Fractional-dose yellow fever vaccination: an antigen-sparing strategy?

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In 2016, the World Health Organization (WHO) endorsed the use of fractional dose yellow fever (YF) vaccination subcutaneously in response to an acute vaccine shortage during a YF outbreak.[1] The rationale for this recommendation was that standard doses of WHO-prequalified (PQ) YF 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. Some countries have considered the use of fractional-dose YF vaccination outside an emergency situation due to vaccine shortages.[2] However, fractional YF vaccination is not yet compliant with the International Health Regulations (IHR). Critical research questions remain including the duration of immunity with a single dose of fractional YF vaccine, the immunogenicity of YF vaccine doses with potency below 1000 IU, and safety and immunogenicity across different populations.

The study by Roukens et al in a recent issue of the Annals of Internal Medicine is therefore an important step forward in our understanding of the use of fractional YF vaccines.[3] The authors studied the 10-year duration of immunogenicity of a 1/5th fractional dose given intradermally (ID). They showed that 40 healthy adults who had received a 0.1 ml fractional dose ID 10 years ago had similar virus-neutralizing antibody responses as 35 persons who had received the standard 0.5 ml dose SC also 10 years ago, with similar results to a recent study on 10 year duration of SC administration of a standard dose.[4] While these results are encouraging and support the long-term immunogenicity of fractional doses as being similar to standard doses when administered by the ID route, important policy questions still remain.

First, this study only investigated ID administration of fractional doses. However, YF vaccine is only licensed and WHO pre-qualified to be given by SC or intramuscular routes. Although the authors argue that viremia levels are equivalent when administered at the same dose by the ID and SC routes, immunogenicity typically differs with ID administration, and a head-to-head comparison of ID versus SC routes on short-term and long-term immunogenicity will be needed to assess equivalence.

Second, the potency of the fractional doses used in Roukens' study was always above 1000 IU and hence their study does not address the knowledge gap on long-term immunogenicity for doses that fall below the WHO minimum recommendation of 1000 IU. The primary study that informed the WHO recommendations to use fractional doses in 2016 was a dose–

response study investigating doses below 1000 IU, as low as 31 IU.[5] In this dose de-escalating study conducted in 2009 in Brazil with the Bio-Manguinhos YF vaccine, doses down to 587 IU showed similar humoral immunogenicity to the full dose (27,476 IU) both given subcutaneously, while the 158 IU and 31 IU doses displayed lower immunogenicity. A recall study of the same subjects undertaken 8 years later showed that seropositivity was maintained in 85% of the participants and was similar across the different potencies.[6]

Third, Roukens` data are restricted to healthy adults and cannot necessarily be extrapolated to other populations. The extent and duration of protection of fractional doses in populations such as children, pregnant women, persons with HIV and other co-morbidities that may result in weakened vaccine responses are currently unknown. The first study on 1/5th dose including children down to two years of age was conducted in DRC after the emergency roll-out of fractional doses, and reassuringly showed high seroconversion one month following SC administration.[7] The results of a randomized controlled non-inferiority trial comparing seroconversion after fractional-dose versus full-dose YF vaccination for each WHO-prequalified vaccine product (ClinicalTrials.gov number, NCT02991495), including in special populations such as children and persons living with HIV, are now much awaited.

Until those questions have been resolved for each WHO-PQ YF vaccine product, fractional YF vaccination is not yet IHR compliant and should only be used in emergency situations during acute vaccine shortage. Should SC fractional YF vaccination be shown to be equivalent to the standard dose, both in terms of long-term protection and safety, then the lower dose could become an antigen-sparing strategy of much broader utility.

Disclaimer:
AWS is consultant to WHO, JH is a WHO employee. 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. KV was on staff at the WHO during the development of its policy on fractional-dose vaccination.

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