

## Is there a silver lining to the Zika virus epidemic in the Americas?

It is hard to find anything positive to say about an epidemic of an emerging virus that infects pregnant women, targets developing fetuses' neural progenitor cells, and disrupts the sequence of neural development to cause a devastating syndrome resulting in lifelong disabilities. Infants with microcephaly became the faces of the Zika virus epidemic in the Americas, which affected almost all countries in the western hemisphere in 2014–17. By the end of 2017, Zika virus has nearly disappeared from the Americas as quickly as it emerged. Now that the dust is settling, what have the scientific and public health communities learned? Is there a silver lining to Zika's devastation?

The American Zika virus epidemic mobilised scientists throughout the region and beyond with a force reminiscent of the response to the emergence of HIV. As emerging infections do not follow the same pace as research funding agencies, many scientists, staff, and students worked without pay early in the epidemic. They understood the urgency of their work and were passionate to uncover the fundamental rules of Zika virus: modes of transmission, accurate diagnosis, spectrum of clinical manifestations, and methods of prevention and treatment. To uncover these rules, scientific teams crossed disciplines—in our case, a virologist, perinatologist, child psychologist, immunologist, and infectious disease specialist often shared calls across countries and time zones. These multidisciplinary research teams endure and will tackle other high burden diseases in the future.

To address the problem of diagnosis of the closely related Zika and dengue viruses, these teams raced to develop novel recombinant antigens and monoclonal antibodies to differentiate the two infections.<sup>1-3</sup> Another major advance came in the use and adaptation of child

development assessment tools. In many low-income and middle-income countries (LMICs), these assessment tools are not in routine use and are not widely available. The response to the Zika virus epidemic resulted in an increasing number of child behaviour specialists who became skilled in using these assessment tools for research. Not surprisingly, with all of these efforts, the number of Zika-related publications in PubMed rose from just three in all of 2013 to an average of 177 publications per month in 2019. We now know the ways in which Zika virus can be transmitted, have improved diagnostics, better understand the full spectrum of clinical disease, and have made major advances in the development of Zika virus vaccine candidates. In carrying out their work, these collaborations between high-income countries and LMICs, and between LMICs, undoubtedly strengthened research and laboratory capacity in the region.

Similarly, the public health communities in countries affected by Zika virus mobilised in response to the epidemic. These institutions strengthened surveillance for birth defects and devised new approaches to surveillance of emerging infections in pregnant women.<sup>4</sup> In most cases, these communities became aware that services for affected children were inadequate. To address the inadequate access to child behavioural specialists in LMICs, UNICEF and others are now implementing early childhood interventions to support the development of children, including those without Zika virus infection.<sup>5</sup> The Zika virus epidemic added momentum to this "imperative for action and measurement at scale"<sup>5</sup> for at-risk children in LMICs. There are also efforts to educate health-care providers on the evaluation of child development and to provide guidance about early stimulation. Many interventions

consider the realities of the local context in LMICs and can be carried out by the child's caregivers. Even simple interventions, when introduced early in a child's life, have been shown to generate lifelong gains.<sup>6</sup> However, these interventions will need to be longitudinal: delayed neurodevelopment, most notably in language, was recently reported in toddlers exposed to Zika virus in utero.<sup>7</sup> An important lesson learned from the HIV epidemic was that affected children and families need a lifetime of psychosocial support and behavioural interventions to complement their medical care.<sup>8</sup> For families affected by Zika virus, a difficult road still lies ahead, and we must continue to provide necessary support services even though the initial urgency of the outbreak has passed.

Whether or not we experience future Zika virus epidemics, we will certainly see the emergence of new pathogens with unanticipated consequences. In applying the lessons of Zika virus to the next epidemic, we should rapidly deploy research funding and prioritise ethical reviews of emerging infection research. We should work to continue to strengthen surveillance systems and be ready to integrate efforts to prevent transmission with maternal, reproductive, and paediatric health services.<sup>9</sup> For Zika virus specifically, a silver lining is that we now understand its fundamental rules, and can confront the next epidemic armed with this knowledge.

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- 1 Balmaseda A, Zambrana JV, Collado D, et al. Comparison of four serological methods and two reverse transcription-PCR assays for diagnosis and surveillance of Zika virus infection. *J Clin Microbiol* 2018; **56**: e01785–17.
- 2 Stettler K, Beltramello M, Espinosa DA, et al. Specificity, cross-reactivity, and function of antibodies elicited by Zika virus infection. *Science* 2016; **353**: 823–6.
- 3 Premkumar L, Collins M, Graham S, et al. Development of envelope protein antigens to serologically differentiate Zika virus infection from dengue virus infection. *J Clin Microbiol* 2018; **56**: e01504–17.
- 4 Gilboa SM, Mai CT, Shapiro-Mendoza CK, et al. Population-based pregnancy and birth defects surveillance in the era of Zika virus. *Birth Defects Res* 2017; **109**: 372–78.
- 5 Richter L, Black M, Britto P, et al. Early childhood development: an imperative for action and measurement at scale. *BMJ Glob Health* 2019; **4**: e001302.
- 6 Boivin MJ, Kakooza AM, Warf BC, Davidson LL, Grigorenko EL. Reducing neurodevelopmental disorders and disability through research and interventions. *Nature* 2015; **527**: S155–60.
- 7 Nielsen-Saines K, Brasil P, Kerin T, et al. Delayed childhood neurodevelopment and neurosensory alterations in the second year of life in a prospective cohort of ZIKV-exposed children. *Nat Med* 2019; **25**: 1213–17.
- 8 Boivin MJ, Ruisenor-Escudero H, Familiar-Lopez I. CNS impact of perinatal HIV infection and early treatment: the need for behavioral rehabilitative interventions along with medical treatment and care. *Curr HIV/AIDS Rep* 2016; **13**: 318–27.
- 9 Beare S, Simpson E, Gray K, Andjelic D. Rapid integration of Zika virus prevention within sexual and reproductive health services and beyond: programmatic lessons from Latin America and the Caribbean. *Glob Health Sci Pract* 2019; **7**: 116–27.