Low-dose yellow fever vaccination in infants: a randomised, double-blind, non-inferiority trial

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SUMMARY

Background: The World Health Organization recommends fractional dose vaccination to address Yellow Fever (YF) vaccine shortages during outbreaks. In adults, a 500 IU dose has recently been shown to be non-inferior to the full standard dose, but the minimum dose for children is unknown.

Methods: We conducted a randomised, double-blind, non-inferiority trial in Kenya and Uganda, involving infants aged 9–12 months old with no prior YF vaccination or infection. Participants were randomly assigned 1:1 in blocks of variable sizes of 4, 6 or 8 to receive either the standard dose (>13,000 IU) or 500 IU of the Institut Pasteur de Dakar 17D-204 YF vaccine, co-administered with measles-rubella (MR) vaccine. The primary outcome was seroconversion 28 days post-vaccination, defined as a four-fold or greater increase in antibody titre at day 28 from the baseline (day 0), as measured by the 50% plaque reduction neutralisation test ($PRNT_{50}$). Non-inferiority was shown if the lower bound of the 95% confidence interval (CI) for the difference in seroconversion rates between doses exceeded −10 percentage points. This study is registered with ClinicalTrials.gov, NCT04059471.

Findings: Between Oct 7, 2021, and Jun 14, 2023, 420 infants were enrolled and randomised (210 participants in each group). The seroconversion rate at day 28 was 99% (95% CI 96 to 100; 177 of 179 infants) for the standard dose and 93% (95% CI 88 to 96; 166 of 179 infants) for the 500 IU dose in the per-protocol population. The difference in seroconversion rate was −6.15 percentage points (95% CI −10.27 to −2.02). Twelve serious adverse events were reported in the study (8 in the 500 IU dose group and 4 in the standard dose group) but all were unrelated to vaccination.

Interpretation: When compared to the full YF vaccine dose, a dose of 500 IU did not meet the non-inferiority criterion suggesting that minimum dose requirements in adults are not generalisable to infants.

INTRODUCTION

Yellow fever (YF) is a mosquito-borne viral zoonotic illness that is endemic in 47 countries in sub-Saharan regions of Africa and tropical South America [1]. YF outbreaks are most common in Africa where over 100,000 severe YF cases are estimated to occur every year [2,3].

The 17D live-attenuated YF vaccine has been in use since 1937 and a single dose of the vaccine provides life-long immunity [4]. However, manufacture is laborious and difficult to scale up rapidly, leading to persistent challenges with vaccine availability, as seen during the 2016 outbreak in Angola and the Democratic Republic of Congo [5]. The World Health Organization (WHO) guidelines support fractional doses (i.e. a fifth of the standard dose) during outbreaks to manage vaccine shortages [6]. This policy is supported by trials indicating that the immunogenicity of a fractional dose is non-inferior to a standard dose for the four WHO-prequalified YF vaccines in healthy adults, children and individuals infected with HIV [7-10] . However, the potency of doses can vary substantially by manufacturers and by batch [7], with the WHO defining a minimum vaccine potency of 1000 international units (IU) per dose. Manufacturers have generally provided potencies substantially in excess of 1000 IU to account for potential potency losses during the three years vaccine shelf-life, and there are limited data available to define a precise minimum potency.

A previous trial in adults in Brazil using the 17DD vaccine sub-strain found that a dose of 587 IU resulted in seroconversion for 96.9% of participants 1-month post-vaccination [11], maintaining similar antibody levels to the full dose up to 8 years post-vaccination [12], and we recently found that 500 IU was the lowest non-inferior vaccination dose at 28 days post-vaccination for adults in Kenya and Uganda [13]. At present there are no data to inform the minimum YF vaccine dose requirements in children. In most YF endemic countries, the YF vaccine is given to infants as part of routine immunisation and is co-administered with other routine vaccines. Both the young age and co-administration with routine vaccines may influence vaccine immunogenicity. For this reason, it is important to determine whether the established minimum effective dose in adults (500 IU) [13] performs just as well as the standard dose in infants. We conducted a further non-inferiority trial to compare 500 IU with a standard dose of the 17D-204 YF vaccine co-administered with measles and rubella (MR) vaccine among infants aged 9 to 12 months in Kenya and Uganda.

METHODS

Study design and participants

This randomised, double-blind, non-inferiority trial was conducted at the Kenya Medical Research Institute (KEMRI)-Wellcome Trust Research Programme Clinical Trials Facility in Kilifi County, Kenya and the Epicentre Mbarara Research Centre in Mbarara city, Uganda. Community meetings were held to explain the study design, the rationale of conducting the fractional dosing study, expectations for participation and the possible impact of the data generated from the study. Informed consent was documented by signature or thumbprint by all parents or authorised guardians of participating infants before any study procedure. Briefly, we included infants aged 9 to 12 months who had no contraindication for YF vaccination or previous history of YF infection or vaccination. We excluded infants whose parents or guardians planned to migrate outside the study areas before the end of the study, or intended to travel to countries requiring YF vaccination within the first year after vaccination. Full trial eligibility criteria are included in the trial protocol [13]. The trial protocol was reviewed and approved by the Oxford Tropical Research Ethics Committee, the KEMRI Scientific and Ethics Review Unit, Mbarara University of Science and Technology Research Ethics Committee, the Kenya National Commission for Science, Technology and Innovation (NACOSTI) and the Uganda National Council of Sciences and Technology. Regulatory approval was obtained from the Kenya Pharmacy and Poisons Board, and the Uganda National Drug Authority. The trial was conducted in accordance with ICH Good Clinical Practice guidelines. This study is registered with ClinicalTrials.gov, NCT04059471.

Randomisation and masking

Enrolled participants were randomly assigned to receive vaccination with YF vaccine at either a standard dose or a dose of 500 IU, both co-administered with MR vaccine manufactured by Serum Institute of India Pvt. Ltd. The potency of YF vaccine batches produced by Institut Pasteur de Dakar ranges from 3.50 to 5.10 $\log_{10}$ IU per standard dose. The vaccine batches used for this trial were at 4.12 and 4.14 $\log_{10}$ IU/dose (i.e. 13,270 or 13,803 IU per standard dose). Scratch-off booklets with unique allocation numbers were prepared in advance by an independent firm (DiagnoSearch LifeSciences, Mumbai, India) using computer-generated random numbers with non-disclosed

variable block sizes of 4, 6 or 8, allocating to a YF vaccine dose in equal allocations, for use in the blinded randomisation.

Procedures

The lyophilised product was reconstituted in vaccine diluent to produce the 500 IU dose as per manufacturer's instructions [13]. This process was masked from the study team, and handled only by the unblinded team, which included vaccinating nurses and a vaccination supervisor (pharmacist and the senior nurse) who had no further role in the study. Both participants and laboratory staff were blinded to treatment allocation. An independent medical monitor had access to unblinded data throughout the trial. The prepared vaccines were kept at 2–8°C until administration and discarded after six hours from the time of dilution, if not used. YF vaccine was administered subcutaneously using 0.5mL graduated syringes with a 25G × 3/4" needle size at a 45-degree injection angle in the left upper arm. The MR vaccine was administered in the right upper arm on the same day as the YF vaccine. The participant was observed for at least 30 minutes after YF vaccine administration to assess for any immediate reactions.

For immunogenicity, a total of 4ml blood samples were collected at baseline (i.e. on the vaccination visit and prior to vaccination), and at 10, 28 and 365 days after vaccination. For viremia monitoring, blood samples were collected at baseline and day 10, and participants were randomly assigned to have one additional blood-sampling visit at day 2, 3, 4, 5, 6, or 7 (i.e., 70 participants on each day) for assessment of post-vaccination viremia by RT-PCR at the WHO-accredited regional YF reference laboratory at the Uganda Virus Research Institute (UVRI), Entebbe, Uganda. Blood was processed for serum that was stored at -80°C until assayed. The plaque reduction neutralisation test (PRNT) assays for this study were conducted at the WHO-accredited regional YF reference laboratory at the Institut Pasteur de Dakar in Senegal using well-described standardised methods [14,15]. The Institut Pasteur de Dakar laboratory functions independently from the YF vaccine production plant.

Outcomes

The primary outcome was non-inferiority of the seroconversion rate of 500 IU dose compared to the standard dose at 28 days post-vaccination using a 50% plaque reduction neutralisation test ($PRNT_{50}$) in the per-protocol (PP) population. The PP population included all randomised participants with a valid PRNT result at baseline and at the specific follow-up visit and were seronegative to YF ($PRNT_{50}$ <1:10) at baseline and had no protocol deviations. Seroconversion was defined as a four-fold or greater rise in neutralising antibody titre between baseline (day 0) and post-vaccination samples [13]. Secondary outcomes included assessing non-inferiority of the proportion of participants who seroconverted using a 90% plaque neuralisation reduction ($PRNT_{90}$) in the PP population, seroconversion using $PRNT_{50}$ and $PRNT_{90}$ in the intention-to-treat population (ITT [comprising all vaccinated participants with at least one blood sample after vaccination]), geometric mean titres (GMT), geometric mean fold increase in titres (GMFI), and GMT ratios and GMFI ratios for the 500 IU dose to the standard dose using $PRNT_{50}$ and $PRNT_{90}$ at days 10, 28 and 365 after vaccination in the PP and the ITT study populations. Safety outcomes comprised adverse events and serious adverse events in the safety population, which included all participants who received a study vaccine dose.

Statistical analysis

The power calculation assumed a 90% seroconversion rate (accounting for lower vaccine immunogenicity reported in children [16]), 90% power, 2.5% alpha for a one-sided test and a non-inferiority margin of 10%, which gave a sample size of 190 infants per dose group. This was increased by 10% to account for losses to follow-up and/or unevaluable participants, resulting into an overall sample size of 420 infants. The 10% noninferiority margin was determined with consideration of the potential public health impact of reduced long-term population immunity as described previously [13,17]. There were no adjustments for multiple comparisons for the secondary outcomes.

The primary outcome analysis was a two-group comparison of the rate of seroconversion for the 500 IU dose versus the standard dose in the PP population. We summarised the number and

percentage of participants seroconverting together with their 95% Agresti-Coull confidence intervals by dose [18]. Non-inferiority was assessed by constructing a two-sided 95% CI around the point estimate of the difference in seroconversion rates between the 500 IU dose and the standard dose groups. The 500 IU dose would be non-inferior to the standard dose if the lower bound of the 95% CI for the difference in the seroconversion rates was greater than -10%. GMT was estimated as the geometric mean of the natural log-transformed titre values and GMFI was estimated as geometric mean of the ratios of post-vaccination titre to pre-vaccination titre. Two-sided 95% CIs of the mean difference of GMT between the standard and fractional dose groups were constructed using the *t*-distribution. These intervals were then transformed to obtain the ratio of the fractional dose to the standard dose for GMT. Similar procedure was performed for GMFI. We produced reverse cumulative distribution plots of antibody titres. These analyses were also performed at days 10 and 365. Missing data handling is presented in the supplementary material (see appendix p 3) [19]. Frequencies of all adverse events up to 28 days after vaccination were summarised according to severity and relationship to vaccination within each vaccine dose group. For each adverse event we estimated the risk ratios and the associated 95% CIs. All serious adverse events were described in detail for each participant. All analyses were performed using Stata version 15 (StataCorp, College Station, TX). Plots were generated using GraphPad Prism version 9.4.0 (GraphPad Software, San Diego, California USA).

Role of the funding source

The authors designed, executed, analysed, and reported the study. The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Between Oct 7, 2021, and Jun 14, 2023, 443 infants were assessed for eligibility of whom 13 were excluded due to ineligibility, 6 eligible declined to participate and 4 eligible did not complete screening. 420 eligible infants were enrolled and randomly assigned to receive either the 500 IU dose (210 participants) or standard dose (210 participants; Figure 1) of YF vaccine co-administered

with the measles/rubella (MR) vaccine. 394 (94%) of 420 participants completed follow-up visits at days 10 and 28, and 387 (92%) completed the last study follow-up visit at day 365. The primary PP analysis included 179 participants in the fractional dose and the standard dose groups. Missing outcome values in the primary ITT and PP population were due to 26 missed visits (i.e. 6% of 420 participants) similarly distributed across the two dose groups and one 500 IU dose group sample collected outside the window. The 40 exclusions from the PP population were due to pre-vaccination YF antibody positivity (Figure 1). The median age at enrolment was 9 months (IQR 9–9), one in ten were seropositive to YF, and one child was HIV exposed at baseline. Baseline characteristics of the participants were similar across the dose groups (Table 1).

At 28 days post-vaccination, seroconversion rates by $PRNT_{50}$ were 99% (95% CI 96–100; 177 of 179 participants) for full dose vs 93% (95% CI 88–96; 166 of 179 participants) for 500 IU on PP analysis. The corresponding rates on ITT analysis were 98% (95% CI 95–99; 193 of 197 participants) vs 91% (95% CI 86–95; 179 of 196 participants) (Table 2). Similar observations were made at day 365. The seroconversion rate 10 days after vaccination was above 90% in the standard dose group, but below 60% in the 500 IU dose group for both the PP and ITT populations (Table 2). The difference in the seroconversion rate 28 days after vaccination was -6.1% (95% CI -10.3 to -2.0) by PP analysis and -6.6% (95% CI -11.1 to -2.2) by ITT analysis (Figure 2). Thus, non-inferiority was not met for the 500 IU dose in either the PP or ITT populations using $PRNT_{50}$. The same conclusions were reached for day 10 and day 365 using $PRNT_{50}$ (Table 2) and by $PRNT_{90}$ (appendix p 4).

28 days after vaccination, the GMTs increased to 512 (95% CI 393–667) in the 500 IU dose group and 915 (95% CI 765–1094) in the standard dose group using $PRNT_{50}$ and continued to increase 365 days after vaccination, with consistently lower antibody responses in the 500 IU dose group by both ITT and PP analysis (Table 2), and with similar results using the $PRNT_{90}$ assay (appendix p 5–10). We observed higher GMTs at day 365 compared with day 28, and this increase was most marked in the Kilifi site (appendix p 12-13). No child was positive for YF vaccine viremia.

125 (60%) of 210 participants in the 500 IU dose group and 109 (52%) of 210 participants in the standard dose group reported an adverse event (AE), accounting for a total of 331 AE. One (<1%;

1 in the 500 IU dose group) of 420 participants reported a severe AE. The rest reported either mild (187 [45%] of 420 participants) or moderate (61 [15%] of 420 participants) AEs.

One participant in the standard dose group had an AE classified as definitely related to the study vaccine and one participant in the 500 IU dose group had an AE classified as probably related to the study vaccine (table 3). The most common AEs were respiratory tract infection (141 [43%] events), diarrhoea (46 [14%]), conjunctivitis (19 [6%]), rash (19 [6%]), fever (17 [5%]), cough (15 [5%]), gastroenteritis (14 [4%]) and abscess (10 [2%]) (appendix p 11–12). There were 12 (8 in the 500 IU dose group and 4 in the standard dose group) serious adverse events reported throughout the study (table 3). These serious adverse events included pneumonia, malaria, lower respiratory tract infection, gastroenteritis, abscess, bronchiolitis, and burns and none of them was classified as related to vaccination (appendix p 14).

DISCUSSION

We found that when compared to the full YF vaccine dose, a dose of 500 IU did not meet the non-inferiority criterion suggesting that minimum dose requirements in adults are not generalisable to infants. Seroconversion rates in the 500 IU dose group were also lower at day 10 and one year post-vaccination. This contrasts results from adults in the same population using the same vaccine, where the 500 IU dose was non-inferior to the standard dose at 28 days post-vaccination and the non-inferiority was sustained throughout the 2-year follow-up of that study [13]. This further adds to the evidence that age at vaccination is an important factor in the immune response induced by YF vaccines [20]. Our data do not support lowering the minimum vaccine potency requirement for infants to 500 IU (as in adults [13]) as this would not be sufficiently immunogenic in infants receiving the YF vaccine as part of the routine EPI schedule.

In a previous study using the 17D-213 YF vaccine we showed that one fifth of a standard dose was non-inferior to the full standard dose in children aged 9-59 months and this was maintained through to the end of follow-up at 1 year [8]. However, the potency of the standard dose used in that study was approximately 67,608 IU such that a fifth of the dose was 13,522 IU [8], at least ten times higher than the WHO minimum requirement and equivalent to the “standard dose” in the present study.

There are no other published randomised studies in children comparing the immunogenicity of fractional dosing to the full YF vaccine dose, but the results of a randomised trial in children 9 to 23 months of age in Uganda are expected soon [21] and another randomised trial is ongoing among infants in The Gambia [22].

Previous longitudinal and cross-sectional studies of children immunised with a full dose of YF vaccine at 9-12 months have observed rapid waning in YF neutralising antibody levels [23,24]. In Brazil, only 59% of children remained seropositive 4 years after vaccination, compared to 85% at 30-45 days post-vaccination [23]. In Mali, seropositivity dropped from 97% at 28 days to 50% at 4.5 years, while in Ghana, it decreased from 73% at 28 days to 28% at 2 years post-vaccination [24]. These data underscore the need to better understand the determinants of YF vaccine immunogenicity in children, including the potential influence of co-administration with EPI vaccines. It is plausible that the 10% non-inferiority margin was too stringent, and that greater reductions in immunogenicity might be acceptable in childhood when responding to an epidemic when vaccine supply is limited. However, the utility of fractional dosing as part of routine immunisation in this age group seems limited given our data. Studies assessing the impact of booster vaccinations will further inform policy decisions regarding YF vaccine schedules [25]. There was limited evidence of YF transmission in Uganda and in central Kenya during the time of the study [26,27], but a dengue outbreak was reported in coastal Kenya during 2023 [28], which is known to raise antibodies cross-reactive to YF virus [29]. This could explain the higher GMTs at day 365 versus day 28 titres at the Kilifi site where higher orthoflavivirus transmission was also observed as compared to Mbarara, based on baseline seropositivity for YF (appendix p 12).

As one of the most effective single dose vaccines globally, the differential immunogenicity of YF vaccination by age (lower seroconversion and titres in infants despite high seroconversion and life-long protection in adults) provides an opportunity to study the underlying age-related mechanisms of vaccine induced immunity that may have broader implications for immunity to other flaviviruses.

Previous studies in children reported that co-administration of measles and YF vaccines was associated with reduced immunogenicity of the YF vaccine [30,31]. However, limited observational data suggested no significant immunological interference [32]. In our study, we co-administered YF vaccine

277 with measles–rubella vaccine so as to provide data relevant to current EPI schedules where co-
278 administration is the norm.

279 Post-vaccination viraemia was not observed in any of the trial participants. This was in contrast with
280 the low frequency viraemia observed in adults receiving the same vaccine doses and whose
281 samples were collected at the same timepoints and assayed in the same WHO-accredited laboratory
282 using the same RT-PCR method [13]. We are aware of no other studies that have assessed post-
283 vaccination viraemia in infants receiving YF vaccine. Further study is needed to understand the
284 potential determinants for this observation, including ruling out the effect of co-administration with
285 other EPI vaccines, young age and other factors. We did not identify any safety concerns in our trial,
286 and none have been raised in previous trials of fractional doses in children or adults [7-9,13,33]. Further
287 titrations of dose in children to establish minimum potency would be safe and may be informed by
288 both long-term data on antibody durability, and on modelling of antibody kinetics based on the totality
289 of evidence acquired to date.
290 Limitations of our trial include testing in two East African populations which may not generalise to
291 other YF endemic regions, and immunogenicity may vary in other parts of Africa, particularly given
292 the data from Mali and Ghana demonstrating lower immunogenicity in Ghana compared with Mali
293 [24]. In addition, we did not measure antibody responses to the co-administered Measles and Rubella
294 vaccines, precluding any analyses of statistical interactions in relation to the observed YF vaccine
295 immunogenicity. Furthermore, our data apply to the 17D-204 vaccine sub-strain used by Institut
296 Pasteur de Dakar, and other manufacturers may need to assess potency requirements for
297 generalisability. In summary, we find that evidence on minimum dosing from adults cannot be directly
298 applied to infants. Infants may require higher vaccine doses to achieve comparable seroconversion
299 rates. Although lower seroconversion with the 500 IU dose might be acceptable in certain outbreak
300 settings with severe vaccine shortages, it is unlikely to be suitable for routine EPI programs where
301 adequate vaccine supplies are available.

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CONTRIBUTORS

PB, GMW, AJG, RFG and BO designed the study; DK, AJG, NSB, MLM, AD, GF, MD, MMH, DN, HKK, JNG, DM, DOO, MH, EO, NK, JW, JB, NS, JM, MJ, JMT, CA, CN, NA, FM, TB, MM, JM-A, JL, JK, and GMW collected the data; BO and SC conducted the statistical analysis; EK, ADB, PK, AAS, RFG, PB and GMW provided study oversight; DK, SC, BO, GMW accessed and verified all the data; DK, BO, AJG and PB prepared the first draft of the manuscript. All authors contributed to the interpretation of data, critically reviewed the manuscript, and decided to publish the paper.

DECLARATION OF INTERESTS

We declare no competing interests

DATA SHARING

Data collected for the study, including de-identified participant data, the data dictionary, and related documents such as the study protocol and statistical analysis plan, will be archived on the KEMRI-Wellcome Trust Research Programme (KWTRP) Research Data Repository (https://dataverse.harvard.edu/dataverse/kwtrp), and may be made available upon reasonable request to dgc@kemri-wellcome.org. Data sharing will follow the KWTRP Research Data Sharing Guidelines and will be in line with the Wellcome Trust's Data Sharing Policy and the WHO statement on public disclosure of clinical trial results.

ACKNOWLEDGEMENTS

We are grateful to the NIFTY study teams at the Kenya Medical Research Institute-Wellcome Trust Research Programme, Kilifi, Kenya and at Epicentre Mbarara Research Centre, Mbarara, Uganda. We thank the study Data and Safety Monitoring Board members namely, Sarah Walker, Charles Mgone and Roma Chilengi. This study was supported by grants from the Wellcome Trust

(203077_Z_16_Z) and from the European and Developing Countries Clinical Trials Partnership (EDCTP- RIA2016V-1633).

RESEARCH IN CONTEXT

Evidence before this study

We searched the International Clinical Trials Registry Platform (ICTRP) for randomised clinical trials assessing fractional doses of yellow fever vaccine in children using the search term “(yellow fever vaccine) AND (fractional doses) AND (children)”, from database inception to April 30, 2025, with no language restrictions. We identified two studies; one compared one-fifth and one-half dose to full dose in Ugandan children aged 9–23 months, reporting comparable safety but no published results on vaccine immunogenicity. The second study was a non-inferiority trial in Kenya and Uganda comparing one-fifth dose to full dose in children aged 9–59 months, finding that the one-fifth dose was safe and non-inferior to full dose with respect to immunogenicity. The fractional doses in these studies were well above the WHO recommended minimum potency of 1000 IU. There are no data to inform the minimum YF vaccine dose requirements in children.

Added value of this study

This study investigates whether the 500 IU dose is comparable to full dose in infants receiving YF vaccine concomitantly with measles and rubella (MR) vaccine at the age of 9–12 months as per the routine expanded programme on immunization (EPI) in Kenya and Uganda. We show that the 500 IU dose does not meet the non-inferiority criteria in infants.

Implications of all the available evidence

The minimum dosing evidence from adults does not generalise to children, in whom higher vaccine doses may be required to assure non-inferior seroconversion rates. Lower seroconversion rates with the 500 IU dose might be acceptable in some outbreak scenarios with marked vaccine shortages, but are unlikely to be acceptable in routine EPI where sufficient vaccine stocks are available.

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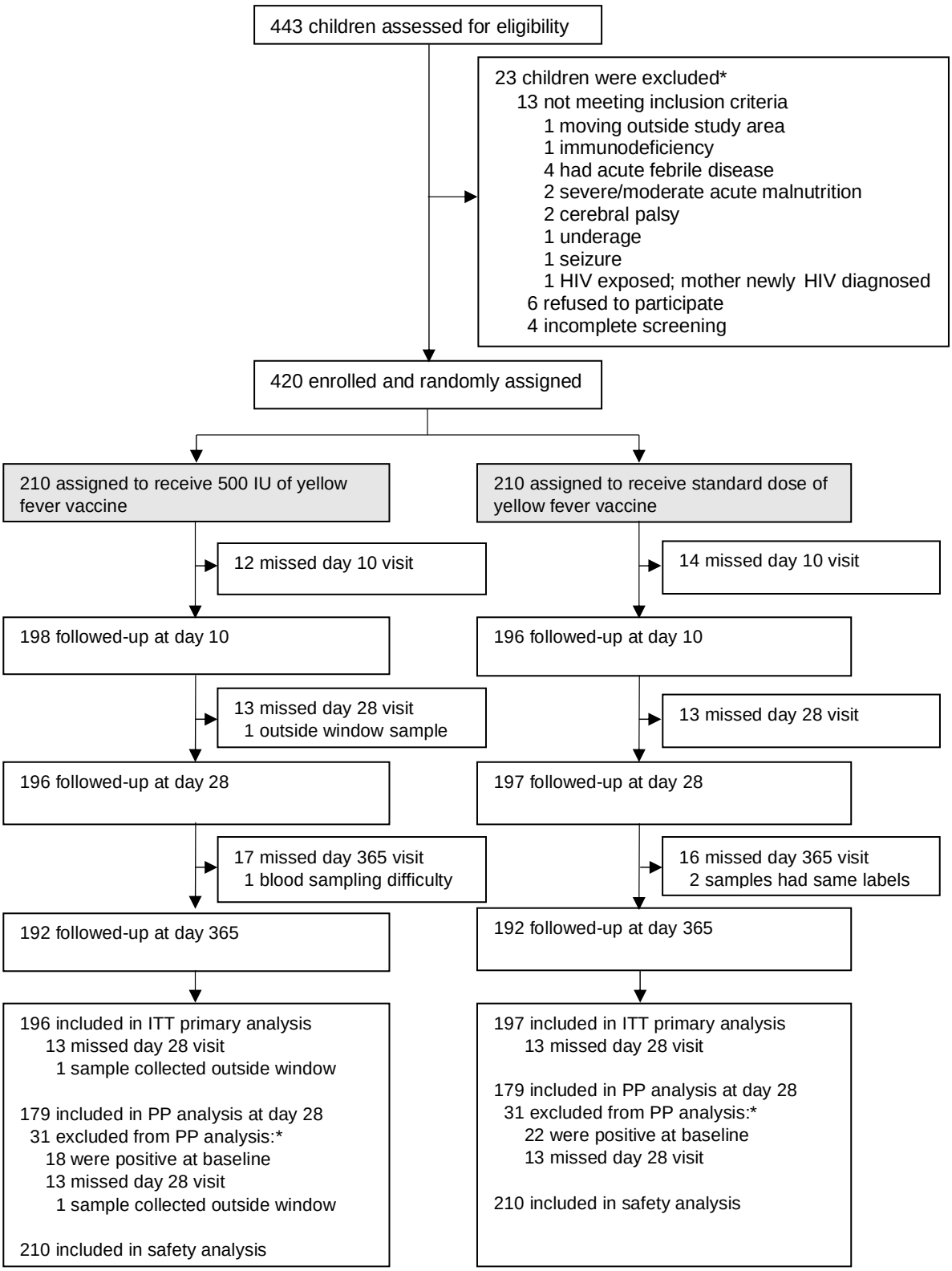
443 **Figures and Tables**



*Reasons are not mutually exclusive.

Figure 1. Study profile

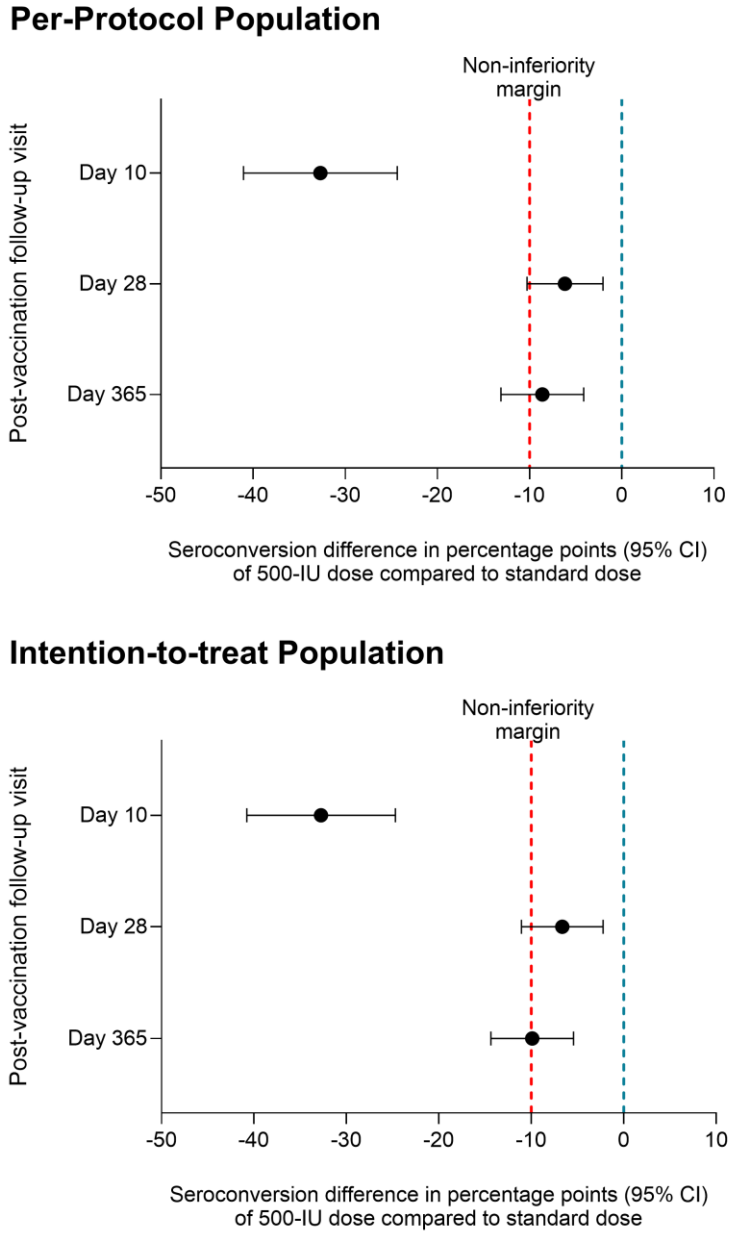


Figure 2. Noninferiority comparison of the seroconversion rate of the 500 IU dose with the full standard YF vaccine dose for the per-protocol (Panel A) and intention-to-treat (Panel B) population using $PRNT_{50}$.

Table 1. Baseline characteristics

	500 IU dose (n=210)	Standard dose (n=210)

Geographical site		
Kilifi	105 (50%)	105 (50%)
Mbarara	105 (50%)	105 (50%)
Median age at enrolment (IQR), months	9 (9–9)	9 (9–9)
Sex		
Female	109 (52%)	105 (50%)
Male	101 (48%)	105 (50%)
Mean temperature (SD), ^{0}C	36.3 (0.4)	36.4 (0.4)
Seropositive for YF at baseline*	18 (9%)	22 (10%)
Reported previous flavivirus infection	0	0
Reported previous medical illness	8 (4%)	9 (4%)
HIV exposed at baseline	0	1 (<1%)

453 Data are n (%) unless otherwise specified. *Defined as $PRNT_{50}$ test ≥10. No participant had missing
454 values for the baseline characteristics. IQR – interquartile range; SD – standard deviation.

455 **Table 2. Seroconversion and geometric mean titre in the per-protocol and the intention-to-treat populations by $PRNT_{50}$**

	Seroconversion*, n/N (%, 95% CI)	Seroconversion difference†, percentage points (95% CI)	Geometric mean titre (95% CI)	Geometric mean titre ratio‡	Geometric mean fold increase titre (95% CI)	Geometric mean fold increase ratio‡ (95% CI)
Per-protocol population						
Day 10		-32.68 (-41.03 to -24.34)		0.11 (0.07 to 0.17)		0.11 (0.07 to 0.17)
500 IU dose	106/180 (59%, 52–66)	-	43.7 (32.3 to 59.2)	-	8.7 (6.5 to 11.8)	-
Standard dose	163/178 (92%, 86–95)	-	388.8 (286.4 to 527.8)	-	77.8 (57.3 to 105.6)	-
Day 28		-6.15 (-10.27 to -2.02)		0.57 (0.41 to 0.79)		0.57 (0.41 to 0.79)
Fractional dose	166/179 (93%, 88–96)	-	525 (400 to 689)	-	105 (80 to 138)	-
500 IU dose	177/179 (99%, 96–100)	-	923 (763 to 1116)	-	185 (153 to 223)	-
Day 365		-8.61 (-13.11 to -4.12)		0.31 (0.2 to 0.47)		0.31 (0.2 to 0.47)
500 IU dose	158/174 (91%, 85–94)	-	596 (425 to 836)	-	119 (85 to 167)	-
Standard dose	171/172 (99%, 96–100)	-	1931 (1514 to 2462)	-	386 (303 to 492)	-
Intention-to-treat population						
Day 10		-32.74 (-40.77 to -24.7)		0.11 (0.08 to 0.17)		0.11 (0.08 to 0.17)
500 IU dose	115/198 (58%, 51– 65)	-	46.7 (35 to 62.2)	-	7.8 (5.8 to 10.5)	-
Standard dose	178/196 (91%, 86–94)	-	414.3 (310.9 to 551.9)	-	68.2 (50.9 to 91.4)	-
Day 28		-6.64 (-11.07 to -2.22)		0.56 (0.41 to 0.77)		0.58 (0.41 to 0.82)
500 IU dose	179/196 (91%, 86–95)	-	512 (393 to 667)	-	87 (65 to 116)	-
Standard dose	193/197 (98%, 95–99)	-	915 (765 to 1094)	-	151 (122 to 185)	-
Day 365		-9.9 (-14.36 to -5.43)		0.31 (0.21 to 0.46)		0.32 (0.21 to 0.48)

500 IU dose	172/192 (90%, 84–93)	-	615 (446 to 848)	-	102 (73 to 143)	-
Standard dose	191/192 (99%, 97–100)	-	1974 (1571 to 2480)	-	321 (251 to 411)	-

*Seroconversion is defined as a ≥4-fold rise in $PRNT_{50}$ titre at each timepoint from baseline; N is the number of infants in the per-protocol or intention-to-treat population; n is the number seroconverted; seroconversion rate, %=n/N multiplied by 100. †Seroconversion difference= 500 IU−Standard dose. ‡Geometric mean titre ratio, Geometric mean fold increase ratio=500 IU÷Standard. A GMT ratio or GMFI ratio less than 1 favours the standard dose and a ratio greater than 1 favours the 500 IU dose.

Table 3. Summary of all adverse events 28 days after vaccination and serious adverse events throughout follow-up for all consented participants

	500 IU dose group (n=210)	Standard dose group (n=210)
Number of adverse events reported	175	156
Number of participants with adverse events*	125	109
Number of serious adverse events reported	8	4
Number of participants with serious adverse events*	8	4
Adverse event severity, no./total no. of events (%)		
Mild	137/175 (78%)	129/156 (82%)
Moderate	37/175 (21%)	27/156 (17%)
Severe	1/175 (1%)	0
Life-threatening	0	0
Participant's adverse event severity, no. (%)†		
Mild	96 (46%)	91 (43%)
Moderate	35 (17%)	26 (12%)
Severe	1 (<1%)	0
Life-threatening	0	0
Adverse event related to vaccination, no./total no. of events (%)		
Not related	154/175 (88%)	143/156 (91%)
Unlikely	15/175 (9%)	7/156 (4%)
Possibly	4/175 (2%)	5/156 (3%)
Probably related	2/175 (1%)	0
Definitely related	0	1/156 (<1%)

464 *****Participants who experience one or more adverse events or serious adverse events are counted
465 only once. †Participants are counted only once within a particular severity grade or relatedness
466 category
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