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

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Summary

Background WHO recommends fractional dose vaccination to address yellow fever 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 effective dose for children is unknown.

Methods We conducted a randomised, double-blind, non-inferiority trial at two centres in Kenya and Uganda, including infants aged 9–12 months with no previous yellow fever vaccination or infection. Participants were randomly assigned 1:1 in blocks of variable sizes of four, six, or eight to receive either the standard dose (>13 000 IU) or 500 IU of the Institut Pasteur de Dakar (Dakar, Senegal) 17D-204 yellow fever vaccine, co-administered with the measles–rubella 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 baseline (day 0), as measured by the 50% plaque reduction neutralisation test. Non-inferiority was shown if the lower bound of the 95% CI for the difference in seroconversion rates between doses exceeded –10 percentage points. Safety was assessed in the safety population, which included all participants who received a study vaccine dose. This study is registered with ClinicalTrials.gov (NCT04059471) and is complete.

Findings Between Oct 7, 2021, and June 14, 2023, 420 infants were enrolled and randomly assigned (210 participants in each group). The seroconversion rate at day 28 was 99% (95% CI 96–100; 177 of 179 infants) for the standard dose and 93% (88–96; 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); therefore, non-inferiority was not met for the 500 IU dose. 12 serious adverse events were reported in the study (eight in the 500 IU dose group and four in the standard dose group), but all were considered unrelated to vaccination.

Interpretation Compared with the standard yellow fever 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. Therefore, standard yellow fever doses should be used for infants in the routine WHO Expanded Programme on Immunization.

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Introduction

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

The 17D live-attenuated yellow fever vaccine has been in use since 1937, and a single dose of the vaccine provides lifelong 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 the Congo.[5] WHO guidelines support fractional doses (ie, 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 yellow fever vaccines in healthy adults and children, and individuals with HIV.[7–10] However, the potency of doses can vary substantially by manufacturer and by batch,[7] with WHO defining a minimum vaccine potency of 1000 IU per dose. Manufacturers have generally provided potencies substantially in excess of 1000 IU to account for potential potency losses during the 3-year vaccine shelf-life, and there are few 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

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Research in context

Evidence before this study

We searched the International Clinical Trials Registry Platform for randomised 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 study compared a one-fifth dose and a one-half dose to a full dose in children aged 9–23 months in Uganda, reporting similar safety but no published results on vaccine immunogenicity. The other study was a non-inferiority trial in Kenya and Uganda comparing a one-fifth dose to a full dose in children aged 9–59 months, finding that the one-fifth dose was safe and non-inferior to the full dose with respect to immunogenicity. The fractional doses in these studies were well above the WHO recommended minimum potency of 1000 IU. We found no data to inform the minimum yellow fever vaccine dose requirements in children.

Added value of this study

This study investigated whether the 500 IU dose is non-inferior to full dose in infants receiving yellow fever vaccine concomitantly with the measles–rubella vaccine at age 9–12 months as per the routine WHO Expanded Programme on Immunization in Kenya and Uganda. We showed that the 500 IU dose does not meet the non-inferiority criterion in infants.

Implications of all the available evidence

The minimum dosing evidence from adults does not generalise to children, in whom higher vaccine doses could 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 the routine Expanded Programme on Immunization where sufficient vaccine stocks are available.

concentrations to the full dose up to 8 years post-vaccination,[12] and in our 2025 study we 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, to our knowledge, there are no data to inform the minimum yellow fever vaccine dose requirements in children. In most yellow fever-endemic countries, the yellow fever vaccine is given to infants as part of routine immunisation and is co-administered with other routine vaccines. Both the young age of recipients and co-administration with routine vaccines could influence vaccine immunogenicity. For this reason, it is important to determine whether the established minimum effective dose in adults (500 IU)[13] performs as well as the standard dose in infants. We aimed to compare 500 IU with a standard dose of the 17D-204 yellow fever vaccine co-administered with the measles–rubella (MR) vaccine among infants aged 9–12 months in Kenya and Uganda.

See Online for appendix

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. There was no patient or public involvement in the design of the study. Community meetings were held to explain the study design, the rationale of conducting the fractional dosing study, expectations for participation, and the possible effect of the data generated from the study. Following these meetings, individuals interested in participation were invited to the study clinics for screening and enrolment. Informed consent was obtained before any study procedure (including screening and enrolment) and documented by signature or thumbprint by a parent or authorised guardian for each participating infant. Trial data were monitored by an independent Data Safety and Monitoring Board.

We included infants aged 9–12 months who had no contraindication for yellow fever vaccination and no history of yellow fever infection or vaccination. We excluded infants whose parents or guardians planned to migrate outside the study areas before the end of the trial or intended to travel to countries that require yellow fever vaccination for entry within the first year after vaccination. Full trial eligibility criteria are included in the trial protocol (appendix).[13]

The trial protocol was reviewed and approved by the Oxford Tropical Research Ethics Committee (OxTREC 2-19), the KEMRI Scientific and Ethics Review Unit (Kenya approval: KEMRI SERU 3797), the Mbarara University of Science and Technology Research Ethics Committee (Uganda approval: MUREC 1/7), the Kenya National Commission for Science, Technology and Innovation, 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 International Council for Harmonisation Good Clinical Practice guidelines. This trial is registered with ClinicalTrials.gov (NCT04059471) and is complete.

Randomisation and masking

Enrolled participants were randomly assigned (1:1) to receive vaccination with yellow fever vaccine at either a standard dose of more than 13 000 IU (standard dose group) or a dose of 500 IU (500 IU dose group). 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 four, six, or eight, to assign participants to a yellow fever

vaccine dose in equal allocations, with participants and study staff masked to treatment assignment. The preparation of all doses 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. An independent medical monitor had access to unblinded data throughout the trial.

Procedures

The potency of yellow fever vaccine batches produced by the Institut Pasteur de Dakar (Dakar, Senegal) ranges from 3·50 $\log_{10}$ IU to 5·10 $\log_{10}$ IU per standard dose. The vaccine batches used for this trial were 4·12 $\log_{10}$ IU and 4·14 $\log_{10}$ IU per dose (ie, 13 270 IU or 13 803 IU per standard dose). The lyophilised product was reconstituted in vaccine diluent to produce the 500 IU dose as per the manufacturer's instructions.[13] The prepared vaccines were kept at 2–8°C until administration and discarded after 6 h from the time of dilution, if not used. Yellow fever vaccine was administered by masked nurses subcutaneously using 0·5 mL graduated syringes with a 25G×0·75-inch needle size at a 45-degree injection angle in the left upper arm. The MR vaccine (manufactured by the Serum Institute of India, Pune, India) was co-administered in the right upper arm. The participant was observed for at least 30 min after administration of the yellow fever vaccine to assess any immediate reactions.

For immunogenicity, 4 mL of blood samples were collected at baseline (ie, on the vaccination visit and before vaccination), and at 10, 28, and 365 days after vaccination. For viraemia 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 (ie, 70 participants on each day) for assessment of post-vaccination viraemia by RT-PCR at the WHO-accredited regional yellow fever reference laboratory at the Uganda Virus Research Institute, Entebbe, Uganda. Blood was processed for serum that was stored at –80°C until assayed. The plaque reduction neutralisation test (PRNT) assays for this trial were done at the WHO-accredited regional yellow fever reference laboratory at the Institut Pasteur de Dakar using standardised methods.[14,15] The Institut Pasteur de Dakar laboratory functions independently from the yellow fever vaccine production plant.

Outcomes

The primary outcome was seroconversion rate of the 500 IU dose compared with the standard dose at 28 days post-vaccination using a 50% PRNT ($PRNT_{50}$). 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 in this Article are non-inferiority of the proportion of participants who seroconverted using a 90% plaque neuralisation reduction ($PRNT_{90}$), seroconversion using $PRNT_{50}$ and $PRNT_{90}$, geometric mean titres (GMTs), geometric mean fold increase (GMFI) in titres, 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, and post-vaccination viraemia. Secondary outcomes that will be analysed and reported outside of this Article are cellular immune responses at days 10 and 28 by vaccine dose, relationship between GMTs and baseline titres to other flaviviruses, and a qualitative analysis on stakeholder priorities and perceptions regarding a change in policy towards use of fractional yellow fever vaccine doses. Safety outcomes comprised adverse events and serious adverse events that were recorded by a study clinician during study visits. The full list of outcomes is included in the appendix (p 16).

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. The sample size was increased by 10% to account for losses to follow-up and unevaluable participants, resulting in an overall sample size of 420 infants. The 10% non-inferiority margin was determined with consideration of the potential public health effect of reduced long-term population immunity, as described in previous papers.[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 per-protocol population, which included all randomly assigned participants with a valid PRNT result at baseline and at the specific follow-up visit and who were seronegative to yellow fever ($PRNT_{50}$ <1:10) at baseline and had no protocol deviations.

The secondary outcome of non-inferiority of the proportion of participants who seroconverted using $PRNT_{90}$ was assessed in the per-protocol population. Seroconversion using $PRNT_{50}$ and $PRNT_{90}$ was assessed in the intention-to-treat population (ITT; comprising all vaccinated participants with at least one blood sample after vaccination). All other secondary outcomes were assessed in both the per-protocol and ITT populations.

We summarised the number and percentage of participants seroconverting together with their 95% Agresti–Coull CIs 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 group and the standard dose group. The 500 IU dose would be considered 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 percentage points. GMT was estimated as the geometric mean of the natural log-transformed titre

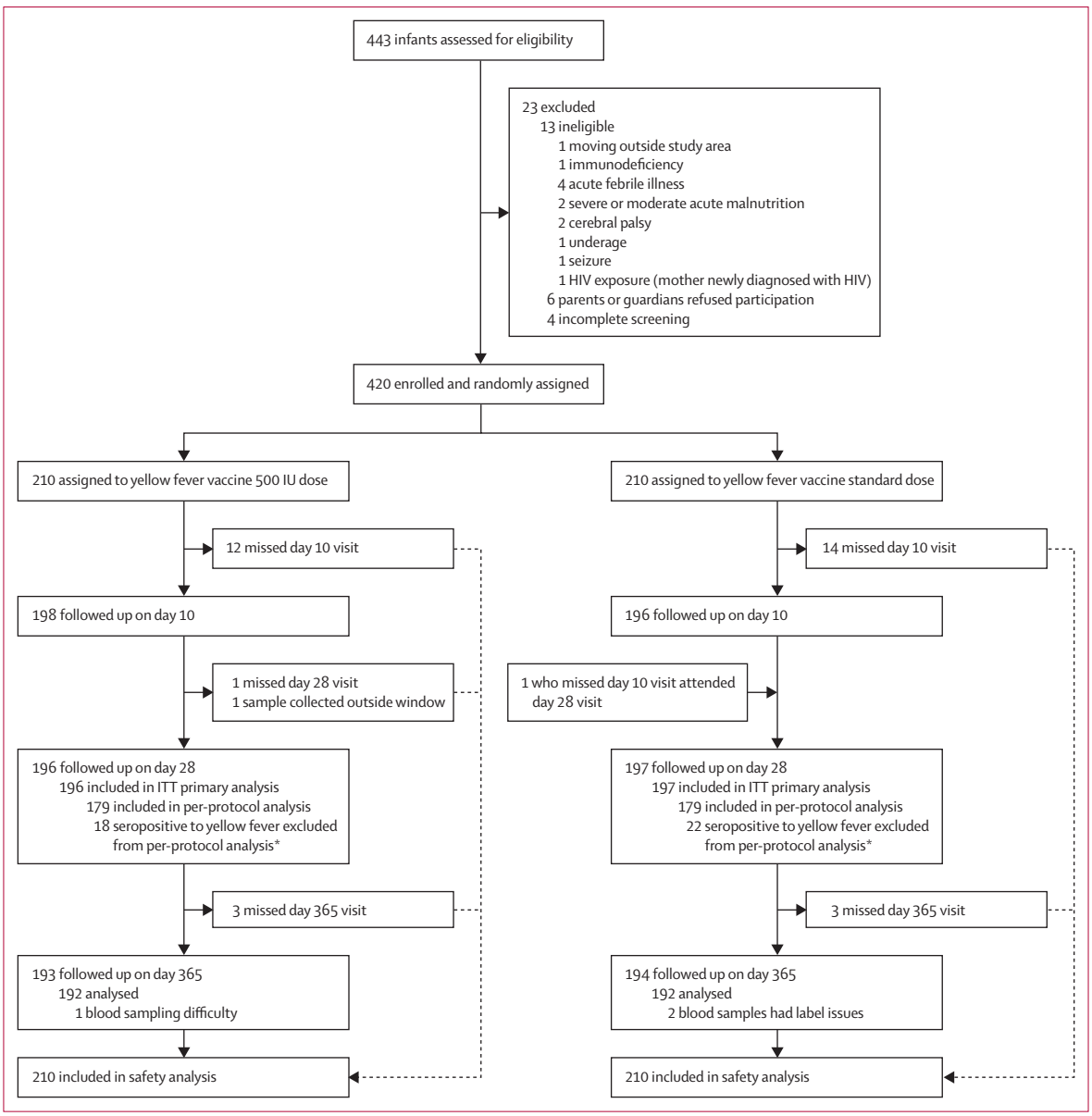

Figure 1: **Trial profile**
ITT=intention-to-treat. *Reasons are not mutually exclusive.

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 dose group and 500 IU dose group were constructed using the *t* distribution. These intervals were then transformed to obtain the ratio of the 500 IU dose to the standard dose for GMT. A 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. Handling of missing data is presented in the appendix (pp 3–4).[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. Safety was assessed in the safety population, which included all participants who received a study vaccine dose.

All analyses were performed using Stata (version 15). Plots were generated using GraphPad Prism (version 9.4.0).

Role of the funding source

The funders 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 June 14, 2023, 443 infants were assessed for eligibility, of whom 13 were excluded due to ineligibility, six were eligible but participation was declined, and four were eligible but 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 yellow fever vaccine co-administered with the MR vaccine. 393 (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 (although only 384 had samples analysed due to sampling or labelling issues). The primary per-protocol analysis included 179 participants in the 500 IU dose group and 179 in the standard dose group. Missing outcome values in the primary ITT and per-protocol populations were due to 13 missed visits (26 [6%] of 420 participants) in each group and one sample collected outside the window in the 500 IU dose group. The 40 exclusions from the per-protocol population were due to pre-vaccination yellow fever antibody positivity (figure 1). Baseline characteristics of the participants are shown in table 1; the median age at enrolment was 9 months (IQR 9–9), one in ten infants were seropositive to yellow fever, and one infant had been exposed to HIV at baseline.

At 28 days post-vaccination, seroconversion rates by $PRNT_{50}$ were 99% (95% CI 96–100; 177 of 179 participants) in the standard dose group versus 93% (88–96; 166 of 179 participants) in the 500 IU dose group in the per-protocol analysis. The corresponding rates in the ITT analysis were 98% (95% CI 95–99; 193 of 197 participants) versus 91% (86–95; 179 of 196 participants; table 2).

	500 IU dose group (n=210)	Standard dose group (n=210)
Geographical site		
Kilifi	105 (50%)	105 (50%)
Mbarara	105 (50%)	105 (50%)
Age at enrolment, months	9 (9–9)	9 (9–9)
Sex		
Female	109 (52%)	105 (50%)
Male	101 (48%)	105 (50%)
Body temperature	36·3°C (0·4)	36·4°C (0·4)
Seropositive for yellow fever 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%)

Data are n (%) or mean (SD). *Defined as 50% plaque reduction neutralisation test ≥10.

Table 1: **Baseline characteristics of all randomly assigned participants**

	Seroconversion*, n/N (%, 95% CI)	Seroconversion difference†, percentage points (95% CI)	Geometric mean titre (95% CI)	Geometric mean titre ratio‡ (95% CI)	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 (0·07–0·17)	..	0·11 (0·07–0·17)
500 IU dose	106/180 (59%, 52–66)	..	43·7 (32·3–59·2)	..	8·7 (6·5–11·8)	..
Standard dose	163/178 (92%, 86–95)	..	388·8 (286·4–527·8)	..	77·8 (57·3–105·6)	..
Day 28	..	−6·15 (−10·27 to −2·02)	..	0·57 (0·41–0·79)	..	0·57 (0·41–0·79)
500 IU dose	166/179 (93%, 88–96)	..	525 (400–689)	..	105 (80–138)	..
Standard dose	177/179 (99%, 96–100)	..	923 (763–1116)	..	185 (153–223)	..
Day 365	..	−8·61 (−13·11 to −4·12)	..	0·31 (0·20–0·47)	..	0·31 (0·20–0·47)
500 IU dose	158/174 (91%, 85–94)	..	596 (425–836)	..	119 (85–167)	..
Standard dose	171/172 (99%, 96–100)	..	1931 (1514–2462)	..	386 (303–492)	..
Intention-to-treat populatin						
Day 10	..	−32·74 (−40·77 to −24·7)	..	0·11 (0·08–0·17)	..	0·11 (0·08–0·17)
500 IU dose	115/198 (58%, 51– 65)	..	46·7 (35·0–62·2)	..	7·8 (5·8–10·5)	..
Standard dose	178/196 (91%, 86–94)	..	414·3 (310·9–551·9)	..	68·2 (50·9–91·4)	..
Day 28	..	−6·64 (−11·07 to −2·22)	..	0·56 (0·41–0·77)	..	0·58 (0·41–0·82)
500 IU dose	179/196 (91%, 86–95)	..	512 (393–667)	..	87 (65–116)	..
Standard dose	193/197 (98%, 95–99)	..	915 (765–1094)	..	151 (122–185)	..
Day 365	..	−9·9 (−14·36 to −5·43)	..	0·31 (0·21–0·46)	..	0·32 (0·21–0·48)
500 IU dose	172/192 (90%, 84–93)	..	615 (446–848)	..	102 (73–143)	..
Standard dose	191/192 (99%, 97–100)	..	1974 (1571–2480)	..	321 (251–411)	..

$PRNT_{50}$=50% plaque reduction neutralisation test. *Seroconversion is defined as a four-fold or greater 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 is %=n/N multiplied by 100. †Seroconversion difference=500 IU dose – standard dose. ‡Geometric mean titre ratio and geometric mean fold increase ratio=500 IU/standard; a geometric mean titre ratio or geometric mean fold increase ratio less than 1 favours the standard dose and a ratio greater than 1 favours the 500 IU dose.

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

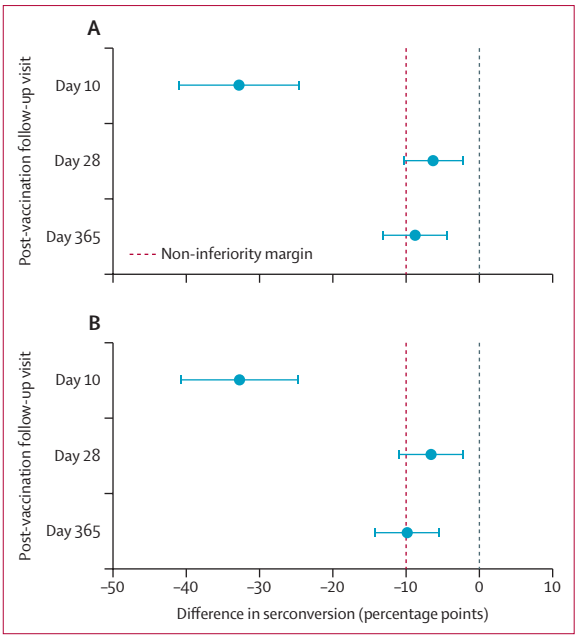

Figure 2: **Seroconversion rate non-inferiority comparison**
Non-inferiority comparison of the seroconversion rate of the 500 IU dose with the full standard yellow fever vaccine dose for the per-protocol (A) and intention-to-treat (B) populations using 50% plaque reduction neutralisation test. Error bars indicate 95% CIs.

	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		
Mild	137/175 (78%)	129/156 (82%)
Moderate	37/175 (21%)	27/156 (17%)
Severe	1/175 (1%)	0
Life-threatening	0	0
Participants' adverse event severity†		
Mild	96 (46%)	91 (43%)
Moderate	35 (17%)	26 (12%)
Severe	1 (<1%)	0
Life-threatening	0	0
Adverse event related to vaccination		
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%)

Data are n, n/N (%), or n (%). *Participants who have one or more adverse events or serious adverse events are counted only once. †Participants are counted only once within a particular severity grade or relatedness category.

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

Similar observations were made at day 365 (table 2). 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 per-protocol and ITT populations (table 2). The difference in the seroconversion rate 28 days after vaccination was –6·15% (95% CI –10·27 to –2·02) by per-protocol analysis and –6·64% (–11·07 to –2·22) by ITT analysis (figure 2). Thus, non-inferiority was not met for the 500 IU dose in either the per-protocol 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 pp 5–6).

From the ITT analysis 28 days after vaccination, the GMTs increased to 512 (95% CI 393–667) in the 500 IU dose group and 915 (765–1094) in the standard dose group using $PRNT_{50}$ and continued to increase to 365 days after vaccination, with consistently lower antibody responses in the 500 IU dose group per both ITT and per-protocol analysis (table 2), and with similar results using the $PRNT_{90}$ assay (appendix p 7). We observed higher GMTs at day 365 than at day 28, and this increase was most substantial for the Kilifi site (appendix pp 7–10, 13). No infant was positive for yellow fever vaccine viraemia.

An adverse event was reported for 125 (60%) of 210 participants in the 500 IU dose group and 109 (52%) of 210 participants in the standard dose group, accounting for a total of 331 adverse events. One (<1%; in the 500 IU dose group) of 420 participants reported a severe adverse event, and the rest reported either mild (187 [45%]) or moderate (61 [15%]) adverse events (the full list of adverse events is in the appendix p 11).

One (<1%) of 210 participants in the standard dose group had an adverse event classified as definitely related to the study vaccine and one (<1%) of 210 participants in the 500 IU dose group had an adverse event classified as probably related to the study vaccine (table 3). The most common adverse events were respiratory tract infection (77 [44%] of 175 events in the 500 IU dose group *vs* 64 [41%] of 156 events in the standard dose group), diarrhoea (25 [14%] *vs* 21 [14%]), conjunctivitis (nine [5%] *vs* ten [6%]), rash (11 [6%] *vs* eight [5%]), fever (11 [5%] *vs* six [4%]), cough (eight [5%] *vs* seven [4%]), gastroenteritis (six [3%] *vs* eight [5%]), and abscess (two [1%] *vs* six [4%]; appendix p 11). 12 serious adverse events were reported throughout the trial (eight in the 500 IU dose group and four in the standard dose group; table 3). These serious adverse events included pneumonia, malaria, lower respiratory tract infection, gastroenteritis, abscess, bronchiolitis, and burns, and none were classified as related to vaccination (appendix p 14).

Discussion

We found that, compared with the full yellow fever 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 1 year post-vaccination than in the standard dose group. These findings contrast with results from a study of adults in the same communities as the infants using the same vaccine, in whom 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] Our study adds further to the evidence that age at vaccination is an important factor in the immune response induced by yellow fever vaccines.[20] Our data do not support lowering of the minimum vaccine potency requirement for infants to 500 IU (as in adults[13]) because this would not be sufficiently immunogenic in infants receiving the yellow fever vaccine as part of the routine WHO Expanded Programme on Immunization (EPI) schedule.

Our 2023 study using the 17D-213 yellow fever vaccine found that a fifth of a standard dose was non-inferior to the full standard dose in children aged 9–59 months, and this non-inferiority was maintained to the end of follow-up at 1 year.[8] However, the potency of the standard dose used in that study was about 67 608 IU, such that a fifth of the dose was 13 522 IU—at least ten times higher than the WHO minimum requirement and equivalent to the standard dose in the present trial.[8] We found no other published randomised studies in children comparing the immunogenicity of fractional dosing to the full yellow fever vaccine dose, but the results of a randomised trial in children aged 9–23 months in Uganda are expected soon,[21] and another randomised trial among infants in The Gambia is ongoing.[22]

Previous longitudinal and cross-sectional studies of children immunised with a full dose of yellow fever vaccine at 9–12 months have shown rapid waning in yellow fever neutralising antibody concentrations.[23,24] A study in Brazil found that only 59% of children remained seropositive 4 years after vaccination, compared with 85% at 30–45 days post-vaccination.[23] In Mali, a study found that seropositivity dropped from 97% at 28 days to 50% at 4·5 years post-vaccination, and in Ghana, seropositivity 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 yellow fever vaccine immunogenicity in children, including the potential influence of co-administration with EPI vaccines. It is plausible that the non-inferiority margin of 10 percentage points 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 the 9–12-month age group seems low given our data. Studies assessing the effect of booster vaccinations will further inform policy decisions regarding yellow fever vaccine schedules.[25] There was little evidence of yellow fever transmission in Uganda and in central Kenya during the time of the trial,[26,27] but a dengue outbreak was reported in coastal Kenya during 2023,[28] which is known to raise antibodies cross-reactive to yellow fever virus.[29] This dengue outbreak could explain the higher GMTs at day 365 versus day 28 titres at the Kilifi site, where higher orthoflavivirus transmission was also observed, compared with Mbarara, based on baseline seropositivity for yellow fever (appendix p 12).

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

Previous studies in children reported that co-administration of measles and yellow fever vaccines was associated with reduced immunogenicity of the yellow fever vaccine.[30,31] However, some observational data suggested no significant immunological interference.[32] In this trial, yellow fever vaccine was co-administered with the MR vaccine so as to provide data relevant to current EPI schedules in which co-administration is the norm.

Post-vaccination viraemia was not observed in any of the trial participants; this was in contrast with the low frequency of viraemia observed in adults receiving the same vaccine doses and whose samples were collected at the same timepoints and assayed in the same WHO-accredited laboratory using the same RT-PCR method.[13] We are aware of no other studies that have assessed post-vaccination viraemia in infants receiving yellow fever vaccine. Further study is needed to understand the potential determinants for the absence of post-vaccination viraemia, including ruling out the effect of co-administration with other EPI vaccines, young age, and other factors. We did not identify any safety concerns in this trial, and none have been raised in previous trials of fractional doses in children or adults.[7–9,13,33] Further titrations of dose in children to establish minimum potency could be informed by both long-term data on antibody durability, and on modelling of antibody kinetics based on the totality of evidence acquired to date.

Limitations of our trial include testing in two east African populations, which might not generalise to other yellow fever endemic regions, and immunogenicity might vary in other parts of Africa, particularly given data showing lower immunogenicity in Ghana compared with Mali.[24] In addition, we did not measure antibody responses to the co-administered MR vaccine, precluding any analyses of statistical interactions in relation to the observed yellow fever vaccine immunogenicity. Our data relate to the 17D-204 vaccine sub-strain used by Institut Pasteur de Dakar, and other manufacturers might need to assess potency requirements for generalisability.

In summary, we find that evidence on minimum dosing from adults cannot be directly applied to infants. Infants might require higher vaccine doses for similar seroconversion rates. Although lower seroconversion with the 500 IU dose might be acceptable in certain outbreak settings with severe vaccine shortages, it is

unlikely to be suitable for routine EPI programmes in which adequate vaccine supplies are available.

Contributors

PB, GMW, AJ-G, RFG, and BO designed the study. DK, AJ-G, NSB, MLN, 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, and GMW accessed and verified all the data. DK, BO, AJ-G, and PB prepared the first draft of the manuscript. All authors had full access to the data and contributed to the interpretation of data, critically reviewed the manuscript, and had final responsibility for the decision to submit for publication.

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, and can be made available from the point of publication 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.

For the **KEMRI–Wellcome Trust Research Programme Research Data Repository** see https://dataverse.harvard.edu/dataverse/kwtrp

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