ORIGINAL ARTICLE

Immunogenicity of Fractional-Dose Vaccine during a Yellow Fever Outbreak — Preliminary Report

Steve Ahuka-Mundeke, M.D., Ph.D., Rebecca M. Casey, M.B., B.S., M.P.H., Jennifer B. Harris, Ph.D., M.P.H., Meredith G. Dixon, M.D., Pierre M. Nsele, M.D., Gabriel M. Kizito, M.D., Grace Umutesi, M.P.H., Janeen Laven, B.S., Gilson Paluku, M.D., M.P.H., Abdou S. Gueye, M.D., Ph.D., Terri B. Hyde, M.D., M.P.H., Guylain K.M. Sheria, M.D., Ph.D., Jean-Jacques Muyembe-Tanfum, M.D., Ph.D., and J. Erin Staples, M.D., Ph.D.

ABSTRACT

BACKGROUND

In 2016, the response to a yellow fever outbreak in Angola and the Democratic Republic of Congo led to a global shortage of yellow fever vaccine. As a result, a fractional dose of the 17DD yellow fever vaccine (containing one fifth [0.1 ml] of the standard dose) was offered to 7.6 million children 2 years of age or older and nonpregnant adults in a preemptive campaign in Kinshasa. The goal of this study was to assess the immune response to the fractional dose in a large-scale campaign.

METHODS

We recruited participants in four age strata at six vaccination sites. We assessed neutralizing antibody titers against yellow fever virus in blood samples obtained before vaccination and 28 to 35 days after vaccination, using a plaque reduction neutralization test with a 50% cutoff ($PRNT_{50}$). Participants with a $PRNT_{50}$ titer of 10 or higher at baseline were considered to be seropositive. Those with a baseline titer of less than 10 who became seropositive at follow-up were classified as having undergone seroconversion. Participants who were seropositive at baseline and who had an increase in the titer by a factor of 4 or more at follow-up were classified as having an immune response.

RESULTS

Among 716 participants who completed follow-up, 705 (98%; 95% confidence interval [CI], 97 to 99) were seropositive after vaccination. Among 493 participants who were seronegative at baseline, 482 (98%; 95% CI, 96 to 99) underwent seroconversion. Among 223 participants who were seropositive at baseline, 148 (66%; 95% CI, 60 to 72) had an immune response. Lower baseline titers were associated with a higher probability of having an immune response (P<0.001).

CONCLUSIONS

A fractional dose of the 17DD yellow fever vaccine was effective at inducing seroconversion in most of the participants who were seronegative at baseline. These findings support the use of fractional-dose vaccination for outbreak control. (Funded by the U.S. Agency for International Development and the Centers for Disease Control and Prevention.)

From the Institut National de Recherche Biomédicale (S.A.-M., P.M.N., G.M.K., J.-J.M.-T.), Division of Global Health Protection, Centers for Disease Control and Prevention (CDC) (A.S.G.), and Programme Elargi de Vaccination, Ministre de la Santé (G.K.M.S.) — all in Kinshasa, Democratic Republic of Congo; Global Immunization Division (R.M.C., J.B.H., M.G.D., G.U., G.P., T.B.H.) and the Epidemic Intelligence Service (R.M.C.), CDC, Atlanta; and Division of Vector-Borne Diseases, CDC, Fort Collins, CO (J.L., J.E.S.). Address reprint requests to Dr. Casey at the Epidemic Intelligence Service, Global Immunization Division, 1600 Clifton Rd., Atlanta, GA 30329, or at rcasey@cdc.gov.

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Yellow fever is a mosquito-borne viral disease endemic to tropical and subtropical regions in Africa and the Americas. Infection with yellow fever virus can result in subclinical to severe illness, characterized by fever, jaundice, and hemorrhage. There were an estimated 51,000 to 380,000 severe cases of yellow fever and 19,000 to 180,000 deaths in Africa in 2013.[1] Treatment is managed to address patients' symptoms. However, the administration of a highly effective vaccine is the primary method for prevention and control. All currently used yellow fever vaccines are live attenuated viral vaccines derived from the 17D strain.[2,3] Nearly all studies have shown that one dose induces seroconversion in more than 98% of recipients, and protection is believed to be lifelong.[2,4,5]

In December 2015, a large yellow fever outbreak began in Angola and spread to the neighboring Democratic Republic of Congo (DRC). The outbreak resulted in 962 confirmed cases and more than 7000 suspected cases across the two countries.[6] Each year, 6 million doses of yellow fever vaccine are maintained by the World Health Organization (WHO) and partners in a global stockpile that can be used for outbreak response at the request of countries with inadequate vaccine supply.[7] However, the outbreaks in Angola and DRC used approximately 30 million doses and depleted the stockpile multiple times during 2016.[6]

Faced with substantial global supply issues, the WHO reviewed available evidence on dose-sparing strategies for yellow fever vaccination, including four studies involving three cohorts of 175 to 749 healthy adult participants.[8-12] Two of three cohorts were limited to male participants. All the studies showed a robust immune response to fractional doses of yellow fever vaccine as small as one fifth to one tenth of the standard dose. On the basis of this evidence, the WHO concluded that a fractional dose of the yellow fever vaccine could be used in adults and in children 2 years of age or older in response to an emergency situation when the current vaccine supply was insufficient.[12]

To prevent the spread of yellow fever in Kinshasa, the government planned a preemptive campaign targeting approximately 7.6 million persons during a 10-day period.[13] However, there was insufficient vaccine supply available to meet campaign needs. Thus, under guidance from the WHO, the government of DRC implemented the campaign using a fractional dose of 17DD vaccine (Bio-Manguinhos) at one fifth (0.1 ml) of the standard dose in all nonpregnant adults and in children 2 years of age or older in August 2016. We evaluated the immunologic response to this fractional-dose vaccine delivered in a large-scale vaccination campaign.

Methods

Study Participants and Design

From August 17 through August 26, 2016, the campaign was conducted at 2404 vaccination sites in Kinshasa.[13] We selected 6 vaccination sites across the three geographic sectors of Kinshasa on the basis of economically diverse catchment populations and logistic feasibility. Participants who presented for vaccination at one of these sites were approached for potential inclusion in a convenience sample for the study, with an equal number of participants from four age strata: 2 to 5 years, 6 to 12 years, 13 to 49 years, and 50 years or older. The cutoffs for these age strata were selected on the basis of data regarding immunologic response to the yellow fever vaccine and other vaccines.[2,14]

All the participants who received fractional-dose vaccination during the campaign were eligible for inclusion unless they reported having immunosuppression, egg allergies, a history of problems with venipuncture, plans to relocate from Kinshasa, or previous yellow fever vaccination within the preceding 2 months. Children under the age of 2 years and pregnant women were ineligible because they received full-dose vaccine according to the campaign operating procedures. The criteria for vaccine administration were determined by the public health authorities in the DRC. All the participants provided limited medical information and written informed consent to obtain blood samples. Parents or legal guardians provided written permission for participants who were 17 years of age or younger. Adolescents between the ages of 13 and 17 years also provided written assent.

Study Oversight

The study was sponsored by the U.S. Agency for International Development and the Centers for Disease Control and Prevention (CDC). The protocol (available with the full text of this article at NEJM.org) was approved by the medical ethics

committee at the University of Kinshasa School of Public Health. In accordance with the human-subjects review procedures of the CDC, it was determined that the CDC was not formally engaged in human-subjects research. The study was designed and supervised by the authors, who vouch for the accuracy and completeness of the data and analyses and the adherence of the study to the protocol.

BASELINE VISIT AND VACCINATION

From each participant, we collected data regarding basic demographic characteristics, history of yellow fever vaccination, and recent symptoms compatible with yellow fever disease (specifically, fever with jaundice). A phlebotomist obtained a baseline blood sample before vaccination. Campaign staff members then administered a subcutaneous dose of 17DD yellow fever vaccine at one fifth of the standard dose (0.1 ml) to 764 participants from one of six lots: 253 participants received vaccine from lot 164VFC002Z, 104 from lot 164VFC003Z, 138 from lot 164VFC004Z, 127 from lot 164VFC005Z, 38 from lot 164VFC007Z, and 94 from lot 164VFC008Z; no lot number was recorded for doses administered to 10 participants.

The 17DD vaccine was recommended by the WHO for use in the campaign on the basis of availability, clinical trial data indicating seroresponse to fractional doses, and 5 years of batch-release data. According to these data, one fifth of a dose of the average batch potency had 8709 IU per dose, and one fifth of a dose of minimum batch potency had 2692 IU per dose. Both of these doses were above the minimum vaccine potency (1000 IU per dose) set by the WHO.[8-10,15] The vaccine was packaged in standard 10-dose vials, which resulted in the use of each vial for approximately 50 fractional doses.[13] Vaccination was observed by study staff members to ensure receipt of the dose. Adverse events after immunization were monitored as part of the campaign procedures rather than as part of this investigation.

FOLLOW-UP AND TESTING PROCEDURES

At 28 to 35 days after vaccination (follow-up period), participants who returned to the health center were asked about yellow fever symptoms and receipt of medications or medical treatment during the interval between visits. A blood sample was obtained. Female participants of reproductive age were also asked about the date of the last menstrual period.

Blood samples that were obtained before vaccination and after vaccination were kept in temperature-controlled coolers during the day and transported each afternoon to the Institut National de Recherche Biomédicale, where they were centrifuged and serum was aliquoted into cryovials and stored at −20°C. Serum samples were then shipped to the CDC Arbovirus Diseases Laboratory in Fort Collins, Colorado, where paired baseline and follow-up samples were tested for the presence of neutralizing antibodies against yellow fever virus with the use of the plaque reduction neutralization test with a cutoff of 50% ($PRNT_{50}$) and a cutoff of 90% ($PRNT_{90}$), as described previously.[16] Here, we report $PRNT_{50}$ titers, since this cutoff is routinely used in vaccination trials of flavivirus vaccines and is recommended by the WHO for establishing sufficient virus-neutralizing antibody in the serum in vaccine immunogenicity studies conducted by vaccine manufacturers.[17-19]

Participants with a $PRNT_{50}$ titer of 10 or higher in their sample at baseline were considered to be seropositive. Those who had a baseline $PRNT_{50}$ titer of less than 10 and who became seropositive at follow-up were classified as having undergone seroconversion. Participants who were seropositive at baseline and had an increase in titer by a factor of 4 or more at follow-up were classified as having an immune response to vaccination.

STATISTICAL ANALYSIS

We determined that a sample of 760 participants would allow for an estimation of the immune response in four age groups, based on an estimated rate of immune response of 92% among the participants, with a 95% Wald confidence interval of ±5% and an attrition rate of 40%. All the participants who had baseline and follow-up samples were included in the analyses.

Estimated proportions and 95% confidence intervals were calculated with the use of the Wilson method. We compared the proportion of participants who had undergone seroconversion in groups according to age and sex using the chi-square test and Fisher's exact test. Among the participants who were seropositive at baseline, we assessed the association between the baseline titer and immune response using the

Cochran–Armitage test for trend. Differences in immune response according to age group and sex were adjusted for baseline titer subgroups with the use of the Cochran–Mantel–Haenszel test. We used the Kruskal–Wallis test and Wilcoxon rank-sum test to compare geometric mean titers. Bonferroni corrections were used with pairwise comparisons.

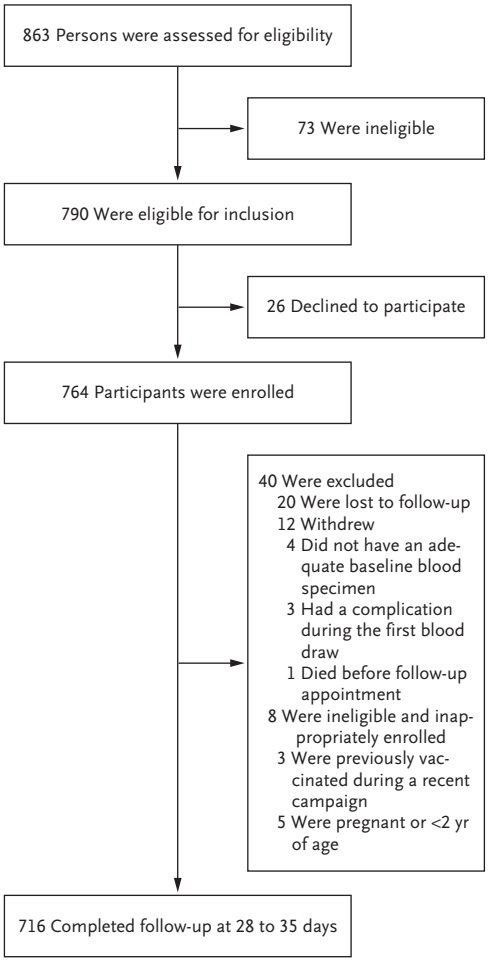

Figure 1. Enrollment and Follow-up.

Of the 40 eligible participants who were excluded after the baseline data collection, 21 (52%) were female. Of the excluded participants, 19 (48%) were between the ages of 2 and 5 years, 4 (10%) were between the ages of 6 and 12 years, 8 (20%) were between the ages of 13 and 49 years, and 9 (22%) were 50 years of age or older. Investigation by the Ministry of Health determined that the single death after enrollment was related to a cardiac event and not to vaccination.

RESULTS

PARTICIPANTS

Of the 863 persons who were screened, 790 met eligibility criteria, 764 were enrolled, and 716 (94%) completed the follow-up visit (Fig. 1). Overall, 89 to 98% in each of the four age groups completed follow-up. Of the participants with complete follow-up data, 50% were female, and 79 (11%) reported having received previous yellow fever vaccination; of these participants, all but 5 were children 12 years of age or younger (Table 1). A history of previous vaccination was based primarily on oral report.

VACCINE RESPONSE IN THE OVERALL POPULATION

Of the 716 participants, 705 (98%; 95% confidence interval [CI], 97 to 99) were seropositive after vaccination (Table 2). The proportion who were seropositive varied slightly according to age (from 97% among those between the ages of 13 and 49 years to 100% among those between the ages of 6 and 12 years) and according to sex (97% among women and 99% among men), although the differences among the groups were not significant. None of the participants who completed follow-up reported symptoms compatible with yellow fever after vaccination.

VACCINE RESPONSE AMONG PARTICIPANTS WHO WERE SERONEGATIVE AT BASELINE

A total of 493 participants (69%) were seronegative for neutralizing antibodies against yellow fever at baseline (Table 3). Among these participants, seroconversion was reported in 482 (98%; 95% CI, 96 to 99). Among age groups, the lowest seroconversion rate was observed among children between the ages of 2 and 5 years, although the between-group differences in seroconversion were not significant (P=0.06). At follow-up, participants between the ages of 13 and 49 years had a significantly elevated geometric mean titer of 2255 (95% CI, 1604 to 3171) as compared with participants in all other age groups; children between the ages of 2 and 5 years had the lowest geometric mean titer at 487 (95% CI, 293 to 810). The seroconversion rate among male participants (99%; 95% CI, 97 to 100) was significantly higher than that among female participants (96%; 95% CI, 93 to 98) (P=0.03). However, the geometric mean titers for male participants and female

Table 1. Characteristics of the 716 Study Participants at Baseline, According to Age Group.*

Characteristic	Age Group				
	2–5 Yr (N=162)	6–12 Yr (N=189)	13–49 Yr (N=189)	≥50 Yr (N=176)	All Ages (N=716)
	number of participants (percent)				
Female sex	89 (55)	87 (46)	102 (54)	80 (45)	358 (50)
Report of previous yellow fever vaccination	41 (25)	33 (17)	1 (1)	4 (2)	79 (11)
Oral report only	37 (23)	29 (15)	0	3 (2)	69 (10)
Vaccination card confirmed	0	3 (2)	1 (1)	0	4 (1)
Source not recorded	4 (2)	1 (1)	0	1 (1)	6 (1)
Report of symptoms compatible with yellow fever in previous month†	2 (1)	1 (1)	1 (1)	3 (2)	7 (1)
Seropositivity at baseline‡	85 (52)	75 (40)	27 (14)	36 (20)	223 (31)

* Percentages in subcategories may not add up to the overall percentage because of rounding.
† Symptoms were fever and jaundice.
‡ Seropositivity for neutralizing antibodies against yellow fever virus was defined as a titer on a plaque reduction neutralization test with a cutoff of 50% ($PRNT_{50}$) of 10 or higher.

participants did not differ significantly (P=0.61). Among the 5 female participants of reproductive age who did not undergo seroconversion, none were pregnant on the basis of reports of menstruation in the interval between vaccination and the follow-up visit.

VACCINE RESPONSE AMONG PARTICIPANTS WHO WERE SEROPOSITIVE AT BASELINE

At baseline, 223 participants (31%) were seropositive for yellow fever (Table 3). In this subgroup, an immune response (titer of ≥4 times the baseline value) was elicited in 148 (66%; 95% CI, 60 to 72). There was an inverse correlation between a participant's baseline titer and the likelihood of having an immune response (P<0.001). All the participants with a titer of 10 or 20 had an immune response, as compared with none of the 11 participants who had a titer of 2560 or higher at baseline (Fig. 2A). An anamnestic response was more notable among those with lower baseline titers (Fig. 2B).

Among the participants who were seropositive at baseline, there was no significant difference in the proportion of male participants versus female participants who had an immune response (P=0.85). However, there was a significant difference among age groups, even after adjustment for the baseline titer (P<0.001); only 33% (95% CI, 20 to 50) of the participants who were at least 50 years of age had an immune response.

DISCUSSION

In our study conducted during a mass vaccination campaign in Kinshasa, we found that detectable antibodies against the yellow fever virus developed in 98% of the participants (≥2 years of age) who were seronegative at baseline and

Table 2. Seropositivity at Follow-up for All 716 Participants, According to Age Group and Sex.*

Variable	Seropositivity at Follow-up		P Value†
	no./total no.	*% (95% CI)*	
All participants	705/716	98 (97–99)	
Age group			0.08
2–5 yr	158/162	98 (94–99)	
6–12 yr	189/189	100 (98–100)	
13–49 yr	184/189	97 (94–99)	
≥50 yr	174/176	99 (96–100)	
Sex			0.06
Male	356/358	99 (98–100)	
Female	349/358	97 (95–99)	

* Seropositivity was defined as a result on $PRNT_{50}$ testing of 10 or higher.
† The P value is for the overall comparison among the subgroups by Fisher's exact test.

Table 3. Seroconversion or Immune Response and Geometric Mean Titer at Follow-up, According to Serostatus at Baseline.*

Subgroup	Seroconversion or Immune Response at Follow-up		P Value	Geometric Mean Titer (95% CI)		P Value
				At Baseline	At Follow-up	
	no./total no.	*% (95% CI)*				
Seronegative at baseline						
All participants	482/493	98 (96–99)	NA	NA	1340 (1117–1607)	NA
Age group			0.06†			<0.001‡
2–5 yr	73/77	95 (87–98)		NA	487 (293–810)	
6–12 yr	114/114	100 (97–100)		NA	1234 (911–1673)	
13–49 yr	157/162	97 (93–99)		NA	2255 (1604–3171)§	
≥50 yr	138/140	99 (95–100)		NA	1368 (999–1872)¶	
Sex			0.03†			0.61‡
Male	251/253	99 (97–100)		NA	1469 (1154–1870)	
Female	231/240	96 (93–98)		NA	1215 (924–1600)	
Seropositive at baseline						
All participants	148/223	66 (60–72)	NA	87 (69–110)	1292 (1039–1607)	NA
Age group			<0.001‖			0.04**
2–5 yr	57/85	67 (57–76)		90 (66–123)	1114 (787–1576)	
6–12 yr	62/75	83 (73–90)		50 (35–72)	1366 (962–1938)	
13–49 yr	17/27	63 (44–78)		160 (65–392)	2252 (1255–4039)	
≥50 yr	12/36	33 (20–50)††		160 (79–324)	1076 (533–2175)	
Sex			0.85‖			0.55**
Male	73/105	70 (60–78)		71 (51–98)	1255 (930–1694)	
Female	75/118	64 (55–72)		105 (76–146)	1326 (964–1823)	

* NA denotes not applicable.
† The P value in this category is for the difference in rates of seroconversion, according to age group or sex, as calculated by Fisher's exact test.
‡ The P value in this category is for global testing of differences in the geometric mean titer at follow-up, according to age group (by the Kruskal–Wallis test) or sex (by the Wilcoxon rank-sum test).
§ Participants in this category had significantly higher titers than those in all the other age groups, as calculated by the Wilcoxon rank-sum test using the Bonferroni correction with an alpha level of 0.05 (0.008 after adjustment for the number of pairwise comparisons).
¶ Participants in this category had significantly higher titers than those who were between the ages of 2 and 5 years, as calculated by the Wilcoxon rank-sum test using the Bonferroni correction with an alpha level of 0.05 (0.008 after adjustment for the number of pairwise comparisons).
‖ The P value in this category is for the difference in immune response, according to age group or sex, as calculated by the Cochran–Mantel–Haenszel test after adjustment for the baseline titer.
** The P value in this category is for the global test for differences in the increase in titer from baseline to follow-up, according to age group (by the Kruskal–Wallis test) or sex (by the Wilcoxon rank-sum test).
†† Participants in this category were significantly less likely to have an immune response than those in all other age groups, as calculated by the chi-square test using the Bonferroni correction with an alpha level of 0.05 (0.008 after adjustment for the number of pairwise comparisons).

who received one fifth of the standard dose of the 17DD vaccine. This rate of seroconversion suggests that the use of fractional-dose vaccination is a viable approach for providing immunity and thus containing yellow fever outbreaks. This finding is important, given the ongoing risk of outbreaks of yellow fever globally, as shown in 2017 in Brazil, where more than 26 million vaccine doses of yellow fever vaccine were distributed to control an outbreak during the beginning of the year.[20]

The proportion of participants who underwent seroconversion was similar to that seen among full-dose vaccine recipients, in whom

more than 98% undergo seroconversion.[2] Our results are also similar to those seen in other studies of fractional-dose vaccination against yellow fever in which participants have received as little as one fifth to one tenth of the standard dose.[8-11] The previously published studies were performed in healthy, mostly male adults participating in well-controlled clinical trials. In contrast, our cohort included children and adults of both sexes, and the vaccine was administered in a mass campaign setting. Given the campaign setting, it is notable that our results were similar to those in the controlled studies.

In 2003 in the DRC, yellow fever vaccine was introduced into the childhood vaccination program and is administered to children at the age of 9 months.[21] The routine use of yellow fever vaccine probably accounts for the higher rate of baseline seropositivity that we found among children 12 years of age or younger than we found among the other age groups. Overall seropositivity at follow-up and rates of seroconversion did not vary significantly across age groups, even though there were differences in follow-up geometric mean titers. In addition, participants who were 50 years of age or older were less likely than younger participants to have an immune response if they had neutralizing antibodies at baseline. Several trials of yellow fever vaccines have suggested a lower immunologic response to vaccination among children than among adults.[5] In addition, data suggest that older adults may not have as vigorous a response to yellow fever vaccine or other vaccines as do younger adults.[2,14,22]

Although we found a slightly lower rate of seroconversion among female participants than among male participants, the geometric mean titers after vaccination were similar in both sexes. The slightly higher immunologic response to the vaccine among male participants has also been reported in trials in which the full-dose yellow fever vaccine was used,[23-25] which suggests that the observed difference is not unique to the fractional dose.

It is unknown whether the kinetics of antibody persistence will differ between fractional and full-dose administration of yellow fever vaccine. The geometric mean titers that were observed in our study suggest that immunity will probably persist for years and possibly be lifelong. Martins et al.[8] found detectable antibodies at 10 months after the administration of various fractional doses of yellow fever vaccine. As part of this evaluation, participants have been followed up at 1 year after vaccination. Testing is currently ongoing.

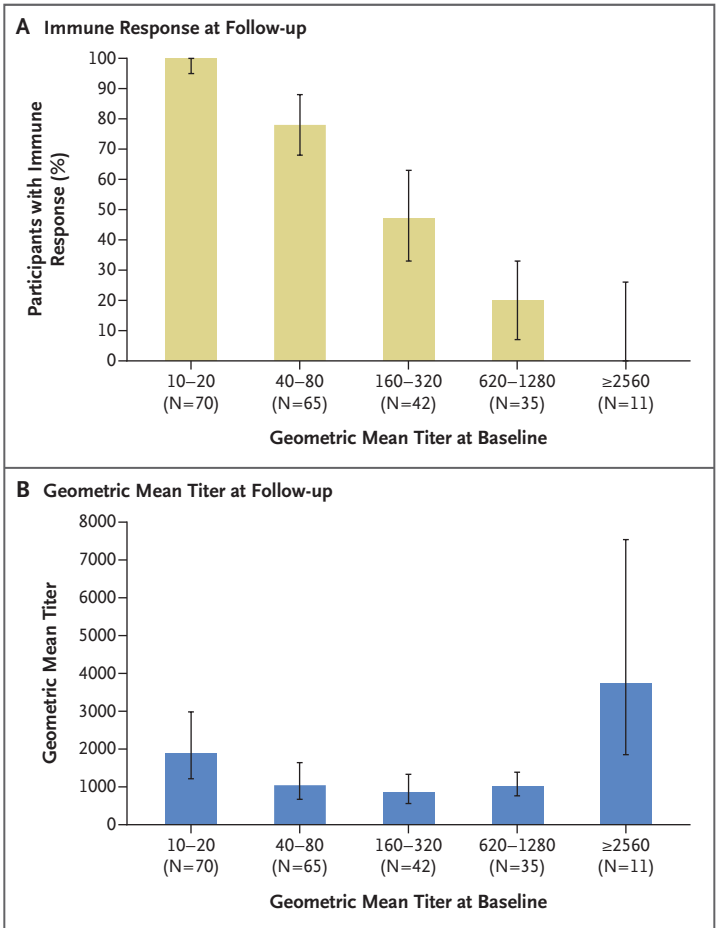

Figure 2. Immune Response and Geometric Mean Titer at Follow-up among Participants Who Were Seropositive at Baseline.

Panel A shows the proportion of participants who had an immune response after fractional-dose vaccination against yellow fever, according to the geometric mean titer of neutralizing antibodies at baseline. Panel B shows the geometric mean titer at follow-up according to the titer at baseline. In both panels, I bars indicate 95% confidence intervals.

Our study has several limitations. First, we did not include a control group of participants who received a full dose of yellow fever vaccine because of technical and ethical issues, so we could not directly compare the immune response after the fractional dose with that after a full dose. Also, the use of $PRNT_{50}$ titers may have caused incorrect classification of participants with low titers as being seropositive for neutralizing antibodies against the yellow fever virus

when in fact the titer was due to cross-reactive antibodies. However, since serum samples were obtained before vaccination and after vaccination from each participant, the specific response to the vaccine could still be assessed. We did not calibrate the yellow fever antibody titers using an international reference preparation, which makes it difficult to compare our titers with those obtained in the other recent studies of fractional-dose vaccination.[17] International standardization of testing results for yellow fever has only recently been recommended, so very few data have been generated. The use of PRNT titers was preferred for this study to allow for comparison with much of the published data. In addition, we did not collect safety data during this evaluation.[26] However, the adverse-event monitoring systems that were in place for the campaign did not identify any acute signals of concern associated with fractional-dose vaccination. Enhanced surveillance detected 0.5 serious adverse events per 100,000 doses after the campaign,[13] a rate that is similar to that after full-dose campaigns conducted in West Africa.[27] Finally, we could not formally assess the effectiveness of the fractional dose with regard to preventing viral transmission during the outbreak, since the outbreak was waning at the time of the campaign. However, no new confirmed cases of yellow fever were detected in Kinshasa after the campaign despite ongoing surveillance.

In conclusion, we found that the immunologic response to a fractional dose of the 17DD yellow fever vaccine was appropriate for a response to a yellow fever outbreak among children 2 years of age or older and among nonpregnant adults. Additional studies are needed to determine whether fractional-dose vaccination provides adequate seroprotection in children under the age of 2 years, in pregnant women, and in persons who are infected with the human immunodeficiency virus.[12] In addition, future studies need to verify that similar results are obtained with other 17D-derived yellow fever vaccines (17D-204 and 17D-213) and in populations with differing exposures to flaviviruses. The use of fractional doses of yellow fever vaccine could reduce the amount of vaccine needed for reactive campaigns and provide flexibility in management of the global stockpile of yellow fever vaccine when outbreaks occur.

The views expressed in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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