EPIDEMIOLOGY

Countering the Zika epidemic in Latin America

Epidemic dynamics are key and data gaps must be addressed

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As evidence grew for a causal link between Zika infection and microcephaly and other serious congenital anomalies (*1*), the World Health Organization (WHO) declared the Latin American Zika epidemic a public health emergency of international concern in February 2016 (*2*). The speed of spread [see the figure, top, and the supplementary materials (SM)] has made effective public health responses challenging. Immediate responses have included vector control (*3*) and advice to delay pregnancy in a few countries (*4*), followed by an extended recommendation to all affected countries by WHO in June 2016. These have merits but are likely to have limited effectiveness (*5*) and may interact antagonistically. Fuller understanding of dynamics and drivers of the epidemic is needed to assess longer-term risks to prioritize interventions.

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, characterized by the reproduction number, R, the average number of secondary infections caused by a typical index case ($R < 1$ stops an epidemic). We provide time-varying estimates of R for Latin American countries where surveillance data are available (see the figure, top chart, and the SM). Country-level trends hide subnational heterogeneity (see SM), which likely reflects geographic variation in vector habitat and climate-driven variation in vector density and competence (*6*).

The generation time (T_g, the time between sequential rounds of infection; see SM) is

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the second key factor that determines the time scale of disease invasions. Taking estimates of R and T_g, we used a stochastic spatial model of Zika transmission (see SM) to illustrate dynamics of the epidemic and possible future waves of transmission (see the figure, center chart). We expect the current epidemic to be largely over in 3 years, with seasonal oscillations in incidence caused by variation in mosquito populations and

> *"[C]ross-reactivity with dengue is a particular concern…and might increase …long-term endemicity…"*

transmissibility. Herd immunity will likely then cause a delay of more than a decade until further large epidemics are possible.

The large-scale connectivity of human populations is the third key factor. Human mobility determines the chance an infection present in one location will be introduced elsewhere. Although the seeding of infection in Brazil was a chance event (*7*), once a full-blown epidemic was under way, export of infections across the Americas was inevitable and rapid and led to the widespread epidemics which unfolded from May 2015 onward (see SM).

Modeling gives insight into how the age distribution of infection will evolve over time—of particular relevance given the risk of congenital Zika syndrome and microcephaly. 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 in future epidemics, given the immunity acquired by older people through past exposure. However, our analysis suggests that this effect is unlikely to be sufficient to prevent ongoing and substantial risk to pregnant women in future Zika epidemics (see the figure, age distribution insets, and the SM). This conclusion

is supported by analysis of historical Zika seroprevalence data (*8*).

### WHAT SHOULD POLICY-MAKERS DO?

Advising against pregnancy has been criticized for being infeasible for many women—especially long term (*4*). Our analysis (see the figure, spatial variation insets) suggests that, at the provincial scale, the timing of epidemic seeding is unpredictable but that the duration of the first wave of transmission is typically <6 months. However, in some locations, the timing of virus introduction can interact with seasonality of transmissibility to extend a local epidemic over two transmission seasons. If recommendations to delay pregnancy were tuned to the local context, in many areas they could be kept in place for a shorter time—making adherence more feasible while retaining potential risk-reduction benefits. Local optimization of control or risk-reduction measures requires timely availability of high-quality geographically stratified surveillance data.

Enhanced vector control is potentially beneficial, but it is critical to set realistic expectations. Evidence (*8, 9*) suggests that traditional insecticide-based control is rarely sufficiently effective to stop dengue epidemics. Effectiveness would need to be considerably higher to stop the first epidemic of a new virus in a naïve population. But vector control with limited effectiveness could—if sustained—reduce attack rates seen in the initial epidemic (see SM). Modeling suggests downsides, however. The epidemic may last longer, which might make it harder for women to adhere to recommendations delaying pregnancy. Also, 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 reducing the delay until new births allow population susceptibility to again reach levels that allow sustained endemic transmission (see the figure, bottom chart, and the SM).

What is the likelihood that the virus will become endemic or that sporadic epidemics will occur with sufficient regularity to pose an equivalent risk? 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 (see SM). 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 by transient reductions in transmission caused by interventions or population behavior change. Also, our model makes the conservative assumption that flavivirus transmissibility in Latin America has not been anomalously high in the past 2 or 3 years (e.g., due to cli-

Zika surveillance data and estimated *R*, Brazil
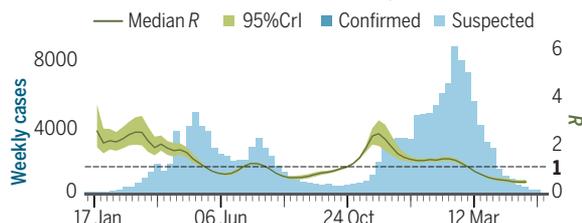
Zika epidemic simulations

No intervention

With intervention to reduce mosquito life span
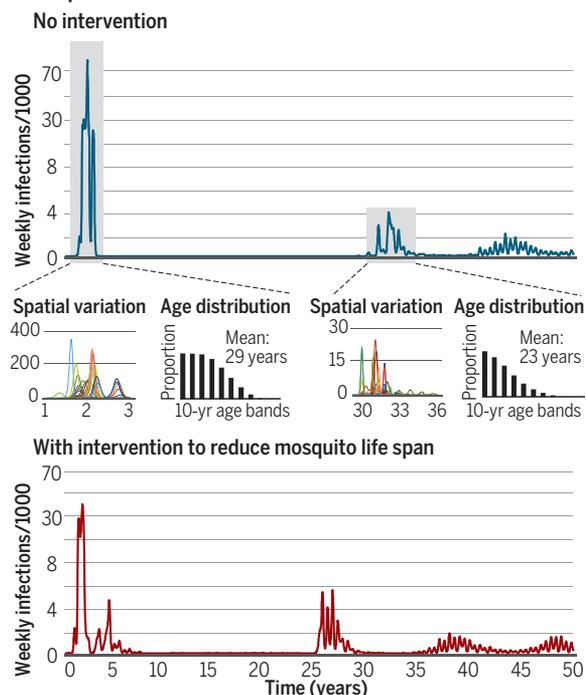
Zika transmission dynamics. (**Top**) Publicly available surveillance data on weekly suspected and laboratory-confirmed Zika cases in Brazil 2015–16 overlaid with estimates of *R* [running 5-week average (green) shown, centered on the middle week]. *R* = 1 threshold shown as dashed line. See SM for other countries and sources, estimation methods, and weekly infections. (**Center** and **bottom**) Typical simulated time series of Zika weekly infection incidence in a population of 600 million for two scenarios: no interventions (blue line) and with interventions that decrease mosquito life span by 20% for 1 year during the initial epidemic (red line). Incidence is plotted on a nonlinear scale to allow later epidemics to be resolved clearly. (Insets) (left) Incidence dynamics in the 20 spatial regions being modeled and (right) the age distribution of infections, for the first two epidemic periods without interventions. Full details are provided in the SM.

matic conditions) and so predicts that the virus will eventually become endemic. This 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 more sporadic, but larger-scale, epidemics when reseeding of infection coincides with favorable 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 (*8*, *10*), background levels of human exposure may increase.

A more precise assessment of long-term risks requires key data gaps to be filled. We need to measure the extent of (and geographic variation in) herd immunity in populations that have experienced recent Zika epidemics. Studies should not be restricted to Latin America. Currently, we cannot assess whether Asia is at risk of a major Zika epidemic—or why the scale of transmission in Latin America has been so much greater than anything previously seen. Multiple hypotheses have been proposed (*8*) but cannot yet be tested: immunological enhancement from prior exposure to dengue, El Niño–driven climate effects, viral evolution, and regional genetic differences in *Aedes aegypti* populations. Although data are currently limited (*11*), 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 might increase the chances of long-term endemicity (see SM). Age-structured seroprevalence surveys are a priority, with assays that 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 (*8*). Long-term cohort studies can provide longitudinal data on individual variation in exposure and clinical and immunological outcomes.

The traditional model for vaccine and antiviral efficacy trials used for endemic diseases poses challenges for emerging infections with sporadic and unpredictable epidemics. Although phase I safety studies do not require active transmission, efficacy studies do. Our analysis suggests that 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

outbreaks, future efficacy trials may need to be preapproved in a large number of potential sites then rapidly initiated in particular sites 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 would be prohibitively expensive, so study protocols need to be adaptive—e.g., start active surveillance in a site only when Zika transmission is detected, even if the outbreak occurs several years after vaccination took place. Evaluating rare end points, such as microcephaly, poses particular difficulties and requires very large scale trials if undertaken in advance of an epidemic, or the risks associated with using a novel vaccine in pregnant women must be accepted if undertaken in the face of an epidemic.

Like Ebola, Zika is a public health crisis in which policy-makers have had to make decisions in the presence of enormous uncertainty. In such contexts, it is natural to reach for policies that mirror those used previously. However, Zika and Ebola epidemiology and thus policy options differ fundamentally. The current 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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