Title: Understanding the invasion dynamics of Zika in Latin America: implications for policy

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Abstract: Epidemiological analysis suggests the ongoing Zika epidemic in Latin America may have already peaked, limiting the scope for interventions to have a major impact, but that herd-immunity will likely supress transmission for a decade or more once the current epidemic concludes, giving a valuable time window for development of vaccines and novel vector controls.

The last three years have seen Latin America invaded by two arboviruses of significant public health concern. Chikungunya swept through the Caribbean in late 2013, causing substantial autochthonous outbreaks in the region from 2014 onwards (*1*). Thought to cause milder disease, Zika initially caused less concern than Chikungunya, but by May 2015, it was clear that the Northeast region of Brazil was experiencing a major epidemic (Fig. 1). The perception of the public health threat posed by Zika changed dramatically in late 2015 when a surge in microcephaly cases in new-borns was seen in areas of Brazil (see Supplementary Material [SM]) following widespread Zika transmission earlier that year (*2*). Evidence for a causal link between Zika infection and microcephaly and other serious congenital anomalies is compelling (*3*), prompting the World Health Organization to declare Zika a public health emergency of international concern in February 2016 (*4*). However, it is far from clear how policymakers should best respond.

The first challenge in formulating an effective public health response has been the sheer speed of the epidemic spread; indeed, surveillance data suggest that the epidemic has peaked in many places as of May 2016, with incidence now declining in the many of the countries for which data are available (Fig. 1). Immediate policy responses to the crisis have included enhanced vector control (*5*) and advice to delay pregnancy in a few countries (*6*), followed by an extended recommendation to all affected countries by WHO in June 2016. Both have merits, but are likely to have limited effectiveness (*7*) and may indeed interact antagonistically. To gain insight into why – and to assess the longer-term risks posed by Zika and prioritise interventions – it is necessary to understand the dynamics and drivers of disease invasion.

Three key factors determine the scale and speed of spread of an emerging infection in a naïve population and the risk of longer-term endemicity. The first is the transmissibility of the infection, characterised by the reproduction number, R – the average number of secondary infections caused by a typical index case. R is typically at its maximum at the start of an epidemic – then termed R_0 (the basic reproduction number) – before population immunity has accumulated. We provide time-varying estimates of R for affected Latin American countries where surveillance data are available (Fig. 1 and see SM). Despite the limitations of current surveillance systems (*i.e.* generally low levels of laboratory confirmation and major changes in surveillance sensitivity over time), a relatively consistent picture is seen: R_0 estimates vary between approximately 1.5 and 6, similar to published values for Zika in French Polynesia and dengue (*8*) (see SM). Trends at the country level hide substantial subnational heterogeneity (see SM), however. Geographic variation in vector habitat quality and spatiotemporal variation in temperature and rainfall affect both vector density and competence, leading us to expect that Zika will show high levels of spatial and seasonal variation in transmissibility, comparable to those seen for dengue (*9, 10*).

The generation time (T_g, the time between cycles of infection in an epidemic, see SM) is the second key factor affecting the timescale of disease invasions. Taking our estimates of R_0 (Fig. 1) and our best estimate of the generation time distribution for Zika (mean 20.0 days, standard deviation 7.4 days, see SM), we use a simple stochastic spatial model of Zika transmission (see SM) to illustrate the dynamics of the initial epidemic and possible future waves of transmission (Fig. 2a). We expect the initial wave of transmission to be largely over in 3 years, with seasonal oscillations in incidence caused by seasonal variation in mosquito populations and transmissibility. Herd immunity will likely then cause a delay of over a

decade until further large epidemics are possible; an epidemic of an immunizing infection peaks when depletion of susceptibles (and consequent growth of herd immunity) drives R down to 1, but transmission then continues as incidence declines – leading to R decreasing to substantially below 1 by the end of the epidemic. Following the epidemic, herd immunity begins to decline (and R to increase) as new births replenish the susceptible population, but sustained transmission is only likely when R exceeds 1 once again. The time required for this to occur depends non-monotonically on R_0, with intermediate values of R_0 (1.5-3.5) giving the maximum delay (see SM).

The large-scale connectivity of human populations is the third key factor affecting the dynamics of disease invasions. Human mobility patterns determine the chance an infection present in one location will be introduced elsewhere, thus fundamentally affecting the early dynamics when numbers of infections are low and spread is highly stochastic. As numbers of infections grow in one area, so does the risk of export to another. Thus, while the seeding of infection in Brazil was a chance event (*11*), once a full-blown epidemic was underway, export of substantial numbers of infections across the Americas was inevitable and rapid, leading to the widespread epidemics which unfolded from May 2015. This is reflected in our modelled dynamics, where we find that the duration of the initial wave of transmission is relatively insensitive to the degree of population connectivity (see SM).

Modelling also gives insight into how the age distribution of infection will evolve over time – of particular relevance to Zika, given the risk of congenital Zika syndrome and microcephaly in infants faced by pregnant women. During the initial epidemic, we would expect all ages to be equally affected unless exposure and/or susceptibility vary substantially with age. The mean age of infection would then fall substantially in future epidemics, given the immunity acquired by older people through past exposure. If R_0 were sufficiently high, then in the long term most infections would be expected to occur in childhood, before the typical age women first give birth (see SM). Unfortunately, our estimates of R_0 (Fig. 1) suggest such a large reduction in the mean age of infection is unlikely to occur for Zika. If Zika becomes endemic, we predict that while the mean age of cases will fall compared with what has been seen thus far, it will still be sufficiently high to pose an ongoing and substantial risk to pregnant women (Fig. 2 and SM). This conclusion is supported by analysis of historical Zika seroprevalence data presented in the companion review article published in this issue (*12*).

How does this analysis inform what policymakers should do now? Advising against pregnancy has been criticised for being infeasible for many women – especially long term (*6*). Our analysis suggests (see SM) that at the provincial scale, the duration of the first wave of transmission is typically under 6 months, though in some locations the timing of virus introduction can interact with seasonality of transmissibility to extend a local epidemic over two transmission seasons. Thus if recommendations to delay pregnancy were tuned to the local (subnational) context and adapted in light of local surveillance data, in many areas they could be kept in place for a shorter time – making adherence more feasible while retaining the potential risk-reduction benefits. This could be even more relevant as microcephaly cases have been reported born to asymptomatic pregnant women (*13*). However, local optimization of this and other control or risk-reduction measures requires timely availability of high-quality geographically stratified surveillance data.

Enhanced vector control is also potentially beneficial, but it is critical for policymakers to set realistic expectations about the likely impact. Evidence (*12*, *14*) suggests traditional insecticide-based control is rarely sufficiently effective to stop dengue epidemics (i.e. achieve $R<1$). Effectiveness would need to be considerably higher to stop the first epidemic of a new virus in a naive population. But vector control with limited effectiveness could – if sustained – reduce the attack rates seen in the initial epidemic (see SM). Modelling suggests there are downsides, however. First, the epidemic may last longer, which might make it even harder for women to adhere to recommendations delaying pregnancy. Second, the epidemic will overshoot the herd-immunity threshold by less than if interventions had not been introduced – leaving a smaller proportion of the population immune and thus reducing the delay until population susceptibility once again reaches levels which allow sustained endemic transmission to occur (Fig. 2).

Assessing the long-term risks posed by Zika is critical to prioritising the development of novel interventions. What is the likelihood that the virus will become endemic or that sporadic epidemics will occur with sufficient regularity to pose an equivalent risk? Modelling gives some insight, but cannot be truly predictive given current knowledge gaps. Our analysis suggests that once the current epidemic is over, herd immunity will lead to a delay of at least a decade before large epidemics may recur (Fig. 2). However, this prediction has caveats: the delay to resumption of transmission might be substantially reduced by high levels of spatiotemporal heterogeneity in exposure risk (not accounted for in our model) or transient reductions in transmission caused by interventions or population behaviour change. In addition, our model makes the conservative assumption that flavivirus transmissibility in Latin America has not been anomalously high in the last 2-3 years and therefore predicts the virus will eventually become endemic. Endemicity in this case does not imply predictable annual epidemics in all regions, but rather that sustained transmission would be expected somewhere in the continent every year – akin to what is seen for individual dengue serotypes today. However, if Zika transmissibility is strongly modulated by longer term climatic variation (such as El Niño), the virus may not be able to sustain endemic transmission, resulting in much more sporadic but larger scale epidemics when reseeding of infection coincides with favourable conditions for transmission. Last, we have assumed a constant risk of reseeding of the infection into the human population; if a sylvatic reservoir for Zika is established in the Americas (*12*, *15*), the background level of human exposure may increase.

A more precise assessment of the long-term risks requires several key data gaps to be filled. We need to measure the extent of (and geographic variation in) herd immunity in populations which have experienced recent Zika epidemics. Studies should not be restricted to Latin America – it is equally important to understand apparent differences in Zika epidemiology between continents. Currently, we cannot assess whether Asia is also at risk of a major Zika epidemic – or indeed, why the scale of transmission in Latin America has been so much greater than anything previously seen. Multiple hypotheses have been proposed (*12*) but cannot yet be tested: immunological enhancement from prior exposure to dengue, El Niño-driven climate effects, viral evolution and regional genetic differences in the *Aedes aegypti* populations may all play a role. While data is currently limited (*16*), cross-reactivity with dengue is a particular concern, as our analysis indicates both cross-protection and enhancement could shorten the time until epidemics can reoccur and increase the chances of long-term endemic transmission (Fig. 2). Age-structured seroprevalence surveys are a

priority, using assays which can distinguish exposure to Zika from exposure to other flaviviruses. Such surveys allow estimation of variation in exposure with time and age, of interactions with other flaviviruses, and of overall transmissibility (e.g. to be compared with those in Fig. 1) (*12*). Long-term cohort studies can provide even richer longitudinal data to examine individual variation in exposure and clinical and immunological outcomes.

Finally, innovation and a global perspective are required when developing and evaluating vaccines and novel vector control measures (*17*) for both Zika and Chikungunya. The traditional model for efficacy trials used for endemic diseases poses major challenges for emerging infections with sporadic and unpredictable epidemics. While phase I safety studies for antivirals and vaccines do not require active transmission, efficacy studies do. Our analysis suggests there is limited time to initiate such studies in the current epidemic before incidence may be insufficient to measure impacts. Given the unpredictable timing and intensity of Zika (and chikungunya) outbreaks, future efficacy trials may need to be pre-approved in a large number of potential trial sites, then rapidly initiated in particular sites only once local transmission has been detected. Efficacy studies for vaccines may need to recruit and vaccinate participants now and follow-up for a longer period than is typical. Active case detection in multiple sites over a long time period would be prohibitively expensive, so study protocols need to be adaptive – such as planning to start active surveillance in a trial site only when Zika transmission is detected, even if the outbreak occurs several years after vaccination took place. Evaluating rare endpoints such as microcephaly poses particular difficulties, requiring very large-scale trials if undertaken in advance of an epidemic, or accepting the risks associated with using a novel vaccine in pregnant women if undertaken in the face of an epidemic.

Zika follows Ebola as a public health crisis where policymakers have had to make decisions in the presence of enormous uncertainty. In such contexts, it is natural to reach for policies which mirror those used previously. We argue that real-time epidemiological analysis based on high quality and publically available surveillance data can critically inform such decision-making. Zika and Ebola epidemiology and policy options differ fundamentally. The current Zika epidemic is not containable; at best interventions can mitigate its health impacts. More optimistically, the natural dynamics of the epidemic are now likely to give a multi-year window to develop new interventions before further large-scale outbreaks occur.

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References

1. S. C. Weaver, Arrival of Chikungunya Virus in the New World: Prospects for Spread and Impact on Public Health. *PLoS Negl Trop Dis* **8**, e2921 (2014).
2. W. Kleber de Oliveira *et al.*, Increase in Reported Prevalence of Microcephaly in Infants Born to Women Living in Areas with Confirmed Zika Virus Transmission During the First Trimester of Pregnancy - Brazil, 2015. *MMWR Morb Mortal Wkly Rep* **65**, 242-247 (2016).
3. S. Cauchemez *et al.*, Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. *The Lancet*, pii: S0140-6736 (2016).
4. World Health Organization, "WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain-Barré syndrome" (2016). http://www.who.int/mediacentre/news/statements/2016/emergency-committee-zika-microcephaly/en/
5. World Health Organization, "Mosquito (vector) control emergency response and preparedness for Zika virus" (2016). http://www.who.int/neglected_diseases/news/mosquito_vector_control_response/en/
6. L. D. Schuck-Paim C, Simonsen L, Alonso W, Unintended Pregnancies in Brazil – A Challenge for the Recommendation to Delay Pregnancy Due to Zika. *PLoS Currents Outbreaks*, (2016).
7. N. K. Tepper *et al.*, Estimating Contraceptive Needs and Increasing Access to Contraception in Response to the Zika Virus Disease Outbreak - Puerto Rico, 2016. *MMWR Morb Mortal Wkly Rep* **65**, 311-314 (2016).
8. A. J. Kucharski *et al.*, Transmission dynamics of Zika virus in island populations: a modelling analysis of the 2013-14 French Polynesia outbreak. *bioRxiv*, (2016).
9. M. A. Johansson, F. Dominici, G. E. Glass, Local and global effects of climate on dengue transmission in Puerto Rico. *PLoS Negl Trop Dis* **3**, e382 (2009).
10. I. Rodriguez-Barraquer, H. Salje, J. Lessler, D. A. Cummings, Predicting intensities of Zika infection and microcephaly using transmission intensities of other arboviruses. *bioRxiv*, (2016).
11. N. R. Faria *et al.*, Zika virus in the Americas: Early epidemiological and genetic findings. *Science* **352**, 345-349 (2016).
12. J. Lessler *et al.*, Assessing the Global Threat of Zika. *Science*, (2016).
13. O. Pacheco *et al.*, Zika Virus Disease in Colombia - Preliminary Report. *N Engl J Med*, [Epub ahead of print] (2016).
14. N. L. Achee *et al.*, A Critical Assessment of Vector Control for Dengue Prevention. *PLoS Negl Trop Dis* **9**, e0003655 (2015).
15. D. Musso, D. J. Gubler, Zika Virus. *Clin Microbiol Rev* **29**, 487-524 (2016).
16. L. M. Paul *et al.*, Dengue Virus Antibodies Enhance Zika Virus Infection. *bioRxiv*, (2016).
17. R. Rodriguez-Roche, E. A. Gould, Understanding the Dengue Viruses and Progress towards Their Control. *Biomed Res Int* **2013**, 690835 (2013).

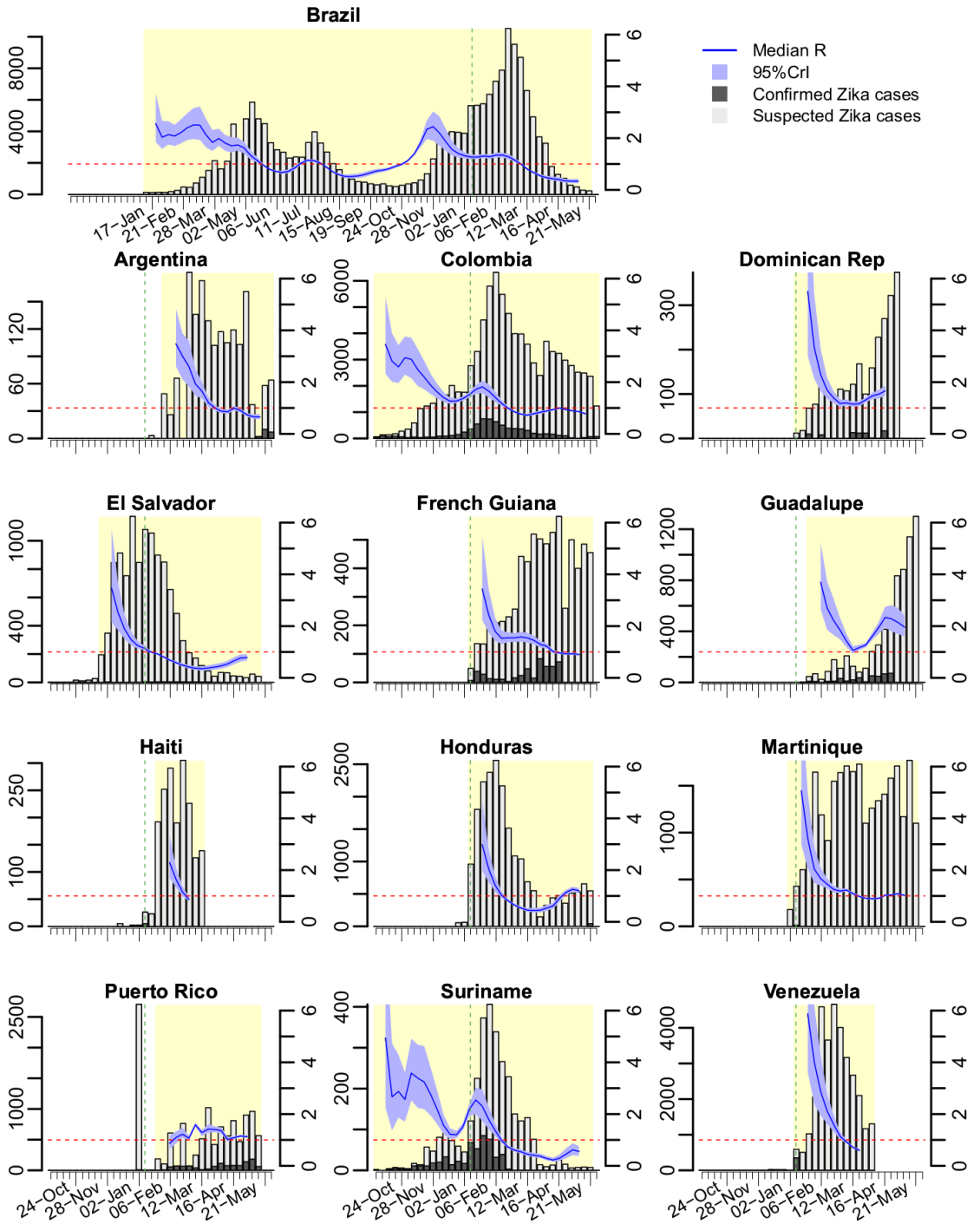


Fig. 1. Publically available surveillance data on weekly suspected (light grey) and laboratory confirmed (dark grey) Zika cases (left axis and bars) overlaid with estimates of the reproduction number, *R*, over time (running 5-week average shown, centred on the middle week). Yellow shading shows the time window over which *R* was estimated, since surveillance in some countries took some weeks to establish. The vertical dashed line marks the first week of 2016 and the horizontal dashed line marks the *R* =1 threshold. Countries with the largest numbers of reported cases are shown; see SM for other countries, sources and estimation methods.

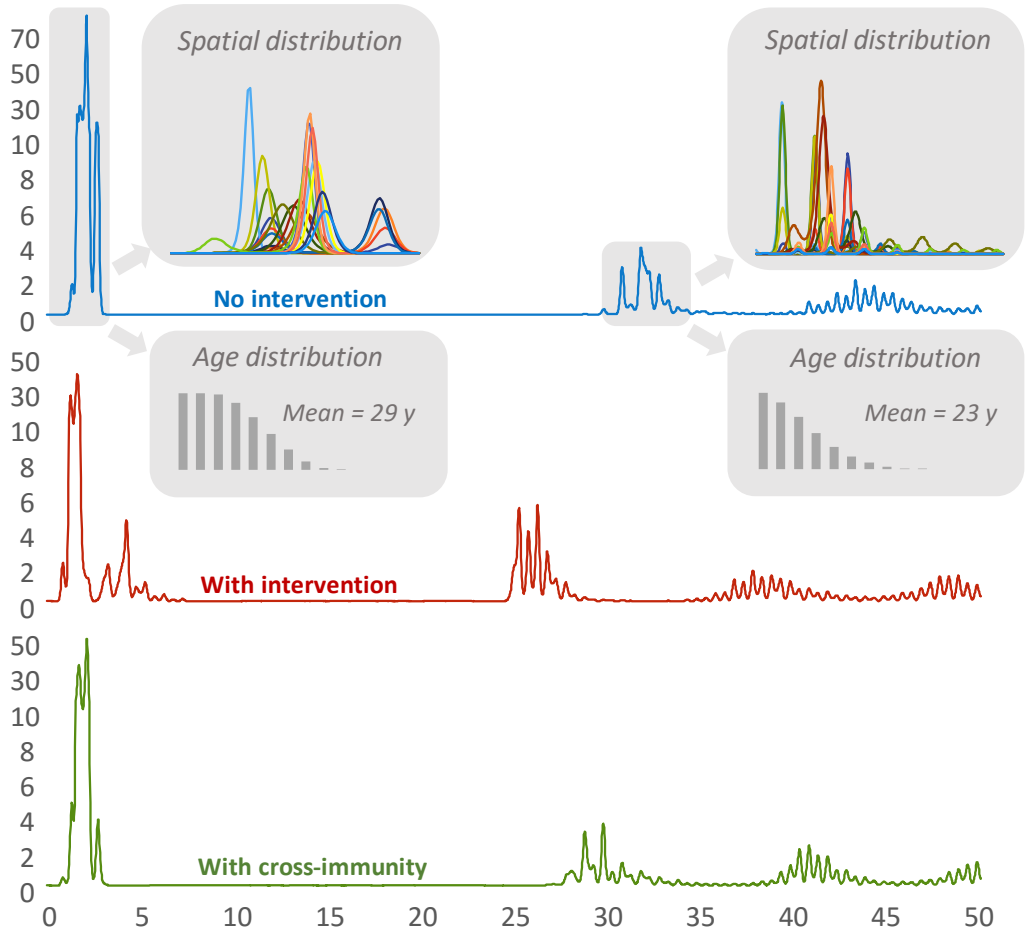


Fig. 2. Typical simulated time series of Zika weekly infection incidence per 1000 people in a population of 600 million for three scenarios: no interventions (blue curve), interventions which decrease mosquito lifespan by 20% for one year during the initial epidemic (red curve), and assuming a degree of cross-immunity in the population from prior dengue exposure (green curve). Incidence is plotted on a non-linear scale (increments of 2 up to 10, then increments of 20) to allow later epidemics to be resolved clearly. Shaded insets show incidence dynamics (coloured curves) in the 20 spatial regions being modelled together with the age distributions (10 year age bands) of infections (dark grey bars) and mean age of infection for the first two epidemic periods in the no intervention scenario. Full details provided in SM.

Supplementary Materials:

Materials and Methods

Supplementary Results

Figs. S1 to S14

Tables S1 to S6

References (18-74)