\frac{m_i^I(t)}{m_i(t)}\right)^{\beta m_i(t)}\,, \qquad (6)$$

where $n_i^{eff}(t)$ is the effective population of a patch i, i.e. the number of residents that remain in patch i plus the visitors from other patches. The former equation accounts for the

probability that, once in a patch i at time t with $m_i(t)$ wild-type mosquitoes, a susceptible agent is infected by at least one bite from an infectious mosquito, being $\beta m_i(t)$ the total number of bites distributed among $n_i^{eff}(t)$ humans. Equation (6) contains three time dependent variables that directly depends on: (i) the epidemiological state of humans ($n_i^{eff}(t)$) in the whole population, (ii) the competition dynamics between *Wolbachia*-infected and wild-type vectors ($m_i(t)$), and (iii) the infection of wild-type mosquitoes by humans ($m_i^I(t)$).

For what concerns the first variable, $n_i^{eff}(t)$, we consider that infected people may not be able to move if developing symptoms. Therefore, considering that a fraction α represents the asymptomatic people[22] that may still remain contagious[23], the effective population of a patch i can be calculated as:

$$n_i^{\text{eff}}(n_i^I(t),\alpha,p) = (1-p)n_i + p(1-\alpha)n_i^I(t) + p\sum_{j=1}^{N} R_{ji}\left(n_j - (1-\alpha)n_j^I(t)\right) , \quad (7)$$

In the same fashion, we can obtain the effective number of infected humans placed in population i at time t:

$$I_i^{\text{eff}}(t) = (1-\alpha p)n_i^I(t) + \alpha p\sum_{j=1}^{N} R_{ji}n_j^I(t) . \quad (8)$$

Now we put our focus on the dynamical evolution of the vector population in each patch. In Eq. (6) we have $m_i(t)$ and $m_i^I(t)$ that depend, respectively, on the competition with *Wolbachia*-infected mosquitoes and the contagion of wild-type mosquitoes by contact with infected humans. As defined previously, these two variables plus $w_i(t)$ define the ecological and epidemiological state of the vector population at patch i. Considering the rules for cross-contagion in the RM model and the competition dynamics, Eqs. (1)-(2), we can write the evolution equations for the number of wild-type mosquitoes in each epidemiological compartment as:

$$m_i^S(t+1) = (1-\alpha_m)m_i^S(t) + r_m\frac{[m_i(t)]^2}{m_i(t)+w_i(t)} - \beta_m m_i^S(t)\left(m_i(t)+w_i(t)\right) - \Pi_i^M(t)m_i^S(t) \quad (9)$$

$$m_i^I(t+1) = (1-\alpha_m)m_i^I(t) - \beta_m m_i^I(t)\left(m_i(t)+w_i(t)\right) + \Pi_i^M(t)m_i^S(t), \quad (10)$$

where $\Pi_i^M(t)$ accounts for the probability that a susceptible wild-type vector in patch i is infected at time t:

$$\Pi_i^M(t) = 1 - \left(1 - \lambda^{HM}\frac{i_i^{\text{eff}}(t)}{n_i^{\text{eff}}(t)}\right)^{\beta} . \quad (11)$$

It is worth stressing that we assume that contracting dengue does not alter mosquito life dynamics and, therefore, Eq. (1) can be simply retrieved by adding Eqs. (9)-(10). Likewise, as it is typically assumed, the form of Eqs. (9)-(10) implies that newborn wild-type mosquitoes are not carriers of DENV even in the case their parents were infected by the virus. However, there is no total consensus on the absence of vertical transmission of the virus, with different empirical evidence for and against this hypothesis. We refer the reader to[26] for a comprehensive review on the topic.

III. TARGETED RELEASE OF *WOLBACHIA*-INFECTED MOSQUITOES

From the evolution shown in Fig. 1.A-B it is clear that once released in a patch, an initially small amount of *Wolbachia*-infected mosquitoes will prevail after some time, thus preventing any contagion from mosquitoes in the immunized patch. However, in a situation of scarce resources, the relevant question is to know which are those patches that, in addition to preventing the spread of mosquitoes within them, allow a greater reduction in the overall dengue prevalence.

Equipped with the formalism presented in the former section we briefly show the behavior of the system in the absence of *Wolbachia* ($w_i = 0\ \forall\ i$). In Fig.2.a we plot the dependence of dengue prevalence $\rho^* = \lim_{t\to\infty}\sum_{i=1}^{N_p} n_i^I(t)/N$ as a function of the active population p and the contagion probability λ (for the sake of simplicity we have set $\lambda^{HM} = \lambda^{MH} = \lambda$). This plot reveals the interesting phenomenon called *epidemic detriment by mobility*[11], that reveals that the epidemic threshold λ_c, i.e., the minimum infectivity that yields an epidemic state, has a nontrivial dependence with p. It is precisely at λ_c where we can extract analytically the information about those patches that play a key role in the unfolding of an epidemic outbreak[12]. This is achieved by inspecting the spectral properties of the so-called mixing matrix $\mathbf{M}\widetilde{\mathbf{M}}$, where:

$$M_{ij} = pR_{ij}\frac{m_j}{\tilde{n}_j^{\text{eff}}} + (1-p)\delta_{ij}\frac{m_i}{\tilde{n}_i^{\text{eff}}} \quad (12)$$

$$\widetilde{M}_{ij} = \alpha pR_{ji}\frac{n_j}{\tilde{n}_i^{\text{eff}}} + (1-\alpha p)\delta_{ij}\frac{n_i}{\tilde{n}_i^{\text{eff}}}, \quad (13)$$

are two matrices that account for vector-to-human and human-to-vector interactions, respectively. This $N_p \times N_p$ matrix rules the evolution of the system for $\lambda \gtrsim \lambda_c$[13]. In particular, while the maximum eigenvalue of the mixing matrix yields λ_c, the components of the associated eigenvector $\vec{V}_{max}(\mathbf{M}\widetilde{\mathbf{M}})$ quantify the contribution of each patch to an epidemic outbreak.

In Fig. 2.b we show the evolution of the components of $\vec{V}_{max}$ for each value of p. Let us focus on the structure of $\vec{V}_{max}$ when the fraction of active population is close to 36% (as observed for the city of Cali[13]). At this value of p (signaled by a grey line in Fig.2.a-b) the three most influential patches according to $\vec{V}_{max}$ are 13, 21 and 16, being 13 far more important compared to the following two. The importance of these patches is validated by considering the system with only wild-type vectors in the steady endemic state, i.e. with a constant prevalence ρ^*. Then, we simulate the release of a small population of *Wolbachia*-infected mosquitoes in a single patch and monitor the effect on the global prevalence ρ. We chose the two most influential patches according to our critical matrix (13 and 21) and 4 additional areas, specifically patches 1,18,19,20, which correspond to the districts selected by the initiative World Mosquito Program (WMP) to implement *Wolbachia* immunization in Cali. Note that the eigenvector centrality $\vec{V}_{max}$ predicts little to no relevance of these areas. The results (solid curves in Fig.2.c) confirm that the release in those poorly influential areas has little impact in decreasing the overall prevalence ρ^* while immunizing influ-

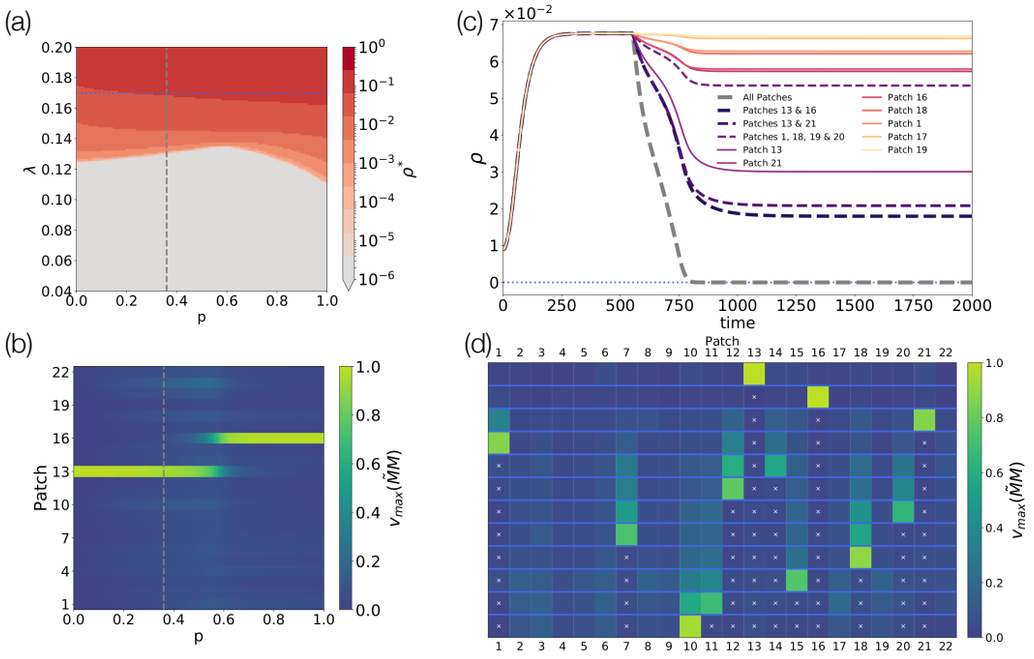

FIG. 2. (a) Prevalece ρ^* as a fucntion of p and $\lambda = \lambda^{HM} = \lambda^{MH}$ for the city of Cali. The vector distribution is obtained from real data[24] and the rest of the parameters of the model are: $\beta = 1$, $\mu = 0.3$[25] and $\alpha = 0.75$[22]. (b) Evolution of the components of the leading eigenvector $\vec{V}_{max}$ of matrix $\mathbf{M}\widetilde{\mathbf{M}}$ as a function of p. (c) Mitigation effect over the steady prevalence ρ^* when *Wolbachia*-infected mosquitoes are released in different patches. Here the value of $p = 0.36$[13] (d) Illustration of the iterative method for ranking patches according to their relevance for mitigation. The first row shows the contribution of each component of $\vec{V}_{max}$. Then, we remove the patch corresponding to the largest component of $\vec{V}_{max}$ (patch 21) in matrix $\mathbf{M}\widetilde{\mathbf{M}}$ and compute the new leading eigenvector, shown in the second row (note that deleted patch 21 appears marked with a cross), and find its largest component (patch 16). This way, each row, say x, shows the composition of the leading eigenvector after removing the $x-1$ most relevant patches in $\mathbf{M}\widetilde{\mathbf{M}}$.

ential patches has a great mitigation effect, especially when the release is implemented in district 13.

When a set of patches is to be simultaneously immunized, as it is the case in usual campaigns[27], the mitigation effect increases. As an example, in Fig.2.c we show the decrease of the prevalence when the four areas (1, 18, 19, and 29) chosen by the WMP are immunized at a time. In the context of simultaneous immunization, one can apply an immunization strategy based on the components of $\vec{V}_{max}$ to immunize in the most efficient way. Then, given that the resources for x patches are available, one should implement the release in those patches corresponding to the x-largest components of $\vec{V}_{max}$. This strategy, considering the first two patches (13 and 21), is shown in Fig.2.c. However, in the same plot, we also present the simultaneous immunization of the first and the third patches (13 and 16) according to their relevance in $\vec{V}_{max}$. From this plot, it is clear that this latter choice outperforms the former one causing larger mitigation of the endemic level ρ^*.

The roots behind the former counter-intuitive result lie in the double mitigation effect caused by the immunization of a single patch. First, at the local level, immunization considerably decreases the contagion of residents, since only imported cases can occur but they will not cause secondary infections within the patch. In addition, at the global level, it also prevents the importation of new cases to those areas connected with the immunized patch. Thus, removing the first patch (21) alters the influence of the remaining patches, changing the rank obtained with $\vec{V}_{max}$. A solution to this problem is to choose the x^{th} patch to immunize by removing the contribution of the previously chosen $x^{th}-1$ patches. This way, instead of choosing the x^{th} largest component of $\vec{V}_{max}$ as the immunization target, one finds the largest component of the leading eigenvector of a $(N_p - x + 1) \times (N_p - x + 1)$ matrix resulting from the removal of the $x-1$ previously immunized patches in $\mathbf{M}\widetilde{\mathbf{M}}$. The iterative method used to find out the x most influential patches is illustrated in Fig.2.d and the complete rank provided by this method is shown in Fig. 1.c. Applying the iterative method we validate that the two most important patches to immunize at a time are 13 and 16, rather than the choice 13 and 21 resulting from the inspection of $\vec{V}_{max}$.

Our previous analyses have focused on identifying the most important patches to concentrate control policies in a few areas. Now, we apply the classification to a more realistic scenario where resources are limited, i.e., we only have a fixed amount of *Wolbachia*-infected vectors to release. Obviously, the more patches we distribute this number of mosquitoes, the greater the final mitigation effect. However, distributing these resources among a large number of patches implies releasing

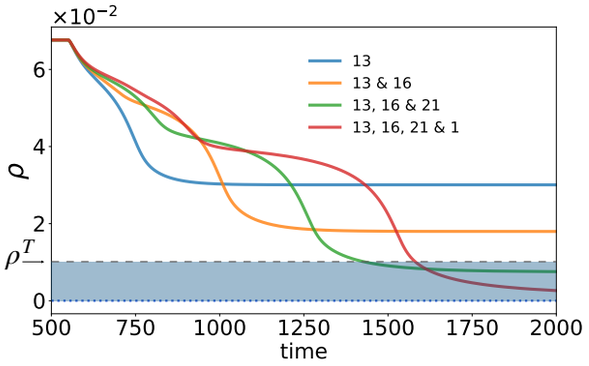

FIG. 3. Time evolution of the global prevalence ρ after $5 \cdot 10^4$ *Wolbachia*-infected mosquitoes is released evenly distributed among a set of patches. The target prevalence is $\rho^T = 10^{-2}$.

small numbers of *Wolbachia*-infected vectors and, therefore, a very long lead time to obtain the desired decrease in prevalence. Therefore, in these circumstances, the question is how many and which patches we should consider achieving a mitigation target ρ^T in the shortest possible time. We can use the ranking obtained and consider different scenarios. Namely, as shown in Fig. 3, we can: (i) concentrate all resources on patch 13, (ii) distribute them equally between the two most important 13 and 16, (iii) spread them between 13, 16, and 21, and so on. For a given $\rho^T = 10^{-2}$ the correct choice corresponds to the distribution of resources among the three most relevant patches, given that the target prevalence is reached faster than when immunizing patches 13, 16, 21 and 1, while the other options do not achieve the given mitigation target.

IV. CONCLUSIONS

Here we have presented a framework that couples different aspects interplaying in the impact that control strategies via *Wolbachia*-infected mosquitoes has on the mitigation of vector-borne diseases. Although the compartmental dynamics of the framework can be easily changed to accommodate different vector-borne diseases such as malaria or zika, here we have focused on the case of dengue and its control in urban areas where this disease is endemic, such as Santiago de Cali in Colombia. The framework incorporates the competition dynamics between *Wolbachia*-infected and wild-type mosquitoes, the cross-contagion between humans and vectors, information about vector abundance and the distribution of human population across patches, and the architecture of human flows due to daily commutes.

The presented framework allows us to derive a mixing matrix whose spectral properties provide information on which patches are best suited to perform *Wolbachia*-infected mosquito releases, especially when these resources are limited. We have shown that, since patch immunization has both local and systemic effects, the ideal way to find out the set of patches to control is to perform the analysis of the leading eigenvector iteratively, i.e. by analyzing successive versions of the mixing matrix in which the patches with the largest contribution to the leading eigenvector has been removed. Our framework paves the way for planning targeted interventions in urban areas, especially those dealing with scarce and difficult means of control, such as *Wolbachia*-infected mosquitoes. In addition, in real scenarios, the goodness of the decision suggested by this methodology can be easily measured by comparing the prevalence data before and after the Wolbachia-infected mosquito releases.

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