HHS Public Access

Author manuscript

Lancet Infect Dis. Author manuscript; available in PMC 2025 June 01.

Published in final edited form as:

Lancet Infect Dis. 2024 June ; 24(6): 611–618. doi:10.1016/S1473-3099(23)00809-5.

Immunological response to fractional-dose yellow fever vaccine administered during an outbreak in Kinshasa, Democratic Republic of the Congo: results 5 years after vaccination from a prospective cohort study

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RMC, TBH, JES, SA-M, DKK, RHD, and J-JM-T designed the study.
RHD, PKM, GMK, LS, and BNU collected the data. RHD and HG did the statistical analysis. JL did the laboratory analyses. RHD prepared the first draft of the manuscript. All authors had access to the data, contributed to the interpretation of data, critically reviewed the manuscript, and decided to publish the paper. RHD and HG directly accessed and verified the data.

For the French translation of the abstract see Online for appendix 1

Declaration of interests
We declare no competing interests.

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Summary

Background—In 2016, outbreaks of yellow fever in Angola and the Democratic Republic of the Congo led to a global vaccine shortage. A fractional dose of 17DD yellow fever vaccine (containing one-fifth [0·1 ml] of the standard dose) was used during a pre-emptive mass campaign in August, 2016, in Kinshasa, Democratic Republic of the Congo among children aged 2 years and older and non-pregnant adults (ie, those aged 18 years and older). 1 year following vaccination, 97% of participants were seropositive; however, the long-term durability of the immune response is unknown. We aimed to conduct a prospective cohort study and invited participants enrolled in the previous evaluation to return 5 years after vaccination to assess durability of the immune response.

Methods—Participants returned to one of six health facilities in Kinshasa in 2021, where study staff collected a brief medical history and blood specimen. We assessed neutralising antibody titres against yellow fever virus using a plaque reduction neutralisation test with a 50% cutoff ($PRNT_{50}$). Participants with a $PRNT_{50}$ titre of 10 or higher were considered seropositive. The primary outcome was the proportion of participants seropositive at 5 years.

Findings—Among the 764 participants enrolled, 566 (74%) completed the 5-year visit. 5 years after vaccination, 539 (95·2%, 95% CI 93·2–96·7) participants were seropositive, including 361 (94·3%, 91·5–96·2) of 383 who were seronegative and 178 (97·3%, 93·8–98·8) of 183 who were seropositive at baseline. Geometric mean titres (GMTs) differed significantly across age groups for those who were initially seronegative with the lowest GMT among those aged 2–5 years and highest among those aged 13 years and older.

Interpretation—A fractional dose of the 17DD yellow fever vaccine induced an immunologic response with detectable titres at 5 years among the majority of participants in the Democratic Republic of the Congo. These findings support the use of fractional-dose vaccination for outbreak prevention with the potential for sustained immunity.

Funding—Gavi, the Vaccine Alliance through the CDC Foundation.

Introduction

Yellow fever is a mosquito-borne viral disease caused by yellow fever virus. It is endemic to sub-Saharan Africa and tropical regions of South America.[1,2] The majority of yellow fever cases (>90%) occur in sub-Saharan Africa and an estimated 84000–170 000 people are affected each year, with approximately 29 000–60 000 deaths.[3] Infection can be subclinical

or result in mild illness; however approximately one in seven can progress to severe illness, with hepatitis, renal failure, haemorrhage, and cardio-vascular shock.[4] It is estimated that 30–60% of people with severe illness die.

Control of yellow fever occurs primarily through vaccination. Since the 1930s, there has been a safe and effective vaccine, derived from the 17D strain of yellow fever virus.[5] A single dose of the vaccine confers sustained, lifelong protective immunity against yellow fever disease in most individuals.[6,7] In yellow fever endemic countries, WHO recommends vaccination for children aged 9 months and older and the majority of countries have introduced the yellow fever vaccine into routine immunisation services. In the past decade, the world has seen a resurgence of yellow fever outbreaks with cases in areas that had previously been disease free.[3] The reasons for this resurgence are likely multifactorial, including decreases in vaccination coverage in endemic areas, competing public health crises, the COVID-19 pandemic, fragile governments, regional conflict, and population movement, in addition to increases in sylvatic transmission, related to climate and vector factors.[8,9] In the African region, yellow fever vaccine coverage was estimated at 45% in 2022,[10] far less than the WHO recommended population immunity (≥80%) to prevent yellow fever outbreaks.[3] It is estimated that more than 393 million people globally will need vaccination to prevent yellow fever outbreaks.[3]

In 2001, WHO created a global stockpile of yellow fever vaccine doses for outbreak response, for countries with inadequate vaccine supply.[11] Despite an increase to the stockpile to 6 million doses in 2003, and changing it to a revolving stockpile in 2016, the increases in yellow fever virus circulation coupled with the vaccine's complicated and limited production capacity has resulted in vaccine shortages and challenges with maintaining the global stockpile.[12]

In 2015, large urban yellow fever outbreaks in Angola spread to the neighbouring Democratic Republic of the Congo, necessitating reactive vaccination campaigns that deployed more than 30 million doses. The global stockpile was exhausted multiple times in 2016, leading WHO and the Strategic Advisory Group of Experts on Immunizations (SAGE) to recommend the use of a fractional yellow fever vaccine dose as a dose sparing strategy.[7] This recommendation was based on scarce data on dose-ranging studies performed using mostly the 17DD strain among adults and fractional yellow fever doses were only recommended in the context of outbreak response during a supply shortage.[7] To improve the understanding of the potential use of fractional-dose yellow fever vaccine, SAGE noted the need for additional data on all prequalified vaccines, on the duration of protection offered by fractional doses, and on the use in specific subpopulations including infants and people with HIV.

Fractional doses of yellow fever vaccine were first used to pre-emptively control an outbreak in Kinshasa, Democratic Republic of the Congo in 2016, where 17DD vaccine (Bio-Manguinhos, Rio de Janeiro, Brazil) at one-fifth (0·1 ml) of the standard dose was administered to more than 7 million non-pregnant adults and children aged 2 years and older.[7,13] According to 5 years of batch release data, one fifth of a dose of the average batch potency had 8709 international units (IUs) of vaccine per dose, and one fifth of a dose

of minimum batch potency had 2692 IU per dose, both more than the minimum vaccine potency (1000 IU per dose) set by WHO.[7] The fractional dose induced seroconversion in 98% of participants who were seronegative at baseline and titres remained greater than the threshold for seropositivity 1 year after vaccination in 96% of participants.[14] Since then, fractional doses of yellow fever vaccine have been used to control outbreaks in Brazil and research has been done for all prequalified vaccines, including specific groups.[2,15-17] In addition to these evaluations, two clinical trials, one in Brazil and one in the Netherlands, looked at the persistence of neutralising antibodies 8 and 10 years, respectively, after vaccination with fractional dose yellow fever vaccine.[18,19] The trials indicated that fractional doses elicited detectable antibodies against yellow fever virus in most healthy male adults at 8 years or adults who received the vaccine intradermally at 10 years after vaccination. There are no data on the immune response to fractional yellow fever vaccines beyond 1 year, in the general population (including children), in which malnutrition and repeat infections with numerous pathogens are common.[18,19] Therefore, we aimed to evaluate the immune response among the same cohort who received the fractional dose yellow fever vaccine during the 2016 pre-emptive vaccination campaign in Kinshasa, and report here on the results 5 years after vaccination.

Methods

Study design

This was the 5-year follow-up of a prospective cohort study.[14] The study took place at six health facilities in Kinshasa, Democratic Republic of the Congo and the 5 year follow-up was conducted from Aug 9 to Aug 23, 2021. This study was reviewed and approved by the Kinshasa School of Public Health ethics review board and by US Centers for Disease Control and Prevention and was conducted consistent with applicable federal law and Centers for Disease Control and Prevention policy.

Participants

Initial study participant selection, vaccination, baseline, and 1-year study visit procedures are described in detail elsewhere.[14] Briefly, from Aug 17 to Aug 26, 2016, a pre-emptive vaccination campaign was conducted in Kinshasa, Democratic Republic of the Congo, at 2404 sites. A convenience sample from six vaccination sites was selected based on economically diverse catchment areas and logistic feasibility, with an equal number of participants from four age strata: 2–5 years, 5–12 years, 13–49 years, and 50 years and older. Vaccination campaign staff members administered a subcutaneous dose of 17DD yellow fever vaccine at one fifth of the standard dose (ie, 0·1 ml). All people aged 2 years and older receiving the fractional dose were eligible for inclusion in the original study unless they self-reported immunosuppression, pregnancy, egg allergies, a history of problems with venipuncture, plans to relocate outside of Kinshasa, or previous yellow fever vaccination in the preceding 2 months. Pregnant women and children aged younger than 2 years received the full dose and were not included in the evaluation.

For the 5-year follow-up, we aimed to include all participants in the initial cohort who completed the baseline and at least one follow-up visit (n=688). Evaluation staff attempted

to reach participants who consented to be recontacted in the future, starting 1 month previously by telephone. Only six (0·8%) individuals from the original study did not consent to be recontacted. When participants were not reachable, staff contacted the family members or friends who were listed as back-up contacts during previous encounters. In addition, study staff contacted participants the day before their follow-up appointment as a reminder. Participants were asked to return to the same health facility they had received the vaccine and where they had originally been enrolled. All participants provided written informed consent at baseline enrolment and were reconsented for the 5-year study follow-up visit. Parents or legal guardians provided written consent for participants who were aged 17 years or younger at the time of the study visit and adolescents from the ages of 13 to 17 years also provided written assent.

Procedures

At the follow-up visit, study staff collected demographic data and information on medical conditions, any medications, receipt of any additional yellow fever vaccination since their last visit, and interim history of yellow fever, Zika, or dengue virus infection or disease. A subset of participants were asked about immunosuppressing conditions, which was added to the questionnaire midway through the survey to ensure data on all possible confounders were collected.

Blood samples were obtained by venipuncture, kept in temperature-controlled coolers, and transported to the Institut National de Recherche Biomédicale in Kinshasa daily. Samples were centrifuged and serum was aliquoted into cryovials and stored at −20°C until shipment. Serum was shipped to the Centers for Disease Control and Prevention Arbovirus Diseases Laboratory in Fort Collins, CO, where samples were tested for the presence of neutralising antibodies against yellow fever virus using the plaque reduction neutralisation test with a cutoff of 50% ($PRNT_{50}$) and a cutoff of 90% ($PRNT_{90}$), as described previously.[14,20] Participants with pre-vaccination titres of 10 or more were considered to be baseline seropositive. We report $PRNT_{50}$ titres, as it is a widely accepted correlate of protection and recommended by WHO for establishing sufficient virus-neutralising antibodies in serum; $PRNT_{90}$ results are in appendix 2 (pp 1-2).[7,19-22]

Outcomes

The primary endpoint was the proportion of those who were seropositive. Geometric mean titres were also assessed.

Statistical analysis

Sample size calculations for the initial cohort have been previously described.[14] A sample size of 190 participants per age strata (n=760) was determined to be sufficient for immune response estimation, assuming 92% immune response rate, with a 95% Wald CI of SD 5%, and a 40% attrition rate.[14] All participants with baseline results and at least one follow-up sample (either 1 month or 1 year) were included in the 5-year analysis. However, individuals who did not seroconvert by 1 month and were revaccinated were excluded from the analysis (n=7).

The primary endpoint, the proportion of those seropositive is presented with corresponding two-sided 95% CI based on Wilson's score method. We also calculated 95% Wilson CIs for the proportion who were seropositive by sex and by age groups. Geometric mean titres (GMTs) and 95% CIs were calculated using generalised linear mix models with unstructured correlation to account for repeated measures. No random effect was specified in the model and a sandwich estimator was used for the covariance estimator for the fixed effect. GMT of age and sex were estimated in separate models for which the dependent variable in the model was the log-transformed titre. Model assumptions were assessed using residual plots. GMTs and their CIs were transformed to their original scale by exponentiating the parameter estimate from the linear model. We assessed differences in seropositivity across age group and sex using the Fisher's exact test. We grouped participants by baseline serostatus as defined previously. We used the Kruskal–Wallis test (for age group) and the Wilcoxon rank-sum (for sex) test to compare differences in antibody titres as appropriate. All analyses were completed using SAS (version 9.4).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Among the 764 participants enrolled at baseline, 716 (94%) completed the 1-month follow-up visit, 684 (90%) completed the 1-year follow-up, and 566 (74%) completed the 5-year follow-up visit. The primary reason for individuals to not be included in the 5-year visit was lost to follow-up (figure 1).

Of those included in the 5-year follow-up, 286 (51%) were female (table 1). Although at least 70% of participants returned in each age cohort, children aged 2–5 years and adults aged 50 years and older at vaccination were less likely to participate in the 5-year follow-up than people aged 6–49 years. No participants reported history of dengue, Zika, or yellow fever disease since their last visit. Among the subset of 319 participants that were asked about immunosuppressing conditions, no one reported being immunosuppressed.

Five years after receiving a one-fifth dose of yellow fever vaccine, 539 (95·2%, 95% CI 93·2–96·7) of 566 participants who originally seroconverted were seropositive (table 2). Seropositivity was similar by sex (p=0·85) and age group (p=0·15). There were also no significant differences in GMT by sex (p=0·39) or age groups (p=0·10). However, titres were lower among those in the 2–5-years age group compared with those aged 13 years and older (table 2).

Among 383 participants seronegative at baseline, 361 (94·3%, 95% CI 91·5–96·2) were seropositive at the 5-year follow-up (table 3). There were no significant differences in proportions seropositive and the GMT by sex. There were significant differences across age groups for both seropositivity (p=0·02) and GMT (p<0·0001), with the lowest titres seen among the 2–5-years age group (23·6, 95% CI 16·1–33·4) and the highest among those aged 13–49 years (67·7, 55·6–82·4) and those 50 years and older (66·1, 48·0–91·0). Although the

titres were significantly lower among the 2–5-years age group, the rate of decline in the titres over time was not as steep as those seen for aged 13 years and older (figure 2).

Among the 183 participants seropositive at baseline, 178 (97·3%, 95% CI 93·8–98·8) were seropositive 5-years after vaccination (table 3). There were no significant differences in the proportions by age group (p=0·22) or by sex (p>0·99) or in the distribution of GMT by age group (p=0·97) or sex (p=0·32). The decline in antibody titres varied slightly among age groups, but five years after vaccination was similar (figure 2).

Discussion

5 years following the receipt of a fractional (one fifth) dose of 17DD yellow fever vaccine during a mass vaccination campaign, we found 95% of all participants and 94% who were seronegative at baseline (eg, initially seroconverted at 1 month) had detectable neutralising antibodies against yellow fever. Overall, the results from our evaluation add to the increasing evidence that a one-fifth dose of yellow fever vaccine elicits an immune response that is sustained for at least 5 years following vaccination if not longer.

Only two studies previously have assessed antibody persistence among those receiving a fractional yellow fever vaccine dose longer than 1 year. In a follow-up study conducted in Brazil among male army recruits receiving different doses of the 17DD strain, 85% of the 318 participants remained seropositive 8 years after vaccination with no significant difference found between the full dose and fractional doses.[18] However, this study only included people who were seropositive at 10 months after their original dose. In a second follow-up study conducted in the Netherlands among 75 university students, 98% of participants remained seropositive 10 years after receiving a fractional dose of 17D-204 vaccine administered intradermally.[19] Both studies were conducted in trial environments with healthy adult participants compared with our Democratic Republic of the Congo cohort in which malnutrition and chronic parasitic infections are common and are likely to affect the immunological response to vaccination.[23]

More recent work has explored the use of fractional dose yellow fever vaccines in other endemic areas, including in young children and people living with HIV. A non-inferiority trial involving healthy, non-pregnant adults in Kenya and Uganda assessed the immunogenicity and reactogenicity of one-fifth yellow fever vaccine compared with full dose for all four prequalified vaccines.[15] The trial showed equivalent safety and high rates of seroconversion for both fractional and full doses of all prequalified vaccines and fractional doses of all vaccines met the qualifications for non-inferiority.[15] Children aged 9–59 months in Kenya and Uganda were also enrolled and vaccinated with one fifth and full-dose 17D-213 yellow fever vaccine.[16] The seroconversion rates at 28 days and at 12–16 months among those receiving a fractional dose were non-inferior to those receiving a full dose. However, non-inferiority was not achieved in all age groups (ie, 9–12 months, 13–35 months, and 36–59 months) and at 10 days after vaccination. GMTs were also lower at all timepoints and for all age groups in children who received fractional doses compared with those who received full doses of the vaccine. Similar results were found among a subpopulation of people with HIV with CD4 counts of more than 200 cells per mL in

Kenya, who either received one fifth or a full dose of 17D-213 yellow fever vaccine.[17] Participants receiving a fractional dose had non-inferior seroconversion rates at 1 month and 1 year compared with those who received a full dose. The seroconversion rates were lower at 10 days for fractional doses and the GMTs were lower at all timepoints among those who received fractional doses compared with those who received full doses.

In our cohort, the youngest age group (2–5 years) had robust seropositivity that is consistent with many other studies looking at initial immune response to yellow fever vaccine.[24] However, children aged 2–5 years had consistently lower GMTs than adults at all timepoints including 5 years after vaccination.[14] This finding is consistent with several studies that have shown vaccinated children frequently have lower antibody titres against yellow fever virus compared with vaccinated adults.[6,22] As seen with other vaccines, it is possible that young children have a less robust immune response than older children and adults, which could be in part due to more concomitant infections or competing maternal antibodies.[25,26] Unlike some of the previous studies that found seropositivity rates drop to 28% several years after a full dose of 17DD vaccine administration to children aged 9 months,[22] we documented relatively high rates of seropositivity at 5 years. We also saw that although GMTs were lowest among those vaccinated when they were aged 2–5 years and seronegative at baseline at all timepoints, the waning of the titres in these groups appears to be more gradual than in young adults (ie, those aged 13–49 years) who develop very high titres 28 days after vaccination, which also decrease more rapidly. Although GMTs were also initially lower among adults vaccinated at age 50 years or older than in the younger adults, their titres were similar at the 1-year and 5-year follow-ups.[14] This supports the previous finding of delayed antibody response because of immune senescence, but also suggests that older adults can develop long-lasting immunity following yellow fever vaccination similar to young adults.[27,28]

Seroconversion rates have been previously reported higher among male participants in both full-dose and fractional dose studies than among females.[2,14,17] At 5 years after vaccination, female participants appeared to have slightly higher GMTs, even when stratified by baseline serostatus.

Unsurprisingly, GMTs remained higher at 5 years among those who were seropositive at baseline compared with those who were seronegative at baseline. At 1 month after vaccination seropositive young children and older adults did not achieve titres as high as young adults. Reasons for these differences could include time since previous yellow fever vaccination or exposure to another flavivirus, or immune senescence in older adults. However, the magnitude of the initial response did not affect the titres 5 years after vaccination, which were not significantly different between age groups. Ideally, people aged 2–12 years should have received a yellow fever vaccine previously as the vaccine was introduced into the routine immunisation services in 2003. However, yellow fever coverage in the Democratic Republic of the Congo has varied from 45% in 2005, to 65% in 2018.[10] Since 2018, yellow fever coverage decreased to 55% in 2022, likely due to the COVID-19 pandemic and other competing public health priorities.[10] The Democratic Republic of the Congo's low vaccination coverage suggests that there is likely a large at-risk population and preventive mass vaccination campaigns might be warranted to increase population coverage.

Our study is subject to several limitations. First, there was no control group, so we were unable to compare the fractional dose to the full dose. Some participants were possibly seropositive for neutralising antibodies against yellow fever virus due to cross-reactive antibodies with other flaviviruses, although no participants reported having an interim infection with yellow fever, dengue, or Zika virus. The prevalence of flaviviruses is estimated to be low in the Democratic Republic of the Congo but is increasing.[29] Past seroprevalence estimates indicate 3·8% and 3·5% of the population have been exposed to dengue or Zika, respectively.[30] Unfortunately, self-report is unlikely to be reliable given that diagnostics and disease knowledge are scarce in the Democratic Republic of the Congo. We were unable to assess all confounders and therefore there is the possibility of uncontrolled confounding. There have been no reports of yellow fever cases in Kinshasa following the large outbreak in 2016 so we are unable to definitively know whether fractional dose yellow fever vaccine in this population is effective at preventing infection at 5 years. We were unable to ask everyone about history of immunosuppressive disease or medications (eg, HIV or chemotherapy); however, among those asked, there were no reports. All medical history was self-reported; therefore, the reliability cannot be ascertained. Although most recent studies on fractional dose yellow fever vaccines use PRNTs,[15-17] none of the titres, including ours, were calibrated using an international reference preparation; thus we are unable to compare the titres with other studies. Finally, the results are specific to this population who received fractional doses of 17DD vaccine, which typically had higher potencies than at least two of the other WHO prequalified yellow fever vaccines.[15]

Prevention of yellow fever outbreaks is important to reduce mortality and morbidity and to avoid disruption of health systems. Fractional-dose yellow fever vaccination is increasingly becoming an accepted dose-sparing strategy in times of vaccine shortage and can be used successfully to pre-empt outbreaks and potentially offer long-term immunity. Additionally, international health regulation requirements are not met after fractional-dose vaccination as WHO guidance only recommends fractional-dose yellow fever vaccine during outbreak situations. Our data support the use of fractional doses of yellow fever vaccine during outbreaks and provide data on long-term immune response generated in a population living in an endemic area. Additional research is needed to determine if alternative fractional doses (eg, one-half dose) can provide similar GMTs to full dose, particularly among children aged 9–23 months and specific populations (eg, people with HIV). Further data on antibody kinetics, both short term and long term, are needed to determine if fractional doses can be used as part of routine childhood programmes or used in travellers who fall under international health regulations in which protection is considered lifelong.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank all the study participants. We also thank the study staff, staff members at Institut National de Recherche Biomedicale, Kinshasa School of Public Health, WHO, the Centers for Disease Control and Prevention, and the Ministry of Health of the Democratic Republic of Congo for their collaboration in implementing this study. We thank Gavi, the Vaccine Alliance and the Centers for Disease Control and Prevention Foundation for their support

in continuing the follow-up of this important work. The views expressed in this Article are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Data sharing

Data collected for the study, including de-identified participant data, the data dictionary, and additional related documents such as the study protocol and statistical analysis plan, will be made available to others upon request by emailing the corresponding author.

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Research in context

Evidence before this study

Large urban yellow fever outbreaks in Angola spread to the neighbouring Democratic Republic of the Congo, necessitating more than 30 million doses of yellow fever vaccine be used in reactive vaccination campaigns. The global stockpile of yellow fever vaccine was exhausted multiple times leading WHO and the Strategic Advisory Group of Experts on Immunization to recommend the use of a fractional yellow fever vaccine dose as a dose sparing strategy. Fractional doses of yellow fever vaccine were first used to pre-emptively control an outbreak in Kinshasa, Democratic Republic of the Congo in 2016, where 17DD vaccine (Bio-Manguinhos, Rio de Janeiro, Brazil) at one-fifth (0·1 ml) of the standard dose were administered to more than 7 million non-pregnant adults (ie, those aged 18 years and older) and children aged 2 years and older. The evidence to support this action was limited; thus, WHO called for additional research to be done. In August, 2023, we searched PubMed for papers published from database inception using the terms, “yellow fever vaccine” and “fractionated”, “fractional” or “partial”; we identified only two studies that have assessed antibody persistence among fractional yellow fever vaccine dose recipients longer than 1 year. However, both studies were conducted in trial environments with healthy adult participants compared with our diverse study population in Democratic Republic of the Congo.

Added value of this study

This is the first study to assess immunogenicity beyond 1 year, in the general population (including children), in which malnutrition and repeat infections with numerous pathogens are common. A fractional dose of the 17DD yellow fever vaccine induced an immunologic response with detectable titres at 5 years among the majority of participants in Democratic Republic of the Congo. These results align with previous studies in Brazil using the 17DD vaccine and in the Netherlands using the 17D-204 yellow fever vaccine, but extend the evidence to a yellow fever endemic setting in sub-Saharan Africa.

Implications of all the available evidence

These findings fill an important knowledge gap to support policy on the use of fractional dosing of yellow fever vaccine for outbreak response. Overall, the results from our evaluation and additional recent publications on children aged 9 to 59 months and people living with HIV suggest that a one fifth dose of yellow fever vaccine can be used for most individuals to elicit an immune response that is sustained. Additional, long-term studies with all yellow fever vaccines that have different potencies are warranted to substantiate the duration of protection.

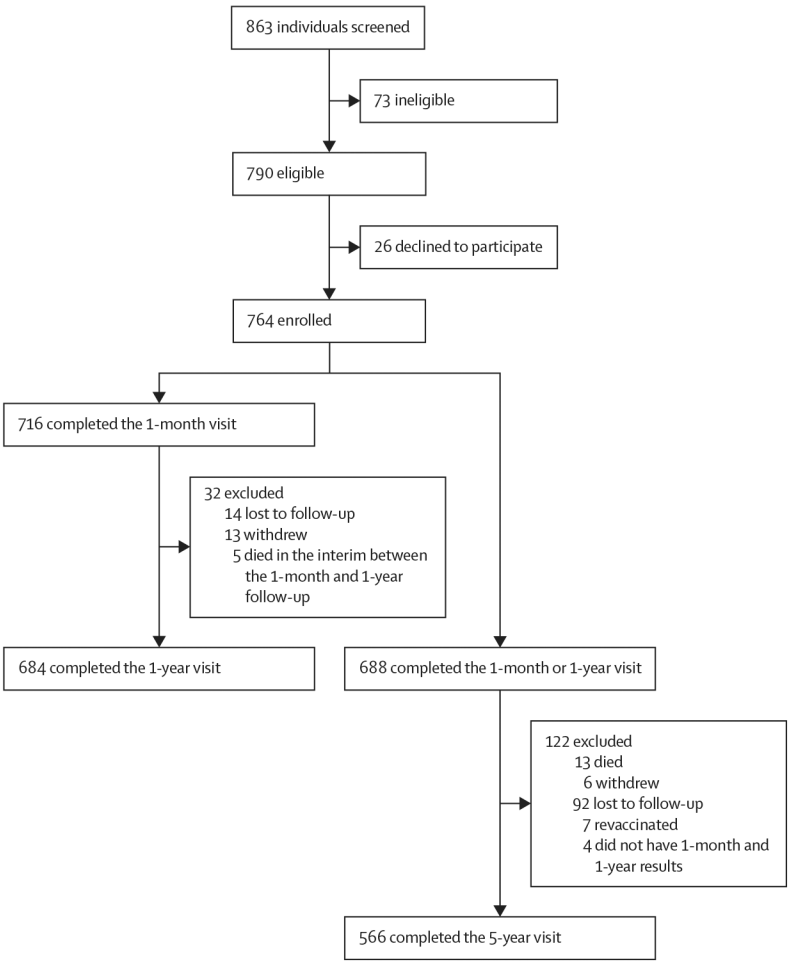

Figure 1: Study profile

Of the 122 participants who were excluded from the 5-year analysis, 50 (41%) were female; 32 (26%) were aged 2–5 years, 25 (20%) were aged 6–12 years, 21 (17%) were aged 13–49 years, and 40 (33%) were aged ≥50 years at the time of vaccination. Among the sites, 19 (16%) excluded participants were from site A, 23 (19%) from site B, 18 (15%) from site C, 26 (21%) from site D, 14 (11%) from site E, and 18 (15%) from site F. Four individuals did not complete the 1-month and 1-year visit and were excluded from the analysis. Four additional participants were included in the 5-year analysis that had not been included in the 1-year analysis; two missed the 1-month visit and two missed the 1-year visit. Seven participants were excluded because they had been revaccinated at the 1-year follow-up visit.

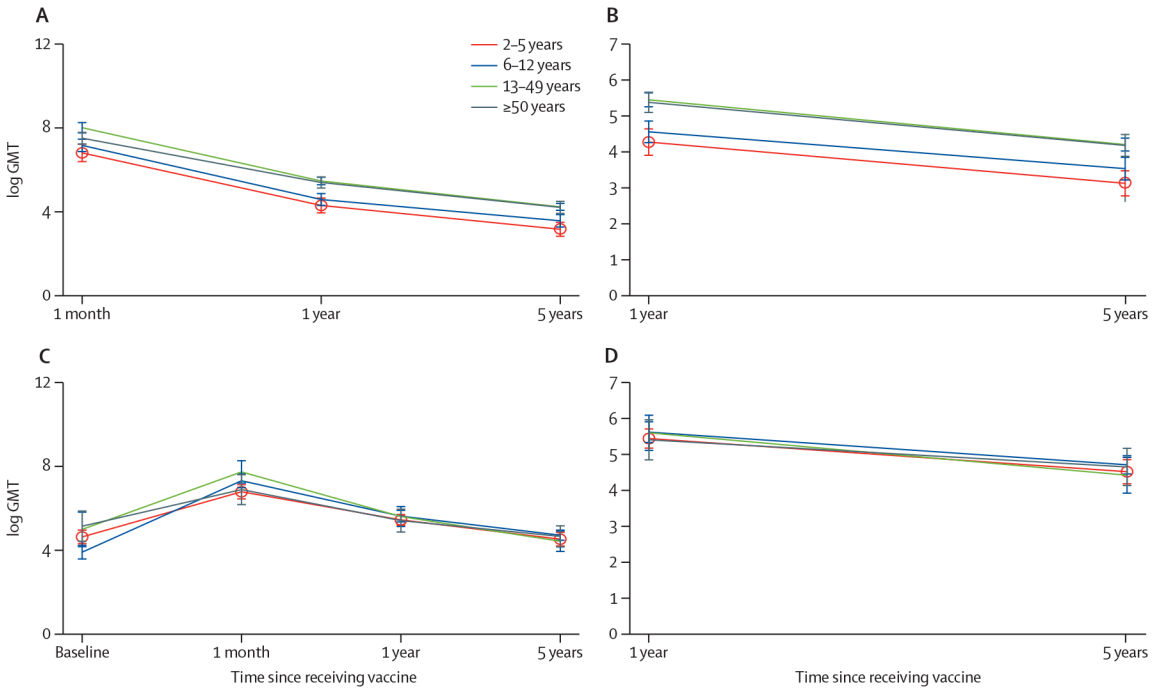

Figure 2: GMT by age group, baseline serostatus, and timepoint for individuals receiving a one-fifth fractional dose of yellow fever vaccine

(A, B) GMT and 95% CIs at follow-up for seronegative participants. (C, D) GMT and 95% CIs at follow-up for seropositive participants. Note the GMTs and 95% CIs were log transformed. GMT=geometric mean titre.

Table 1:

Characteristics of participants with a blood sample at 5 years following a fractional-dose yellow fever vaccination, by age group [*] (N=566) [†]

	All participants	Aged 2–5 years (n=118) [‡]	Aged 6–12 years (n=158) [‡]	Aged 13–49 years (n=162) [‡]	Aged >50 years (n=128) [‡]
Sex					
Female	286 (51%)	66 (56%)	76 (48%)	88 (54%)	56 (44%)
Male	280 (49%)	52 (44%)	82 (52%)	74 (46%)	72 (56%)
Serostatus at baseline [§]					
Seropositive	183 (32%)	63 (53%)	64 (41%)	26 (16%)	30 (23%)
Seronegative	383 (68%)	55 (47%)	94 (59%)	136 (84%)	98 (77%)
Self-reported history of yellow fever disease, dengue, or Zika					
Yes	0	0	0	0	0
No	565 (100%)	118 (100%)	158 (100%)	162 (100%)	128 (100%)

Data are n (%). *Age group represents age at vaccination and not current age. †Includes four participants not included in the study by Casey and colleagues[14] analysis at 1 year. ‡At baseline, there were 162 children aged 2–5 years, 189 aged 6–12 years, 189 aged 13–49 years, and 176 aged ≥50 years; participation rates were 73%, 84%, 86%, and 73% respectively by age group at the 5-year follow-up. §Seropositivity for neutralising antibodies against yellow fever virus was defined as a titre on a plaque reduction neutralisation test with a cutoff of 50% of 10 or higher.

Table 2:

Seropositivity[*] and geometric mean titre at 5 years, by age group[†] and sex

	n/N	Seropositive % (95% CI)	p value[‡]	Geometric mean titre (95% CI)	p value[‡]
All participants	539/566	95·2 (93·2–96·7)	··	61·7 (54·6–69·8)	··
Age group, years	··	··	0·15	··	0·10
2–5	109/117	93·2 (87·1–96·5)	··	48·8 (36·7–64·8)	··
6–12	149/158	94·3 (89·5–97·0)	··	55·9 (43·8–71·2)	··
13–49	159/162	98·2 (94·7–99·4)	··	70·0 (58·2–85·3)	··
≥50	122/129	94·6 (89·2–97·4)	··	73·7 (55·9–97·2)	··
Sex	··	··	0·85	··	0·39
Female	273/286	95·5 (92·4–97·3)	··	64·4 (54·5–76·1)	··
Male	266/280	95·0 (91·8–97·0)	··	59·2 (49·4–70·8)	··

[*] Seropositivity was defined as a result on a plaque reduction neutralisation test with a cutoff of 50% testing of 10 or higher.

[†] Age group represents age at vaccination and not current age.

[‡] p values for the overall comparisons among the subgroups were calculated with a Fisher's exact test.

Table 3:

Seropositivity* and geometric mean titre at 5 years, by baseline serostatus, age group, and sex

	Baseline geometric mean titre (95% CI)	Seropositive, n/N	Seropositive % (95% CI)	p value†	Geometic mean titre at 5 years (95% CI)	p value†
Seronegative at baseline						
All participants	NA	361/383	94·3 (91·5–96·2)	..	49·1 (42·3–57·1)	NA
Age group, years	..	..	..	0·02	..	<0·0001
2–5	NA	49/54	90·7 (80·1–96·0)	..	23·6 (16·1–33·4)	..
6–12	NA	85/94	90·4 (82·8–94·9)	..	34·8 (25·0–48·4)	..
13–49	NA	134/136	98·5 (94·8–99·6)	..	67·7 (55·6–82·4)	..
≥50	NA	93/99	93·9 (87·4–97·2)	..	66·1 (48·0–91·0)	..
Sex	..	..	..	0·83	..	0·96
Female	NA	177/187	94·7 (90·4–97·1)	..	49·3 (40·1–60·6)	..
Male	NA	184/196	93·9 (89·6–96·5)	..	49·0 (39·4–60·9)	..
Seropositive at baseline						
All participants	91·4 (70·7–118·1)	178/183	97·3 (93·8–98·8)	..	99·6 (82·1–120·8)	..
Age group, years				0·22		0·97
2–5	103·0 (72·1–147·3)	60/63	95·2 (86·9–98·4)	..	92·3 (64·7–131·7)	..
6–12	49·7 (34·8–70·9)	64/64	100·0 (94·3–100·0)	..	111·9 (85·1–147·1)	..
13–49	147·7 (62·7–347·8)	25/26	96·2 (81·1–99·3)	..	83·7 (49·9–140·3)	..
≥50	171·9 (80·6–366·3)	29/30	96·7 (83·33–99·4)	..	105·5 (61·7–180·4)	..
Sex	..	..	..	>0·99	..	0·32
Female	115·13 (81·04–163·57)	96/99	96·97 (91·47–98·96)	..	106·63 (82·64–137·58)	..
Male	69·60 (48·22–100·47)	82/84	97·62 (91·73–99·34)	..	91·88 (68·42–123·38)	..

NA=not applicable. *Seropositivity was defined as a result on a plaque reduction neutralisation test with a cutoff of 50% testing of 10 or higher. †p values for differences in the percentage of participants who were seropositive at 5 years were calculated according to age group and sex using the Fisher's exact test; p values for the test of differences in the geometric mean titre at 5 years were calculated using the Kruskal–Wallis test (for age groups) and the Wilcoxon rank-sum test (for sex).