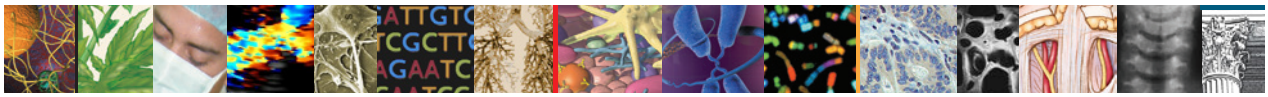

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Perspective

# Fractional-Dose Yellow Fever Vaccination — Advancing the Evidence Base

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In 2016, a global shortage of yellow fever vaccine occurred as a result of major yellow fever outbreaks in Angola and the Democratic Republic of Congo (DRC). By October, 7136 cases and 493 deaths were reported in the two countries. Reactive vaccination campaigns were conducted in areas with autochthonous transmission during the summer of 2016, but many people were still living in areas of risk. In Kinshasa, the capital of the DRC, a preventive campaign targeting roughly 10.5 million people was needed to mitigate the risk of an urban yellow fever outbreak. However, only 5.8 million vaccine doses were available from the World Health Organization (WHO) stockpile. A solution was urgently needed.

Fractionating the available yellow fever vaccine doses and administering a reduced volume of vaccine was one proposal. Faced with the options of using off-label fractional-dose vaccine to meet the supply needs or using the full-dose vaccine but leaving millions of people at risk for yellow fever, the DRC, in close consultation with the WHO, opted to use one fifth of the standard 0.5 ml volume of vaccine (0.1 ml) in its vaccination campaign. More than 7 million people received the fractional-dose vaccine in Kinshasa in August 2016.

This decision was based on simple math. WHO-prequalified yellow fever vaccines are highly potent, with average doses between 12,874 and 43,651 international units (IU) — far above the WHO's recommended minimum of 1000 IU. In principle, the quantity of vaccine virus in fractional doses of standard vaccine would therefore still exceed the WHO's minimum requirement.

But fractionating yellow fever vaccine doses is not without complexity. Average doses vary substantially among vaccine manufacturers and among product batches from a given manufacturer. Fractionating doses from vaccine vials at the lower end of the dosage range could result in doses close to or below the WHO minimum. Furthermore, potency can wane when vaccines are nearing the end of their shelf life, which for WHO-prequalified yellow fever vaccines is 36 months. Even the WHO's recommended minimum dose must be regarded with some caution, since it is based on studies in animals rather than rigorous dose-finding studies in humans. Thus, it is important to

**Research Questions to Support Near-Term Policy Recommendations for Fractional-Dose Yellow Fever Vaccination.**

- Are all WHO-prequalified yellow fever vaccines suitable for fractional-dose vaccination on the basis of immunogenicity, safety, and programmatic considerations?
- Is fractional-dose vaccination sufficiently immunogenic in children 9 months to 2 years of age?
- Are immunogenicity and vaccine effectiveness 5 or more years after vaccination affected by the fractional dose?
- Are immune responses to fractional-dose yellow fever vaccination similar in populations with variable environmental exposures (e.g., exposure to other flaviviruses or flavivirus vaccination) and genetic backgrounds?
- Is fractional-dose vaccination sufficiently immunogenic in people with asymptomatic HIV infection?
- Does the incidence of severe adverse events after vaccination with fractional-dose yellow fever vaccine differ from that with standard-dose vaccine?

ensure that the immunogenicity of fractional doses is equivalent to that of standard doses of currently used vaccines.

At the time of the 2016 outbreak, there were three publications from two studies on the safety and immunogenicity of fractional-dose yellow fever vaccine administered through the recommended route (intramuscular or subcutaneous). Since the older study was based on a vaccine formulation no longer in use, the primary study that informed the WHO recommendations was a dose–response study conducted in Brazil in 2009, using a vaccine produced by Bio-Manguinhos.[1] In that study, 900 men were randomly assigned to receive one of six de-escalating doses of the 17DD yellow fever vaccine, ranging from 27,476 to 31 IU. Thirty days after vaccination, seroconversion rates were 97 to 99% for vaccine doses of 587 IU or higher. Among people who originally seroconverted, more than 97% of those who received vaccine doses of 158 IU or higher still had detectable antibodies roughly 10 months after vaccination. An analysis of the cellular immune response showed equivalence to the full dose down to the tested dose of 3013 IU, but not at doses of 587 IU or lower.[2] Although these data were considered reassuring, they were restricted to a single country, manufacturer, and population (male adults).

In the context of the emergency situation and vaccine shortage, the WHO considered these data sufficient to proceed with a fractional-dose vaccination campaign. Full-dose vaccination was still recommended for young children and pregnant women.

The WHO published its official position on fractional-dose yellow fever vaccination in June 2017. The agency recommends fractional-dose vaccination during a yellow fever outbreak only if there is a shortage of full-dose vaccine and emergency-response needs exceed the capacity of the global stockpile. Furthermore, it is still recommended that some groups, such as children less than 2 years of age and pregnant women, receive the full-dose vaccine, given the lack of data demonstrating the safety and immunogenicity of fractional doses. Because of limited data on duration of protection, fractional-dose vaccination also does not qualify people for international travel under the International Health Regulations, a document signed by 196 countries to help the international community prevent and respond to acute public health risks. Without assurances that a fractional-dose vaccine provides the same lifetime protection as a full-dose vaccine, people who receive fractional doses will need to be revaccinated before traveling to countries where yellow fever is endemic and where the International Health Regulations require proof of vaccination.

In light of important knowledge gaps related to fractional-dose vaccination, the WHO developed a research agenda to stimulate scientists, policymakers, funders, and industry to address policy-relevant research questions (see box). The global community immediately responded. A small observational study conducted during the August 2016 fractional-dose yellow fever vaccination campaign in the DRC demonstrated 98% seroconversion among people who were seronegative at the time of vaccination.[3] Participants from the dose-finding study by Bio-Manguinhos[1] were reexamined to assess long-term immunogenicity: of 318 participants who seroconverted after vaccination in the original study, 85% were still seropositive 8 years later.[4] A randomized noninferiority trial was recently launched comparing seroconversion after fractional-dose and full-dose yellow fever vaccination for each WHO-prequalified vaccine product (ClinicalTrials.gov number, NCT02991495). This study will evaluate fractional-dose vaccination in adults living with HIV and in children. Other studies are examining the immunogenicity of fractional-dose vaccines in children, using various fractional volumes and routes of administration.

Use of fractional-dose vaccination in mass vaccination campaigns presents an opportunity to compare the safety of fractional-dose and full-dose yellow fever vaccines — particularly rates of rare, serious adverse events such as vaccine-associated neurotropic and viscerotropic disease. Preliminary data from routine safety monitoring during campaigns involving more than 5 million people in Brazil who received a fractional-dose vaccine are reassuring.

The 2016 outbreak in central and southern Africa was a reminder of the delicate supply-and-demand situation for yellow fever vaccines. Beyond the WHO vaccine stockpile, there is limited capacity to respond to demand peaks during larger outbreaks. Limited market incentives and a long manufacturing process requiring embryonated chicken eggs have created barriers to market entry and manufacturing surge capacity.

Recently, another vaccine shortage has prompted fractional-dose vaccination campaigns in large cities in Brazil, including areas not previously recognized as being at risk for yellow fever and thus with largely susceptible populations. Although the yellow fever vaccine stockpile is in place to address peaks in demand, it is less suited to cover the surge capacity needed for major urban vaccination campaigns. During the 2016 outbreak, the stockpile was depleted three times. Compounding this problem is the fact that global vaccine coverage is well below the 80% target that is expected to maintain a sufficiently high level of population immunity to eliminate outbreak risk: a recent study estimated that at least 393.7 million people living in high-risk settings (43%) remain unvaccinated.[5] International air travel may introduce yellow fever virus to new cities suitable for transmission. The best defense against future vaccine shortages is to achieve adequate routine vaccine coverage in all affected areas.

Other countries have considered a broader application of fractional-dose yellow fever vaccination outside emergency shortages. However, core questions remain. Although available evidence supports the use of fractional-dose vaccination when needed, a larger evidence base will be important to ensure optimal use and protection. Ongoing studies will provide much-needed information about specific products, target populations, and duration of protection to strengthen vaccination policies.

Continued dialogue and coordination among the policy, research, and funding communities are critical to ensure that when public health emergencies arise, there is sufficient evidence to make robust policy decisions quickly. Policy-driven research agendas are important tools for facilitating such coordination.

The views expressed in this article are those of the authors and do not necessarily represent the decisions or policies of the World Health Organization. Dr. Vannice was on staff at the WHO during the development of its policy on fractional-dose vaccination.

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