

Fractional Doses of Yellow Fever Vaccine

Literature Watch Review

Ahuka-Mundeke S, Casey RM, Harris JB, et al. **Immunogenicity of fractional-dose vaccine during a yellow fever outbreak - preliminary report.** *N Engl J Med.* 2018;doi:10.1056/NEJMoa17110430. [Epub ahead of print]

Conclusions

- ▮ Vaccination with one-fifth the standard dose of yellow fever (YF) vaccine in an outbreak setting elicited an antibody response in 98% of initially seronegative recipients and a ≥ 4 -fold increase in geometric mean titer (GMT) of YF neutralizing antibodies in 66% of initially seropositive recipients.
- ▮ Fractional doses of YF vaccine may be useful in controlling an outbreak of YF when supplies of vaccine are constrained.
- ▮ Fractional doses of YF vaccine are not generally recommended for travelers because duration of efficacy and safety data are still inadequate, and an International Certificate of Vaccination or Prophylaxis (ICVP) for YF cannot be issued.

Abstract

In December 2015, an outbreak of YF in Angola spread to the Democratic Republic of the Congo (DRC), resulting in 962 confirmed and more than 7,000 suspected cases across the 2 countries. Approximately 30 million doses of YF vaccine were used, and the global stockpile of YF vaccine was depleted multiple times. WHO reviewed available evidence on dose-sparing strategies for YF vaccination. Four studies showed a robust immune response to fractional doses of YF vaccine as small as one-fifth to one-tenth the standard dose, leading WHO to conclude that a fractional dose could be used in nonpregnant adults and in children ≥ 2 years in response to an emergency situation in which the current vaccine supply is insufficient. The government of DRC planned a pre-emptive campaign targeting about 7.6 million persons in Kinshasa during a 10-day period, but sufficient vaccine was unavailable. In August 2016, under WHO guidance, a fractional dose of 17DD vaccine (Bio-Manguinhos, Brazil), at one-fifth (0.1 ml) the standard dose, was administered to all eligible participants. This article evaluates the immunologic response to this fractional dose of YF vaccine delivered in a large-scale vaccination campaign.

Six of 2,404 vaccination sites were selected for this study. Potential vaccinees were recruited for inclusion in a convenience sample, with an equal number of participants from 4 age strata: 2 to 5 years, 6 to 12 years, 13 to 49 years, and ≥ 50 years. Demographic data, history of YF vaccination, and recent symptoms compatible with YF disease were recorded. A baseline blood sample was taken before subcutaneous administration of one-fifth (0.1 ml) the standard dose of YF vaccine. This fractional dose of YF vaccine from a batch with average potency had 8,709 IU per dose and from a batch with minimum potency had 2,692 IU per dose, well above the minimum vaccine potency (1,000 IU per dose) set by WHO. At 28 to 35 days after vaccination (follow-up period), participants were asked about YF symptoms, and a blood sample was taken. Sera were frozen and transported to the CDC Arbovirus Disease Laboratory (Fort Collins, CO) where paired baseline and follow-up samples were tested for neutralizing antibodies to YF virus using the plaque-reduction neutralization test (PRNT), with cut-offs of 50% (PRNT₅₀) and 90% (PRNT₉₀). Statistical methods are described in the article.

Participants with a baseline PRNT₅₀ titer ≥ 10 were classified as seropositive; participants with a baseline PRNT₅₀ of less than 10 and who became seropositive at follow-up were classified as seroconverted; participants who were seropositive at baseline and had a ≥ 4 -fold increase in titer at follow-up were classified as having an immune response to vaccination.

Of 863 persons screened, 764 were enrolled; 716 (94%) completed the follow-up visit; 50% were female; 79 (11%) reported previous YF vaccination (74 of whom were aged ≤ 12 years). None reported symptoms compatible with YF.

- ▮ In the overall population of 716 participants, 705 (98%; 95% confidence interval [CI], 97-99) were seropositive after vaccination, with no significant differences between age groups or sex.
- ▮ At baseline, 493 (69%) participants were seronegative.
 - ▮ Of these, 482 (98%; 95% CI, 96-99) seroconverted. The lowest seroconversion rate was in children aged 2 to 5 years, but the between-age differences were not significant ($P = .06$).
 - ▮ At follow-up, participants aged 13 to 49 years had a significantly higher GMT of 2,255 (95% CI, 1,604-3,171) compared with participants in all other age groups.
 - ▮ The seroconversion rate was significantly higher among males (99%; 95% CI, 97-100) than females (96%; 95% CI, 93-

98; $P = .03$). GMTs, however, did not differ significantly between males and females.

- | At baseline, 223 (31%) participants were seropositive.
 - | An immune response to the vaccine was elicited in 148 (66%; 95% CI, 60-72).
 - | An inverse correlation was found between baseline titer and the participant's likelihood of having an immune response (P less than .001): All participants with a baseline titer of 10 or 20 responded, compared with none of the 11 participants with a baseline titer $\geq 2,560$.
 - | A significant difference in immune response rates occurred between certain age groups; only 33% of participants aged > 50 years developed an immune response. The highest rate, 83%, was in participants aged 6 to 12 years.

Commentary

The most important finding of this careful study was that in the real-life setting of mass vaccination during a YF outbreak, a fractional dose at one-fifth the standard dose of YF vaccine elicited an antibody response in 98% of recipients who were seronegative at base line and a ≥ 4 -fold increase in GMT overall in 66% of participants who were seropositive at baseline. Thus, this fractional dose may be adequate and effective for the control of YF outbreaks.

In its position paper of 2017, WHO recognized that fractional dosing, which involves repeated puncture of the vaccine vial cap, was not technically problematic, was well understood by the local population, and elicited an adequate immune response in vaccinees. WHO stated that "A fractional YF vaccine dose can be used as part of an emergency response to an outbreak if there is a shortage of full-dose YF vaccine that exceeds the capacity of the global stockpile. This is not intended to serve as a longer-term strategy or to replace established routine immunization practices." The minimum dose should preferentially contain 3,000 IU (and not less than 1,000 IU), administered in at least 0.1 ml volume. WHO pointed out that fractional dosing is off label; long-term protection has not been demonstrated; requirements under the International Health Regulations have not been met; proof of vaccination for international travel still requires vaccination or revaccination with a standard dose; and children aged less than 2 years and pregnant women require the standard dose.

The situation of travelers intending to depart to YF endemic and at-risk countries is less clear, and to date, few countries have issued guidelines. In Canada, the Committee to Advise on Tropical Medicine and Travel (CATMAT) reviewed the available literature (prior to this study) and concluded that fractional doses of one-fifth and one-tenth the standard YF vaccine dose induced all the known markers of immunity to YF and were likely to provide protection. CATMAT issued recommendations for travelers going to endemic countries to the effect that health care professionals should emphasize the importance of travelers receiving the standard dose or should recommend postponing the trip. If travel were urgent and could not be postponed and a standard dose could not be obtained, a one-fifth fractional dose of YF vaccine should be administered; a full dose should be administered when it became available, and an ICVP should be issued then. The CDC currently recommends against using fractional doses of vaccine until more evidence is available.

A potential problem that remains to be addressed involves the attitude of personnel at the point of entry in nonendemic countries (that require a valid ICVP for YF) toward a traveler who has exited an endemic or at-risk country and arrives without such a certificate. For now, decisions to recommend fractional-dose vaccination should be made after discussion with the individual traveler, considering the necessity of travel and the consequences of not having a valid ICVP for YF.

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