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Simple visit behavior unifies complex Zika outbreaks

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Abstract

New outbreaks of Zika in the U.S. are imminent. Human nature dictates that many individuals will continue to revisit affected 'Ground Zero' patches, whether out of choice, work or family reasons – yet this feature is missing from traditional epidemiological analyses. Here we show that this missing visit-revisit mechanism is by itself capable of explaining quantitatively the 2016 human Zika outbreaks in all three Ground Zero patches. Our findings reveal counterintuitive ways in which this human flow can be managed to tailor any future outbreak's duration, severity and time-to-peak. Effective public health planning can leverage these results to impact the evolution of future outbreaks via soft control of the overall human flow, as well as to suggest best-practice visitation behavior for local residents.

Keywords: Infectious disease, Public health, Applied mathematics

1. Introduction

Future human outbreaks of the Zika virus (ZIKV) within the United States are inevitable. In addition to sparking the first ever U.S. government health warning for travel within the continental United States, the 2016 Zika outbreak was notable for the geographical resolution with which the three Ground Zero areas were specified, i.e. Wynwood (Fig. 1a), Miami Beach and Little River which are all separated from each other by a short drive within the Miami area. These areas have a high throughput flow of both locals and tourists, which presumably impacted the evolution of the outbreaks. However to date, there is no report of a quantitative
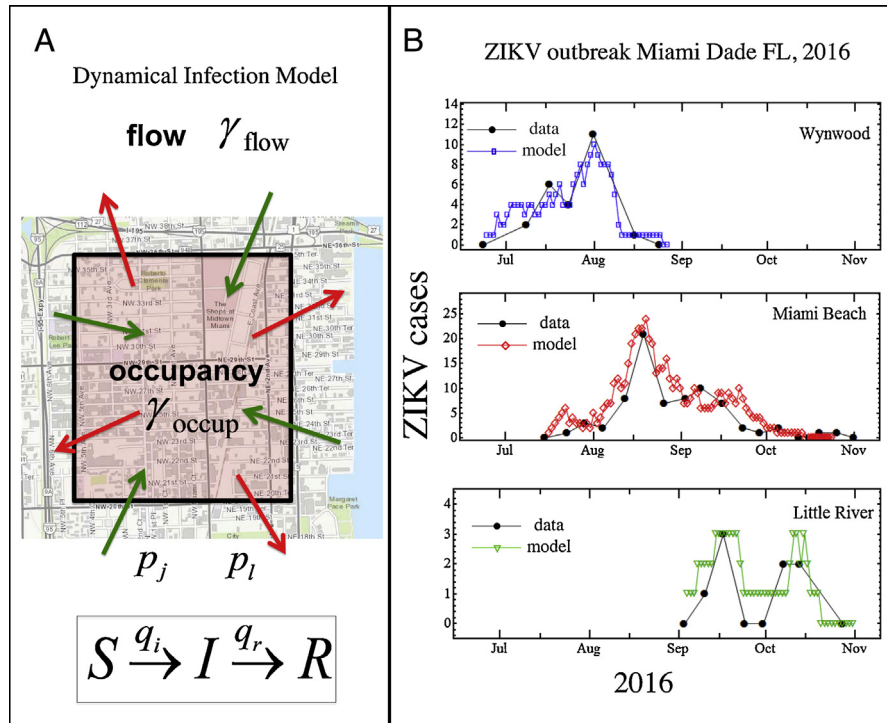
Fig. 1. Unifying visit-revisit mechanism. **A**: Ground Zero (red shaded area) and our visit-revisit model parameters. The patch shown corresponds to Wynwood, however the same model applies to all Ground Zero patches, and indeed patches at any geographic scale. Potential visitors to Ground Zero at timestep t enter with probability p_j and leave with probability p_l. Their total number is N and susceptible (S) individuals within Ground Zero have a probability q_i of getting bitten and becoming infected (I) while infected individuals have a probability q_r of recovering (R). The map was generated by the open source software Esri (http://www.esri.com/data/basemaps). **B**: Temporal distribution of reported ZIKV cases on a weekly basis for three affected areas in Miami Dade County, FL (Wynwood, Miami Beach, and Little River) during 2016 [11, 12] compared to the output of our visit-revisit model. Parameter values are all obtained from realistic independent estimates (see text): $q_i = 0.00014$, $q_r = 0.23$, $N = 10,000$, $\gamma_{flow} = 0.05$, and $\gamma_{occup} = 0.25$.

model that has incorporated this visit-revisit feature and has then been able to reproduce these three U.S. Ground Zero outbreaks. While such a lack of understanding is undesirable from a scientific perspective given that these time-series of human cases comprise the only record of ZIKV outbreaks in the U.S., it is also troubling from a public health perspective in that it leaves in limbo the question of what potential visitors should do in terms of visits − despite the fact that many people by necessity must revisit such a Ground Zero during an outbreak on a daily or weekly basis, either because they work or live there, or have family there. As we show in this paper, it also leaves un-utilized a potentially powerful public health control tool of human throughput.

There is of course a vast literature on modeling viral outbreaks that covers a wide variety of scenarios, includes a broad range of models, and adopts many

sophisticated modeling techniques. For example, many important recent works in the complex systems and networks field consider the process of contagion in tandem with links between individuals being broken or formed in time [1, 2, 3, 4, 5, 6, 7, 8, 9, 10] (see Supplementary Information (SI) for more details of prior works). However the issue of how visits and revisits by, for example, a local population whose work, residence or family bring them reasonably frequently into an affected Ground Zero area on a daily basis, is not well understood, nor does it feature in many (if any) generative models. As an example of the most recent analysis on human Zika outbreaks, Grubaugh et al. [11] provide a remarkable investigation of ZIKV genomes from infected patients and *Aedes aegypti* mosquitoes, and conclude that multiple introductions of the virus contributed to this 2016 outbreak in Florida; that local transmission likely started several months before its initial detection; and that ZIKV moved among transmission zones in Miami. However, Ref. 11 provides no proof that these mechanisms can reproduce the three Ground Zero human ZIKV outbreak profiles (reproduced in Fig. 1B here) − even though these profiles of human cases represent the key measurement from a scientific and public policy perspective. Though the mosquito abundance showed itself as somewhat correlated with portions of the profiles [11], in some cases the mosquito abundance remained long after the outbreak of human cases had ended.

The results that we present here show that by overlooking this visit-revisit behavior (Fig. 1A) such previous works have missed an important driving mechanism which can not only explain the observed time-series of human cases in all three of the 2016 three Ground Zero outbreaks (Fig. 1B) but also opens an opportunity for a new control tool (Fig. 2A and B). The full details of our model are given in the Supplementary Information document. Instead of the impractical measure of shutting off essentially all flow through Ground Zero areas, or the opposite extreme of relying on self-imposed preventative behavior by individuals, our results show that outbreaks can be curtailed by soft control of this human flow − and counter-intuitively, under certain circumstances this curtailment is achieved by *increasing* the flow through the Ground Zero (Fig. 2B). Moreover the model that we present is simple enough that it can be represented by a set of coupled differential equations which reproduce the numerical simulations with good accuracy (see SI for details). These equations can now be developed and generalized in the future in order to explore general attractor behaviors of the system in richer sets of scenarios.

2. Results

Before we show the results, we wish to stress that understanding real outbreak data in human populations is a highly complex problem. Limitations of our study − like most others − therefore include the fact that it is impossible to uniquely pinpoint the actual process through which a given disease spreads, given that the human population is mobile and highly heterogeneous in its activities including both
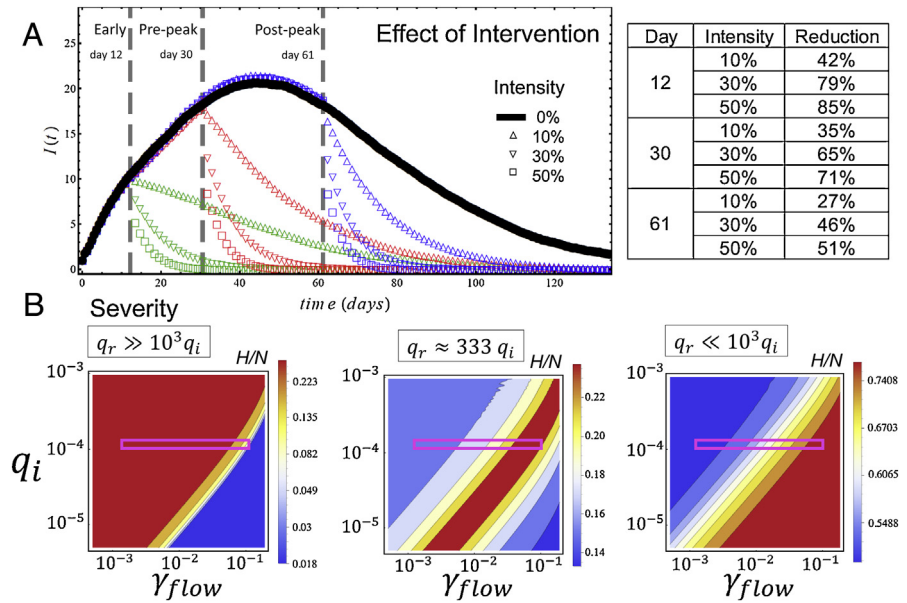
Fig. 2. Predictions and policy implications. **A.** Impact of intervention on the infection profile (number of infected individuals). The interventions are applied on different days (vertical gray lines) from the beginning of the outbreak, and with different intensities (symbols). Colors distinguish the times of the intervention: day 12 (green), day 30 (red) and day 61 (blue). The intervention comprises the removal of a specific percentage (10%, 30% and 50%) of N, the number of likely visitors. The black thick line is the infection profile without intervention. Each curve is visually smoother than any individual run (c.f. Fig. 1B) since it is an average profile that is averaged over 1000 model runs. The end of the outbreak (i.e. duration T) is determined by the day on which the average number of infected individuals becomes smaller than one, i.e. $I(t) < 1$. Right panel shows the effect of the intervention on the duration of the outbreak. For each start day of intervention and its intensity, the reduction in the duration is shown with respect to the original unperturbed outbreak. The model parameters are $q_i = 0.00014$, $q_r = 0.23$, $N = 10,000$, $\gamma_{flow} = 0.05$, and $\gamma_{occup} = 0.25$. **B.** Severity (H/N) of the outbreak in the scenario that individuals remain infectious for a far shorter time than in **A** (left panel), a far longer time (right panel), and a critical time that divides the two behaviors (middle panel). Pink box points to the contagion probability region associated to the ZIKV outbreak in 2016. In all cases, average individual recovery time $\propto 1/q_r$.

during the day and night. In addition, individuals may change their movement patterns, take different precautions against mosquitos, and also differ in their intrinsic physiology. There is also the problem of identifying which cases could be labeled as travel related and hence imported, and which ones are endemic to the local area. Moreover, the case numbers are small and just represent one realization of the outbreak. Furthermore, not all people may report their symptoms. However, such concerns affect any modeling of such outbreaks, and are not an intrinsic issue with our approach. Indeed, in the case that such corrections are themselves like stochastic noise, they should to some extent average out. With these limitations in mind, we proceed to present our results.

Fig. 1 shows the results of our model in which the simple visit-revisit feature is the only mechanism (Fig. 1A). As noted above, the full details of our model are given in the Supplementary Information document. Our model applies equally well to any Ground Zero patch; it scales up to any population and patch size; and it uses only a minimal number of parameters, each of which has a realistic value that is based on empirical observations. The model comprises a population of N individuals that can access a given Ground Zero patch. At every timestep, each individual has a probability p_j to enter the Ground Zero patch, while individuals already inside have a probability of p_l to leave. In this way the model accounts for individuals who may revisit Ground Zero 2, 3, 4, . . . etc. times during the period of study, as well as those who only visit once at most. Moreover, its stochastic nature yields a range of times between individual revisits, with the result that some individuals can show long periods between two particular successive visits while others by chance may end up revisiting nearly every day (e.g. mimics individuals who work in Ground Zero). Our visit-revisit model (Fig. 1A) yields an average human flow through the Ground Zero (i.e. average number of individuals entering and leaving) given by $\gamma_{flow}N$ where $\gamma_{\text{flow}} = 2p_jp_l/\left(p_j + p_l\right)$ and N is the total number of humans within the Miami area who wish to visit that Ground Zero [9, 10]. Hence the turnover of individuals within Ground Zero is dictated by γ_{flow} for any N.

At any timestep in the steady-state, it follows that there are on average $\gamma_{occup}N$ individuals inside Ground Zero who are potentially exposed to infection, where $\gamma_{\text{occup}} = p_j/\left(p_j + p_l\right)$ for any N. We note that scaling p_l and p_j by a factor r leaves the Ground Zero occupancy unchanged but scales the flow by a factor r, meaning that the flow is allowed to change within the model while leaving the same average occupancy. More generally both can also vary over time within the model on a daily or weekly basis, though for simplicity we treat the former case here. The infection rate for a susceptible individual (S) within Ground Zero is q_i; the individual recovery rate for an infected individual (I) is q_r. Here for convenience we take one timestep as one effective day where there is flow of individuals in and out of Ground Zero, though this can easily be generalized.

We estimate the infection parameters from official sources recently released [11, 12]. For example, the probability of an individual in Ground Zero getting infected emerges from the percentage of infected mosquitoes collected and tested in pools from June to November 2016 [11]. These findings indicate that one in every 1600 *Aedes aegypti* mosquitoes carried the virus. Hence, the probability of getting infected is $q_i = 0.00014$ per timestep assuming that on average one out of every four people was bitten by a mosquito in a given timestep. The symptoms associated with ZIKV disappear between two and seven days [13] which yields an average recovery probability of $q_r = 0.23$ per timestep. In Fig. 1B, we use the estimate $N = 10,000$ of which one quarter occupy the Ground Zero region at a given timestep

(i.e. $\gamma_{\text{occup}} = 0.25$) with a flow of 500 new or returning individuals (i.e. $\gamma_{\text{flow}} = 0.05$). Running the simulation of the model produces sets of simulated human case time-series for the ZIKV outbreak for each Ground Zero, as shown in Fig. 1B. Even though simulations will vary somewhat from run to run, the statistical likelihood of getting such non-monotonic profiles as Fig. 1B from a standard epidemiological model simulation, is negligible. By contrast, standard SIR epidemiological model simulations invariably produce infection profiles with simpler, typically single peaked forms having less structure, less extended durations, and an absence of multiple peaks. We quantified the goodness of fit of our model and the empirical data, and compared it to the fit of a standard SIR model with no flow, by calculating the time-series overlaps of each with the real outbreak data as well as the respective residual sum of squares. The results show that our visit-revisit model outperforms the static approach in every case (see SI for details). The sequential nature of the three profiles in Fig. 1B in calendar time also strongly suggests that there is a simple shift in the human visit and revisit behaviour from Wynwood over to Miami Beach, then to Little River, as Wynwood then Miami Beach became successively declared publicly Ground Zeros.

The good agreement with all three Ground Zeros in Fig. 1B means that the parsimonious visit-revisit mechanism in Fig. 1A can be used to inform day-to-day human flow management in order to understand the likely future evolution of an outbreak that has started − and even to help contain it. Fig. 2A presents the model's prediction of how changing the human flow will impact the outbreak profile, where the unperturbed scenario is the black curve. This impact is quantified in terms of the outbreak duration and analyzes the results by averaging over 5000 simulations. It predicts that by reducing the flow by 10% during the early stage of the outbreak ($t = 12$ days) the outbreak's duration drops 42% compared to the unperturbed case. Reductions of 30% and 50% during the same early stage reduce the outbreak duration by 79% and 85%, respectively. Later interventions at subsequent stages of the outbreak (pre-peak and post-peak) still help in reducing the outbreak duration, however in smaller percentages (see Fig. 2A right panel). These results point to the need for prompt action to control the human flow and hence maximize the potential benefits.

The visit-revisit mechanism also has highly counterintuitive policy implications − not just for Zika but also for future strain variants that are transmitted person-to-person via an infected mosquito in a similar way [14]. For example, Fig. 2B illustrates the outbreak severity for more general values of the human recovery rate q_r. As can be seen going from left to right panels in Fig. 2B, there is a remarkable nonlinear switch in the dependency of the outbreak severity on increasing human flow through any Ground Zero. For a fast recovery rate (left panel) the severity decreases with increasing flow because the chance of individuals still being infectious when they revisit is now small. By contrast for a slow recovery rate

(right panel) the severity increases with increasing flow because many individuals will still be infectious when they revisit. In between, there is a critical value (middle panel) for which the severity increases in a non-monotonic way with increasing flow.

3. Discussion

Our results help advance the scientific understanding of what drives human ZIKV outbreaks in urban areas. They also provide a convenient simulation tool for helping gauge the evolution of a future outbreak, and its possible management by soft control of human flow. In addition, the fact that the run-average output of our simple visit-revisit simulation (Fig. 1A) can be represented quantitatively by a set of coupled differential equations with good accuracy (see SI for details) opens up the study of visit-revisit dynamics, and their use in control, to the wealth of tools that exist for dynamical stability analysis within the mathematical science community [15].

As stated succinctly by the authors of Ref. 13, policy-makers have to make decisions in the presence of enormous uncertainty and it is natural to reach for policies that mirror those used previously. However, our findings warn that urban Ground Zero policies need updating to incorporate the unavoidable flow of local residents. We stress that although the inputs in Fig. 1B are necessarily appropriate to Wynwood, Miami Beach and Little River, similar values are to be expected for other residential Ground Zeros in similar urban settings. Also the trends shown in Fig. 2A and B are potentially valid for other viruses and parasite-borne diseases [14].

Since 'popular patches' as in Fig. 1A exist on all geographic scales and yet the total flow and occupancy in our visit-revisit model scale directly with N, the same findings apply in principle whether Ground Zero is a square mile like Wynwood, or an entire city (e.g. Miami) or county (e.g. Miami-Dade), or a state (e.g. Florida), or a country (e.g. U.S.A.) or a region (e.g. the Caribbean) or part of a continent (e.g. South America). In each case, the corresponding results in Fig. 2 should broadly hold. In this way, the international country-level ZIKV travel data presented in Ref. 11 could ultimately be incorporated into a multi-level version of Fig. 1A in which there are patches within patches. In addition, at each level it is possible to connect together multiple Ground Zero patches into a network. In this way, the respective public health agencies at each level can use the insight from Fig. 2 to account for the counterintuitive way in which visit-revisit human flow affects the outbreak's duration, severity and time-to-peak at each level of geographical resolution.

Since our model can also be represented by a set of partial differential equations, the role that each parameter plays in the system's dynamics is well-defined. A deeper analysis of the model's differential equations can be found in Refs. [9, 10].

Here we further explore the uncertainty and sensitivity of the parameters by considering the impact of noise on the input parameters. Specifically, using the estimates for the current ZIKV study, we look at variations of the outbreak features (i.e. duration, severity and time-to-peak) due to 10% added noise. We compute 5000 realizations where noise is added to each of the infection parameters (i.e., q_i and q_r) as well as the mobility (i.e., p_j and p_l) parameters. Our results show that for the infection parameters, noise does not affect the overall outbreak duration more than 3%, while for the mobility parameters it produces less than 1% change. Regarding severity of the outbreak, we find that noise generates changes from 10–23% with the infection probability and the rate of leaving representing the highest sensitivity. Finally, we find that the time-to-peak is decreased from 0.4–4.5%, mainly due to noise in the mobility parameters, while the infection parameters tend to show robustness with variations no larger than 1.8%.

Our model obviously has various limitations. First, Ground Zero areas are sometimes hard to define and so a hard boundary between what is inside and outside may be a challenge. However natural and artificial geographical features such as freeways can help with this regard. Second, we have not included details of the precise process of mosquito biting and hence transmission between individuals, other than saying that an infected individual and a susceptible individual get bitten in succession by the same mosquito as part of its blood meal. Third, additional information about particular species of mosquito could also be incorporated, as could allowance for aerial spraying. Fourth, we have assumed that the transmission rate is uniform within Ground Zero whereas it is of course not. However as future information becomes available about trap locations and capture in real-time, it should be possible to modify the scale of the analysis by breaking up Ground Zero into a few interconnected sub-patches. Fifth, there is likely heterogeneity in individuals' prevention measures (and hence transmission probabilities) as a result of decisions to cover up and wear repellant. However, while all these complications could be addressed within the model to a greater or lesser extent, this would come at the expense of increasing model complexity and therefore losing the clarity of our results in Fig. 2, while not necessarily increasing the good fit observed in Fig. 1B.

4. Materials and methods

4.1. Model Design

The model described in the paper was designed to feature a parsimonious mechanism to account for the visit-revisit behavior to Ground Zero that is followed in particular by local residents, workers, and family members. While the details are given in the main paper and in the SI, we note that at every timestep, each member of the simulated population of N individuals is considered, and a random number

generated in the standard way to decide whether they enter or leave the Ground Zero according to the respective probabilities p_j and p_l. The computer program used is provided in the SI. The infection rate for a susceptible individual (S) within Ground Zero is q_i; the individual recovery rate for an infected individual (I) is qr. We take one timestep as one effective day where there is flow of individuals in and out of Ground Zero, though this can easily be generalized.

4.2. Comparison with empirical data in Fig. 1B

The model parameters are estimated from official sources [11, 12] with the values described in the main text. Running the simulation of the model produces sets of simulated human case time-series for the ZIKV outbreak for each Ground Zero. The best fit from 20 runs is presented in Fig. 1B, though other runs in the 20 were of comparable goodness in terms of the average deviation. Fig. 2A presents the model's output by averaging over 5000 simulations, as does Fig. 2B. The statistical overlap between our model, or the standard SIR model, and the real data, was calculated by numerically integrating the product of the normalized time-series. The residual sum of squares was also calculated between the real data and simulation (dynamic and static) time series. Full details and comparative numbers are given in the SI. There was no further statistical analysis beyond this.

Declarations

Author contribution statement

Pedro Manrique: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

John Beier: Conceived and designed the experiments; Wrote the paper.

Neil Johnson: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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