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Vaccine development during global epidemics: the Zika experience

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The North and South American continents experienced a major epidemic of Zika virus in 2015–16, which infected up to 70% of the population in some areas.[1] Until then, Zika virus infection had been considered a benign viral infection with minor health consequences. However, during the 2015–16 epidemic, it was recognised that Zika virus infection can lead to neurological diseases of the peripheral and central nervous systems, including Guillain-Barré syndrome and congenital syndrome, which was initially characterised by microcephaly. The spectrum of clinical presentations of congenital Zika syndrome is still not fully described. Studies have shown that about 20% of babies of mothers exposed to Zika virus during pregnancy who were born with no initial signs of birth defects presented impaired cognitive development and other neurological abnormalities later in life.[2,3] Zika is endemic in all tropical areas of the world, following a pattern of global distribution similar to that of dengue. Nearly half of the global population lives in areas at risk of Zika transmission, and the chance for future Zika epidemics remains very real. 5 years after the 2015–16 outbreak, we still do not have a licensed Zika vaccine despite substantial efforts throughout this time period.[4]

In *The Lancet Infectious Diseases*, Kathryn Stephenson and colleagues[5] report the final results of a phase 1 clinical trial on the safety and immunogenicity of a Zika purified inactivated virus vaccine given via standard, accelerated, or shortened schedules. The authors showed that their Zika vaccine formulation was well tolerated, immunogenic, and did not show signs of inducing any significant adverse medical outcome (eg, Guillain-Barré syndrome) through 52 weeks of follow-up. A two-dose prime–boost regimen of the vaccine, administered either via a standard schedule (weeks 0 and 4) or an accelerated schedule (weeks 0 and 2), elicited a robust Zika virus neutralising antibody response that peaked 2 weeks after the final vaccination, and then declined to a geometric mean titre of less than 100 by study week 16. The sharp decay in Zika virus neutralising antibody titres might be linked to poor induction of cellular immune responses by the inactivated vaccine.[6] This antigen formulation is still far from an ideal vaccine, and efforts to develop or refine promising Zika vaccine candidates must remain a priority. However, because of the progresses made we might be somewhat better prepared should a new Zika outbreak occur.

Despite low antibody durability after boost, it is possible that the level of immunological memory elicited by this vaccine formulation would allow for a quicker humoral immune response to a Zika infection, as has been shown for other flavivirus vaccines.[7,8] This quick response might reduce levels of replicating virus enough to inhibit fetal infections. Nevertheless, safety issues still need to be addressed.

The small number of participants in Stephenson and colleagues' trial[5] does not allow the risk that this formulation can induce Guillain-Barré syndrome to be completely ruled out. Moreover, it is still uncertain whether low levels of anti-Zika antibody can affect the clinical outcome of dengue infection. Anti-dengue antibodies have been shown to enhance Zika virus infection in in-vitro, ex-vivo, and animal models, but the role of anti-Zika antibodies in dengue infections remains unclear.[9] In an ex-vivo human skin model, low titres of anti-Zika antibodies enhanced dengue infection of macrophages and dendritic cells, suggesting that a vaccine formulation that induces low immunogenicity might increase the risk for severe

dengue.[10] This potential risk could probably be mitigated by administering Zika vaccine to individuals who have already been exposed to dengue.

We have learned a lot from efforts to develop a Zika vaccine, and the experience acquired during the Zika outbreak is reflected by the rapid response to the call for development of vaccines for coronavirus disease 2019. However, we should not forget or underestimate the challenges involved in vaccine development and that real solutions can occur only with consistent efforts and sustained investments. Our technological state allows a rapid head start, but vaccine development is not a sprint race, it is a marathon. Efforts to develop Zika vaccines must continue to be supported financially if we are to be prepared for future outbreaks.

We declare no competing interests.

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Sequential inactivated and oral poliovirus vaccine schedules: a balancing act

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Inactivated poliovirus vaccine (IPV), developed by Jonas Salk and colleagues and licensed in 1955, was the first poliovirus vaccine.[1] Salk IPV, a mixture of all three poliovirus types, was developed by inactivating wild polioviruses, a method that continues to be used for IPV production. Although multiple safeguards exist to prevent release of wild polioviruses from IPV production facilities, the continued use of Salk IPV poses a substantial risk for disease outbreak because of the potential for accidental release. The last case of indigenous wild poliovirus type 2 was reported in India in 1999.[2] However, in 2000, and then again in 2002–03, wildtype 2 poliovirus was detected in multiple patients with acute flaccid paralysis in India.[3] Genomic sequence analysis determined the type 2 poliovirus to be the MEF-1 strain, which is used for manufacturing IPV. The detection of the MEF-1 strain highlights the importance of using safer strains for IPV production, ideally those that are non-infectious to humans and stable enough to not acquire paralytic potential.

In 2012, Japan licensed IPV manufactured with Sabin strains, the live-attenuated strains of poliovirus used to manufacture oral poliovirus vaccine (OPV).[4] China licensed Sabin IPV in 2015, which helped to mitigate the effect in the country of a global shortfall in Salk IPV supply.[4] Although Sabin strains are infectious, they do not generally cause paralysis unless they can mutate and acquire neurovirulence. Therefore, manufacturing IPV using Sabin strains presents a lower risk if there is a containment breach than using wild poliovirus strains.

Over the past 5 years, despite some setbacks, the Global Polio Eradication Initiative has achieved two commendable milestones: certifying the global eradication of indigenous wild poliovirus types 2 and 3.[5] With the world closer to global polio eradication, there is need to refine poliovirus vaccination schedules. Use of OPV, the principal tool to achieve eradication, would