



Retracing Zika's footsteps across the Americas with computational modeling

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For much of 2016, it was hard to look at the news without seeing a headline about Zika. Images of parents holding newborn children with microcephaly grabbed the world's attention and spurred the World Health Organization to make a rare declaration of a Public Health Emergency of International Concern (1). Despite widespread awareness of Zika and considerable will to contain its spread, data were scarce and initial predictions about Zika's future were little more than conjectures loosely informed by historical statistics about the epidemiology of other diseases (2). A variety of issues continued to plague efforts to assess the threat posed by Zika, among them a high rate of asymptomatic infection, challenges associated with the interpretation of data on past exposure to Zika virus, and inconsistencies in case reporting (3). In PNAS, Zhang et al. (4) leverage the power of computational modeling to make the most of available data and offer new insights about what may have happened as Zika virus marched across the Americas.

Retracing Zika's Footsteps

The power of the computational model developed by Zhang et al. (4) lies in its ability to tie together disparate empirical observations, each of which provides a glimpse into the spread of Zika virus but none of which tells the whole story. In a sense, this situation mirrors the parable of the blind men and the elephant. What Zhang et al. (4) have accomplished amounts to being provided with a description of an elephant's trunk and tail and successfully predicting its tusks and ears. Such is the potential of a detailed computational model guided by a refined set of biological assumptions and informed with extensive data about factors deemed important by those assumptions.

In more specific terms, Zhang et al. (4) adapted a model used previously to investigate global patterns of influenza virus spread (5). A primary strength of that model is its highly realistic portrayal of human demography and air travel patterns at a resolution that is granular enough for assumptions of mass action contact at local scales to not be completely unreasonable. To adapt that model for Zika virus, which is transmitted

primarily by *Aedes* mosquitoes, Zhang et al. (4) added features consistent with those typical of models of mosquito-borne pathogen transmission (6) and parameterized their model with additional data on factors of relevance to virus transmission by *Aedes* mosquitoes—including temperature (7), mosquito occurrence estimates (8), and a spatially resolved economic index (9)—that served as a proxy for mosquito-human contact. Some model parameters were informed by relevant estimates from the literature and others were calibrated based on two data sources: the 2013 Zika epidemic in French Polynesia (10) and the timing of peak incidence of Zika in Colombia (11).

Based on essentially only one piece of information about the Zika epidemic in the Americas, the model's performance in validation exercises to independently recreate estimates of other features of the epidemic is impressive. Empirical estimates of cumulative cases-by-department in Colombia, weekly incidence of Zika-associated microcephaly in Brazil, and Zika virus importation patterns into the United States and Europe were all consistent with the model's output (4). In addition, the estimated timing of Zika virus' introduction to the Americas was consistent with estimates based on phylogenetic evidence (12, 13), and the model's country-level estimates of the cumulative proportion infected were consistent with other model-based estimates (14).

Backed with the confidence of successful out-of-fit validation, Zhang et al. (4) describe several interesting results that derive from their estimates. First, their model suggests that the entry point of Zika virus into the Americas may have been Rio de Janeiro, given its much higher flow of air travelers compared with alternative points of entry. This conclusion is not firm, but even the uncertainties around this estimate provide insight in the sense that they draw attention to interactions between the timing of introduction and time-sensitive local transmission potential in different areas. Second, the model provides estimates of the timing of Zika virus' introduction in numerous countries that are all considerably earlier than the first case reports in those countries. Although there is

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uncertainty around these estimates, they show that detection lags as long as 3–6 mo may be typical in the situation of a newly emerging disease with largely benign symptoms that resemble more common diseases. Third, the model yields estimates of the timing and magnitude of Zika-associated microcephaly in countries throughout the region. Even if these numbers do not align with case reports of microcephaly in the final analysis, the outputs of this model constitute valuable information as scientists work to assemble the many pieces of the microcephaly puzzle.

Next Steps for Modeling

The model by Zhang et al. (4) has had laudable success in its debut, but future tasks may be more challenging. In a directly comparable example involving the invasion of chikungunya virus in the Americas in 2013–2014, two models (15, 16) both performed well in predicting the sequence of the invasion across the Caribbean. More generally, it has been proposed that spatial spread patterns of emerging pathogens may often be quite predictable provided that the network along which the pathogen spreads is well characterized (17). These and other past successes (18) should by no means diminish the achievements of Zhang et al. (4). It simply must be recognized that future successes may be harder won as Zika's epidemiology in the Americas shifts into a state in which immunity plays an increasingly important role in shaping its transmission dynamics. The interplay between extrinsic forces, such as weather, and intrinsic forces, such as immunity, are well known to pose inherent challenges to predicting infectious disease dynamics (19). Being handicapped by a paucity of data on past exposure to Zika virus—and presumably the acquisition of immunity to it—do not make this task any easier.

One important place where the past and future of Zika modeling intersect is the question of why the epidemic in the Americas seems to have mostly died out. The analysis by Zhang et al. (4) corroborates a hypothesis proposed previously (20) that the Zika epidemic would soon be extinguished by herd immunity, much like a flame that runs out of oxygen. Although herd immunity will

undoubtedly play a major role in shaping Zika's future in the near to medium term, the extent to which other forces—such as mosquito control, modified human behavior, stochastic fade-outs at local scales, or reporting fatigue—may have contributed to Zika's apparent decline is not well understood. Addressing this question is vitally important though. The health of communities across the Americas, as well as the prospect of assessing the efficacy of Zika vaccine candidates in phase III trials (21, 22), depend on the overall extent and geographical distribution of naturally acquired immunity. Models such as the one by Zhang et al. (4) have an essential role to play in resolving this outstanding question, but they will need help in the form of improved diagnostics for past exposure to Zika virus (23) and timely and accurate results from surveillance efforts across the region (24).

Whether it be the future of Zika or the next emerging disease, it is vitally important to have a standing capability to respond with state-of-the-art modeling to the needs of policymakers whose questions cannot be answered by data alone (25). For that to be possible, funders must recognize modeling as a scientific pursuit worthy of investment in its own right and should make those investments on a consistent basis. Advances will come most readily when researchers have the support necessary to explore new ideas not only in response to public health emergencies but in anticipation of them. Researchers too can take steps to hasten advances in the field by making early versions of their analyses available on preprint servers, as did Zhang et al. (26) before publication in PNAS. In this and many other respects, the paper by Zhang et al. (4) exemplifies the potential of computational modeling to contribute to solutions for the growing list of public health challenges that society faces.

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