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Inactivated Poliovirus Vaccine Supply Shortage: Is There Light at the End of the Tunnel?

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In April 2016, all 155 oral poliovirus vaccine (OPV)–using countries and territories in the world discontinued use of Sabin poliovirus type 2 by switching from trivalent OPV (tOPV) to bivalent OPV (bOPV), containing Sabin poliovirus types 1 and 3, in their national immunization schedules [1]. This event was the largest recall of a medicinal product in history and the fastest introduction of a new vaccine—bOPV. At the same time, all OPV-using countries attempted to introduce at least 1 dose of inactivated poliovirus vaccine (IPV) into the childhood immunization schedule for risk mitigation, primarily to minimize the number of paralytic poliomyelitis cases, should poliovirus type 2 be reintroduced or emerge [2].

Programmatically, the switch was conducted in a globally synchronized manner and, for the most part, was a resounding success [3]. The countries prepared specific plans of action for the withdrawal of tOPV that were carefully implemented and monitored. A coordinated approach among manufacturers, the World Health Organization (WHO), and national authorities ensured that regulatory and programmatic issues were addressed for both bOPV and IPV. Specific instructions were provided for the destruction of unused vials of tOPV [2]. Epidemiologically, the final verdict regarding whether the switch was successful has not been reached. In the vast majority of countries, the switch was unremarkable; however, in a few countries (ie, Somalia, Democratic Republic of the Congo, and Nigeria) there was suboptimal coverage with tOPV prior to the switch that led to the emergence of circulating vaccine-derived poliovirus type 2 (cVDPV2), causing multiple polio outbreaks with international spread and a continuing cause of concern [4]. In addition, field investigations in response to detection of type 2 OPV after the switch found breaches in OPV2 withdrawal, with isolated evidence of continued inadvertent use of tOPV in several countries [5].

The introduction of IPV into routine immunization schedules was affected unexpectedly by supply constraints. By the end of 2017 (almost 2 years after the switch), 28% of countries (35 of 125) still had not been able to introduce IPV because of supply constraints or

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experienced a stock-out of vaccine, meaning that IPV was not resupplied after the initial shipments. The main reason for the IPV shortage was delay in rapidly expanding the global production capacity. In addition, only 2 of 4 existing producers of Salk strain–based IPV agreed to supply the vaccine for the public sector market in developing countries through United Nations Children's Fund procurement. The crisis continued until 2018, when sufficient supplies of IPV finally were available for all countries to introduce a dose into routine immunization schedules, but the multiple birth cohorts that had not received IPV remain unvaccinated and will require catch-up vaccination [6]. Approximately 43 million children will need catch-up vaccination with IPV.

Solutions were developed to conserve limited IPV supplies, including introduction of the multidose vial policy, determination of the preferred vial size (a 5-dose vial), and perhaps most importantly, development of a schedule of 2 fractional doses of IPV (each 20% of a full dose) to replace the single full IPV dose. The fractional-dose schedule is both dose sparing and more immunogenic than the single full-dose IPV schedule [7, 8] and has been implemented in several countries in South Asia (including India, Sri Lanka, Bangladesh, Nepal) and in the Americas (in Cuba and Ecuador).

However, the most ambitious goal, pursued by the Global Polio Eradication Initiative (GPEI) in collaboration with Intravacc (Bilthoven, the Netherlands), has been the development of IPV produced from Sabin strains (sIPV) and the technology-transfer program to establish production capacity by manufacturers in developing country [9]. Since 2010, of the 7 initially selected technology-transfer recipients, 5 remain in the program, including 2 in China (Sinovac Biotech and Beijing Minhai Biotechnology), 2 in India (Serum Institute of India and Panacea Biotec), and one in the Republic of Korea (LG Chem) [10]. Additional applications to the technology-transfer program are in process. In parallel, sIPV was developed in-house and licensed in Japan (in 2012) and China (in 2017). Once these manufacturers come on line or fully expand production, it is anticipated that the IPV supply situation will greatly improve.

In this issue of *The Journal of Infectious Diseases*, Hu et al [11] present the results of a phase 3 study in China demonstrating that sIPV is comparable to Salk strain–based IPV in inducing immunity against the 3 poliovirus strains in Chinese infants. The study met noninferiority criteria and demonstrated a comparable safety profile to that of conventional Salk strain–based IPV. This is a milestone for the technology-transfer program and offers hope that this vaccine can be licensed soon in China and then be considered for WHO prequalification, to allow purchase by United Nations agencies.

Although much progress has occurred in developing safe and effective sIPV vaccines in China, there are regulatory obstacles that affect all current and future sIPV manufacturers, including the prescribed presentation (only a single-dose vial or a prefilled syringe) and the prohibition of adding preservatives or adjuvants to the vaccine. These regulations substantially increase the cost of goods. To make sIPV produced in China competitive for global public sector procurement, either the regulatory obstacles would need to be removed or a new regulatory pathway created for export. Such regulatory pathways (ie, export licenses) exist in several countries [12], including the European Union (article 58),

Canada, Switzerland, and Korea, which allow national regulatory authorities to approve vaccines especially suited for the global public sector market.

In summary, the article by Hu et al [11] brings good news that Sinovac Biotech has developed a safe and effective vaccine. On the other hand, there is concerning news that the cost of goods might be high, which would make it less likely that this product will be competitive for procurement by United Nations agencies for the global public sector market. Thus, further efforts by the producer and the national regulatory authority will be needed to ensure that this new sIPV will be suitable for public sector market procurement and can contribute to global supply, as was intended when the GPEI launched the technology-transfer program for sIPV to help alleviate the continuing global IPV supply shortage. Unfortunately, the IPV shortage is expected to persist for at least another 3 years.

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