



Published in final edited form as:

Vaccine. 2026 February 27; 74: 128131. doi:10.1016/j.vaccine.2025.128131.

Adverse events following immunization (AEFI) with fractional one-fifth and one-half doses of yellow fever vaccine compared to standard dose in children 9–23 months old in Uganda, 2019–2022 — final report

Scarlett E. Lee^a, Marjorie Najjengo^b, Anna Shaum^a, Arthur B. Sekiziyivu^b, Grace Carlock^a, Rebecca M. Casey^a, Irene Lubega^b, Conrad Tumwine^b, Ellon Twinomuhwezi-Oyet^b, Winfred Nansozi Nakato^b, Courtney N. Sciarratta^a, Terri B. Hyde^a, Susan Y. Chu^a, Reena H. Doshi^a, Andrew Kambugu^b, Jane F. Gidudu^{a,*}

^aCenters for Diseases Control and Prevention, Atlanta, GA, USA

^bInfectious Diseases Institute, Kampala, Uganda

Abstract

Background: Lacking adequate safety data, the World Health Organization (WHO) recommends a full dose of yellow fever (YF) vaccine to children two years or younger. In older age groups in outbreak settings, the WHO recommends a fractional dose of YF due to vaccine shortages. Therefore, in children aged 9–23 months, we conducted a single-blind randomized controlled trial

*Corresponding author at: U.S. Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329, USA. bwv5@cdc.gov (J.F. Gidudu).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CDC Disclaimer

The opinions expressed in this article are the author's own and do not reflect the view of the Centers for Disease Control and Prevention, the Department of Health and Human Services, or the United States government.

CRediT authorship contribution statement

Scarlett E. Lee: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation. **Marjorie Najjengo:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation. **Anna Shaum:** Writing – review & editing, Visualization, Validation, Methodology. **Arthur B. Sekiziyivu:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation. **Grace Carlock:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Data curation. **Rebecca M. Casey:** Writing – review & editing, Data curation, Conceptualization. **Irene Lubega:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Conrad Tumwine:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Ellon Twinomuhwezi-Oyet:** Writing – review & editing, Validation, Supervision, Project administration. **Winfred Nansozi Nakato:** Writing – review & editing, Validation, Supervision, Project administration, Investigation. **Courtney N. Sciarratta:** Writing – review & editing, Software, Project administration. **Terri B. Hyde:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Susan Y. Chu:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Reena H. Doshi:** Writing – review & editing. **Andrew Kambugu:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation. **Jane F. Gidudu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry.

to compare the safety of fractional 1/2 and 1/5 doses of BioManguinhos 17DD YF vaccine with the full dose. This paper presents the final safety analysis for this trial.

Methods: At three study sites in Uganda, healthy children aged 9–23 months were recruited for inclusion. Data on adverse events following immunization (AEFI) was collected from March 26, 2019, to December 30, 2022, using active surveillance for 28 days post-vaccination. A diary card and a thermometer were used for the first 14 days post-vaccination. Serious adverse events (SAE) were investigated by an independent team from the Uganda AEFI committee.

Results: 1066 (60 %) of 1770 enrolled children reported at least one non-serious adverse event (NSAE), with the most reported events being fever 610 (34 %) and diarrhea 608 (34 %). Fever and diarrhea prevalence both peaked two days post-vaccination, and fever prevalence was statistically higher in the full dose group than either fractional dose group. Thirty (1.7 %) of participants reported a SAE, with no difference by study arm; this included three SAEs reported to be vaccine product-related by the causality committee. Although six deaths occurred during the study, none were causally associated with the vaccine.

Conclusions: Our study did not identify any unexpected safety issues with the YF fractional or full dose vaccine and Vaccine-related SAEs were rare. Although our study was not powered to identify associations for the safety outcomes monitored, our findings provide further evidence on the safety of YF fractional dosing in children aged 9–23 months ([NCT03725618](#)).

Keywords

Yellow fever; Fractional dose yellow fever vaccine; Fever; Adverse events following immunization (AEFI); Serious adverse event (SAE)

1. Introduction

Yellow fever (YF) virus is transmitted by mosquitos and causes an infection, which can result in an acute viral hemorrhagic fever. As of 2023, YF was endemic in 34 countries in Africa and 13 countries in Latin America [1]. The primary method of prevention for YF is vaccination with one of four prequalified YF vaccines containing an attenuated 17D strain. The World Health Organization (WHO) currently recommends a single dose of YF vaccine in children and adults aged nine months of age and older, which confers lifelong protective immunity against YF disease in most individuals. However, due to global supply shortages of the YF vaccine and large recurring outbreaks, the Strategic Advisory Group of Experts on Immunization (SAGE) in 2016 recommended the use of fractional 1/5 dosing of the YF vaccine in children aged 2 years or older in emergency situations as a dose sparing strategy [2]. For children two years of age and younger, SAGE currently recommends a standard dose of vaccine due to a lack of evidence on the immunogenicity and safety of fractional dosing.

Studies on fractional dosing of the yellow fever vaccine among children are limited [3]. Only a single study has evaluated the safety of fractional YF in children 9–59 months, which found a similar incidence of adverse events following a standard dose (80 %) and fractional (1/5) dose (73.3 %). In a sample of 420 participants, the most frequent events reported among children after receiving the fractional dose YF vaccine included upper respiratory

tract infections, diarrhea, rhinorrhea, and conjunctivitis [3]. However, in adult populations multiple studies and systematic reviews have found no differences in the incidence of studied adverse events following immunization (AEFI) between standard and fractional doses, but studies in adults lack standardization in AEFI reporting and are difficult to compare [4,5].

In order to provide comprehensive evidence on the use of fractional YF vaccines in children, we designed a single-blind randomized clinical trial comparing a standard dose (0.5 ml), one-half dose (0.25 ml) and one-fifth dose (0.1 ml) YF vaccine administered to Ugandan children aged 9–23 months. As part of the larger study looking at immunogenicity and safety, this paper presents the final safety data from the trial, including both pre-specified and unspecified AEFI reported using comprehensive active surveillance monitoring. Immunogenicity data will be published elsewhere. This paper builds upon the interim results that were previously published: among 1053 enrolled children, 672 (64 %) were reported to have a non-serious AEFI (NSAE) and 17 (2 %) were reported to have a serious adverse event (SAE) of which none were determined to be causally related to YF vaccination [6]. This paper includes an additional 717 children, tracked for YF related AEFI for the entire length of the study.

2. Methods

2.1. Study design and participants

We conducted a single-blind randomized clinical trial in Uganda comparing the safety of a standard dose, fractional one-half dose, and fractional one-fifth dose YF vaccine in children aged 9–23 months from March 26, 2019, to December 30, 2022. This trial was registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03725618) (NCT03725618). Full study details are described in the preliminary analysis [6]. Children were eligible for inclusion if they lived in the catchment area of the three study sites, which included three large public-sector health facilities that provide routine vaccination through the Ministry of Health of Uganda's Expanded Programme on Immunization. Exclusion criteria included plans to relocate or participate in another trial, previous YF disease or vaccination, contraindications to YF vaccination, history of receipt or planned receipt of another live attenuated vaccine, immunoglobulin or other blood derivatives within 28 days, and receipt of measles containing vaccine on the same day. Eligible children were randomized using block randomization to one of three vaccination groups: one-fifth fractional dose (0.1 ml), one-half fractional dose (0.25 ml) or standard dose (0.5 ml). A single dose of Bio-Manguinhos 17DD YF vaccine was administered subcutaneously.

2.2. Study visits and safety monitoring

A pharmacovigilance plan was created consistent with WHO guidelines on AEFI surveillance and standard operating procedure with comprehensive tools used to assess and prospectively monitor AEFI [7]. An adverse event was considered serious (i.e. a serious adverse event (SAE) if the event led to hospitalization or prolongation of existing hospitalization, persistent disability or incapacity, any life-threatening illness or death [8]. The thirteen pre-specified SAE included seizures, anaphylactic shock, cranial nerve

abnormalities, encephalitis/encephalopathy, myelitis, acute disseminated encephalomyelitis, Guillain-Barré Syndrome, renal failure, liver failure, rhabdomyolysis, septicaemia, and thrombocytopenia. All other adverse events occurring 0–28 days post-vaccination were classified as non-serious adverse events, which included these pre-specified conditions: fever, seizures, rashes, persistent crying for ≥ 3 h, local pain, local swelling, vomiting, diarrhea, bleeding, jaundice, lethargy, and obtundation. Unspecified conditions were also collected through free-text responses. Uganda's National AEFI committee for causality assessment investigated all SAEs, including any death regardless of time interval since vaccination. WHO methods for conducting causality assessment were utilized by the committee [9].

Following vaccination at the baseline visit, children were monitored by staff for one hour for any immediate AEFI. At the baseline visit, parents were given a diary card and a thermometer and instructed on how to measure and record the child's temperature and record any parent/caregiver conditions twice per day for two weeks after vaccination on the supplied diary card. At day 3 follow-up, study staff called parents/caregiver to document any AEFI and troubleshoot the diary card if needed. Week 2 (14–17 days) and 1-month (28–42 days) after vaccination follow-up visits occurred in person during which AEFIs reported on the diary card were confirmed and documented on corresponding AEFI reporting forms and entered into the electronic data system (Fig. 1).

2.3. Statistical analysis

Sample size calculations were not powered for detecting rare safety events, with details published elsewhere on sample size calculation for the immunogenicity study [6]. Safety data collected from the entire study, from March 26, 2019, to December 30, 2022, were included in this analysis. Immunogenicity data and detailed study methods will be published separately. Participants were included in the NSAE analysis if they completed any visits within 28 days of vaccination. We analysed each NSAE by days since vaccination. Deaths were reported at any time during the study timeline. R software, Version 4.4.0, (R Foundation for Statistical Computing) was used for all analyses. Chi-square test was used to compare proportion of participants.

2.4. Ethics approval

The study was sponsored by the U.S. Centers for Disease Control and Prevention (CDC). The protocol was approved by the Uganda Virus Research Institute Research & Ethics committee (UVRI REC) and the Uganda National Council for Science and Technology (UNCST) and the National Drug Authority. CDC staff did not have any contact with participants or access to their personal identifying information (PII); thus, CDC was not engaged by human subjects' research standards.

3. Results

3.1. Participants

Of 1872 children that were assessed for eligibility, including 11 that were re-screened, 1788 (96 %) participants were enrolled at baseline. A total of 1785 children were randomized and

received a YF vaccine. Prior to randomization, two children withdrew due to not having a blood draw, and one was not randomized because they had received another non-YF vaccine. 1752/1784 (98 %) of randomized children completed the week 2 visit and 1769/1784 (99 %) completed the diary card. Fourteen children withdrew from the study, including seven that were lost to follow-up and seven for whom the parents withdrew consent. Follow-up was completed at one month by 1752 children, while 18 additional participants did not complete follow-up at one month but did complete a later visit ($n = 1770$ children with follow up; 99 %) (Fig. 2). Additionally, one child was re-vaccinated from the one-half dose arm at the 12 month visit due to a lack of immune response to the first dose; this child was not excluded from the analysis as they did report an AEFI after the first dose, but not the second dose.

Of the 1770 children with follow up, 895 (50 %) were female, and the mean age was 14.2 months. Three participants reported controlled HIV infection or other chronic condition. History of first dose of pentavalent vaccine was 582 (99 %) and history of first dose of measles containing vaccine was 580 (98 %). No significant differences in baseline characteristics were reported across study arms (Table 1).

3.2. Non-serious adverse events

3.2.1. Solicited non-serious adverse events: In the first 28 days post-vaccination, there were 1999 solicited non serious adverse events (NSAE) across the three arms of the study among 1770 participants. Fever was the most common NSAE, reported by 610 (34 %) of children. Notably, 231 (39 %) 231 children in the standard dose arm reported fever while 32 % of the 1/2 (188) and 1/5 (191) dose arms reported fever in the first 28 days post vaccination (Table 2). The higher incidence of reported fever in the full-dose group compared to the 1/2 and 1/5 dose groups was statistically significant ($P = 0.007$). Notably, the largest difference between arms in fever incidence was observed on day two post vaccination with 18.5 % of standard-dose recipients reporting fever compared to 12.4 % of 1/5 dose and 11.2 % of 1/2 dose (Fig. 3). Reports of fever after day 3 were similar across all arms. Other commonly reported NSAEs were diarrhea 608 (34 %), rash 326 (18 %), and vomiting 256 (15 %). Diarrhea also displayed a peak at two days post-vaccination for all arms (18.2 % at day 2 and 1.4 % at day 28). None of the other solicited or unsolicited NSAEs were significantly different in frequency by arm at any time point.

3.2.2. Unsolicited non-serious adverse events: In addition to the solicited NSAEs, commonly reported unsolicited NSAEs among the 1770 participants in the first 28 days post immunization, included flu-like symptoms (250;14 %), cough (222; 13 %), and loose stool (104;6 %) (Supplementary table 1). Diarrhea was a solicited NSAE and was defined as three or more loose or watery stools in a 24-h period, as opposed to loose stools which was defined as fewer than three loose stools in a 24-h period. None of the unsolicited NSAEs were significantly different in frequency across arms at any time point. Additionally, no unsolicited NSAEs showed a temporal peak in incidence.

3.3. Serious adverse events

Among 1770 participants, 30 (1.7 %) SAEs were reported during the study, 14/597 (2.3 %) in the 1/5 arm, 6/598 (1.0 %) in the 1/2 arm and 10/585 (1.7 %) in the standard arm.

Twenty-five (83 %) of the 30 total SAEs occurred within 50 days of vaccination and 3 (11 %) were determined to be product-related (Fig. 4). The three vaccine product-related SAEs were febrile seizures in the 1/5 arm 17 days after vaccination, type 1 hypersensitivity skin reaction one day after vaccination in the 1/2 dose arm, and febrile seizures one day after vaccination in the full dose arm. Additionally, one serious febrile seizure in the full dose arm one day post-vaccination was determined to be indeterminately linked to yellow fever vaccination due to a consistent temporal link but no definitive evidence for the vaccine causing febrile convulsions. Further, there were five SAEs with final diagnosis of malaria or cerebral malaria during the study, all deemed coincidental by causality assessment (Table 3).

None of the deaths reported during the study were deemed to be vaccine-related by causality assessment. Two deaths occurred within 50 days of vaccination, including one death at 20 days post-vaccination due to an acute febrile illness that did not undergo causality assessment because the causality committee could not access the patient or the caretakers and another death at 43 days post-vaccination due to a non-accidental injury. Additional deaths during the duration of the study included a death at 138 days deemed coincidental by the causality committee, a death at 353 days due to a fall from a height, a death at 283 days deemed coincidental, and a death at 665 days for which no causality assessment was completed due to parental decline.

4. Discussion

Our paper presents the largest study to date evaluating the safety of the use of fractional doses of YF vaccine among children aged 9–23 months and provides further reassuring evidence on the safety of fractional dosing of YF vaccine in children. This is the first trial in children to assess the safety of fractional dose Bio-Manguinhos 17DD Yellow Fever vaccine. At this time, the vaccine is considered the best candidate vaccine for fractional dosing given the prior studies conducted, including in the Democratic Republic of the Congo, as well as its high potency [10,11].

Compared to the interim safety data for this trial, this final analysis includes 717 more children and includes three occurrences of SAEs determined to be vaccine-related and two additional deaths not included in the original report. Additionally, we present a temporal analysis of both NSAE and SAE prevalence as compared to time post-vaccination. Although our study found a high incidence of solicited NSAEs (1999 events in 1770 participants), with 60 % (1066/1770) of children reporting at least one solicited NSAE event, this incidence is similar to what was reported in the interim data for this trial (64 %), as well as the literature for fractional and full dose YF vaccine dosing in adults (48–63 %) and children receiving full dose YF vaccine in Peru (59.8 %) [6,12,13]. The most common solicited NSAEs reported both in this analysis and in the interim analysis were fever (34 % final, 33 % interim) and diarrhea (34 % final, 34 % interim), which are common events seen in this age group in sub-Saharan Africa. SAE incidence in our trial (1.7 %) was similar to the interim report (2 %) and no difference was reported across arms in the occurrence of SAEs. Increased frequency of reporting of AEFIs is not inherently related to the safety of the vaccine, and studies with active AEFI surveillance may report more AEFIs than studies with passive surveillance [14,15].

Since the publication of the interim analysis for this fractional YF trial, only one other clinical trial has published results on the use of fractional YF vaccine in children less than two years of age [3]. A 2019 clinical trial (YEFE trial) enrolled 420 children in Uganda under the age of two equally divided between the standard and fractional (1/5) dose arms with safety outcomes collected 30 min after vaccination and two clinical visits 10 and 28 days post vaccination during medical visits [3]. No major differences were found in the incidence of AEFIs between the standard (80 %) and fractional (73 %) dose arms and the most common AEFIs including upper respiratory tract infections (51 % in fractional and 54.3 % in standard), diarrhea (11 % in both arms), rhinorrhea (10.5 % in fractional and 12.19 % in standard), rash-papular (6.2 % in fractional and 10.5 % in standard), and conjunctivitis (8.1 % in fractional and 5.2 % in standard). Our trial used active surveillance, including the use of a diary card and thermometer for the first two weeks post vaccination, with solicited AEFI events established prior to the trial, which may explain the increased incidence of fever and diarrhea in our trial compared to the passive surveillance used in the YEFE trial. Compared to a trial of two full dose YF vaccines (17D-213 YF vaccine) in children aged 9 months to 10 years in Peru, our trial reported more cases of diarrhea (34 % in our trial vs. 10.8 % and 12.3 % in YEFE trial), but similar prevalence of fever (34 % in our trial vs 26.7 % and 26.6 % in YEFE trial). A possible reason for the difference in diarrhea prevalence may be a higher baseline prevalence in Uganda and the younger age group in our trial [16–18]. Given the prevalence of respiratory NSAEs in both the YEFE trial and our unsolicited AEFI, future fYF trials in children should consider including this as a solicited event. However, our analysis found no temporal relationship between respiratory or flu-like symptoms and receipt of vaccine as compared to diarrhea and fever, which both displayed a peak in prevalence two days post vaccination.

The YEFE trial also reported a higher incidence of SAEs (30/420; 7.1 %) than in our trial (28/1770; 1.6 %), although none were classified as related to the study vaccine. In our trial, three SAEs were classified as vaccine product-related. Two deaths occurred within 50 days of receipt of vaccination, including one death due to an acute febrile illness that presented like viscerotropic disease that occurred 20 days after YF vaccination, which is outside the usual expected time (within 1 week) for viscerotropic disease related to YF vaccination. Comparing causality assessment across post-marketing trials can be challenging, as some trials (like ours) implemented WHO methods for assessing causality through an independent committee, while other studies (like the YEFE trial) relied on investigator decision alone. Standardizing causality assessment in post-marketing data in the future is essential as more LMICs develop expert independent committees for causality assessment [19,20].

Our analysis found a temporal relationship between the two most prevalent NSAEs, fever and diarrhea, and receipt of vaccination, with a clear peak for both two days after receiving a YF vaccine. Since parents were recording symptoms using a diary card, our trial may have been able to provide superior temporal evidence of NSAEs compared to prior trials. Although this peak may have been a result of the Day 3 call eliciting greater recall on that day post-vaccination, however, this peak was not found for any of the other solicited or unsolicited NSAEs. Our trial also found a significant difference in fever prevalence in the full dose compared to either fractional dose arm both at Day 2 and overall. Immunologic studies indicate a peak of genes responsible for innate pro-inflammatory immune function

at day 1 but not 3 days after live YF vaccination in adults; however similar studies have not been performed in children and studies in adults have not found a correlation between probable AEs and immunogenicity [21–23]. The higher fever prevalence in the full dose arm may be due to the dose effect of increased YF antigen, possibly detected in our study due to rigorous use of the diary card and that thermometers were provided to the families of study participants. Future studies on YF vaccines should consider using our methods of diary card recordings and thermometers for better detection of AEFIs post vaccination, including properly training caregivers to use thermometers in the home setting.

5. Limitations

Limitations of our study include that the study was powered to detect differences in immunogenicity rather than safety outcomes, which require larger samples due to the rarity of each individual AEFI. Our safety data largely relied on the diary card reporting of parents/caregivers rather than medical professionals which may have impacted data reliability. These limitations reflect the challenges of post marketing vaccine safety studies in resource limited settings without electronic health records to verify health outcomes. Additionally, the population in this study may not be a representative sample since the children in the study are healthy and had prior routine immunization as well as low prevalence of chronic conditions and HIV.

6. Conclusion

Our results provide further reassuring evidence on the safety of fractional dosing of YF vaccine. Vaccine-related serious events were rare among our cohort, and no difference was observed across arms for NSAE, excluding fever, which revealed a higher percentage in the standard dosing arm. Future studies on fYF should evaluate safety as a primary endpoint using active surveillance methods and standardized causality assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank the study participants, the study team, Uganda Ministry of Health and Expanded Programme on Immunization, the Makerere Infectious Disease Institute, Uganda Adverse Events Following Immunization Committee and Chair, Uganda Virus Research Institute and Uganda National Drug Authority.

Funding

The study was sponsored by the U.S. Centers for Disease Control and Prevention (CDC).

Data availability

The data that has been used is confidential.

Appendix A.: Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2025.128131>.

References

- [1]. World Health Organization. Yellow fever [Internet] [cited. 10]; Available from, <https://www.who.int/news-room/fact-sheets/detail/yellow-fever>; 2025 Feb.
- [2]. WHO Team Communicable Diseases DCiHE. Global yellow fever update, 2019. *Wkly Epidemiol Rec* 2020;34(95):393–408.
- [3]. Juan-Giner A, Namulwana ML, Kimathi D, Grantz KH, Fall G, Dia M, et al. Immunogenicity and safety of fractional doses of 17D-213 yellow fever vaccine in children (YEFE): a randomised, double-blind, non-inferiority substudy of a phase 4 trial. *Lancet Infect Dis* 2023;23(8):965–73. [PubMed: 37127047]
- [4]. Hansen CA, Staples JE, Barrett ADT. Fractional dosing of yellow fever live attenuated 17D vaccine: a perspective. *Infect Drug Resist* 2023;16:7141–54. [PubMed: 38023411]
- [5]. Nnaji CA, Shey MS, Adetokunboh OO, Wiysonge CS. Immunogenicity and safety of fractional dose yellow fever vaccination: a systematic review and meta-analysis. *Vaccine* 2020;38(6):1291–301. [PubMed: 31859201]
- [6]. Casey RM, Najjengo MS, Lubega I, Sekiziyivu AB, Twinomuhwezi-Oyet E, Nakato WN, et al. Adverse events following immunization (AEFI) with fractional one-fifth and one-half doses of yellow fever vaccine compared to full dose in children 9–23 months old in Uganda, 2019–2020 - preliminary report. *Vaccine* 2024;42(22):126197. [PubMed: 39153293]
- [7]. Organization WHO. Global manual on surveillance of adverse events following immunization. 2016.
- [8]. MODULE 3. Adverse events following immunization - WHO Vaccine Safety Basics E-learning course [Internet] [cited. 10]; Available from, <https://vaccine-safety-training.org/overview-and-outcomes-3.html>; 2025 Feb.
- [9]. Pharmacovigilance WT. Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification, 2nd ed., 2019 update. Edited by Organization WH 2021:88.
- [10]. Doshi RH, Mukadi PK, Casey RM, Kizito GM, Gao H, Nguete UB, et al. 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. *Lancet Infect Dis* 2024;24(6):611–8. [PubMed: 38335976]
- [11]. Casey RM, Harris JB, Ahuka-Mundeke S, Dixon MG, Kizito GM, Nsele PM, et al. Immunogenicity of fractional-dose vaccine during a yellow fever outbreak - final report. *N Engl J Med* 2019;381(5):444–54. [PubMed: 29443626]
- [12]. Juan-Giner A, Kimathi D, Grantz KH, Hamaluba M, Kazooba P, Njuguna P, et al. Immunogenicity and safety of fractional doses of yellow fever vaccines: a randomised, double-blind, non-inferiority trial. *Lancet* 2021;397(10269):119–27. [PubMed: 33422245]
- [13]. Belmusto-Worn VE, Sanchez JL, McCarthy K, Nichols R, Bautista CT, Magill AJ, et al. Randomized, double-blind, phase III, pivotal field trial of the comparative immunogenicity, safety, and tolerability of two yellow fever 17D vaccines (Arilvax and YF-VAX) in healthy infants and children in Peru. *Am J Trop Med Hyg* 2005;72(2):189–97. [PubMed: 15741556]
- [14]. BATTERY JP, Clothier H. Information systems for vaccine safety surveillance. *Hum Vaccin Immunother* 2022;18(6):2100173. [PubMed: 36162040]
- [15]. Isaacs D, Lawrence G, Boyd I, Ronaldson K, McEwen J. Reporting of adverse events following immunization in Australia. *J Paediatr Child Health* 2005;41(4):163–6. [PubMed: 15813867]
- [16]. Omona S, Malinga GM, Opoke R, Openy G, Opiro R. Prevalence of diarrhoea and associated risk factors among children under five years old in Pader District, northern Uganda. *BMC Infect Dis* 2020;20(1):37. [PubMed: 31931735]

- [17]. Nantege R, Kajoba D, Ddamulira C, Ndoboli F, Ndungutse D. Prevalence and factors associated with diarrheal diseases among children below five years in selected slum settlements in Entebbe municipality, Wakiso district, Uganda. *BMC Pediatr* 2022;22(1):394. [PubMed: 35799163]
- [18]. Auma B, Musinguzi M, Ojuka E, Kigongo E, Tumwesigye R, Acup W, et al. Prevalence of diarrhea and water sanitation and hygiene (WASH) associated factors among children under five years in Lira City northern Uganda: community based study. *PloS One* 2024;19(6):e0305054. [PubMed: 38848329]
- [19]. Blau EF, Balakrishnan MR, Skold H, Santhana Gopala Krishnan RS, Lundquist P, pal S, Gidudu JF: Progress in immunization safety monitoring - worldwide, 2020–2022. *MMWR Morb Mortal Wkly Rep* 2023;72(49):1321–6. [PubMed: 38060432]
- [20]. Organization WH. Global vaccine safety blueprint. In. Edited by Immunization VaB: WHO Press; 2012.
- [21]. Chan CY, Chan KR, Chua CJ, Nur Hazirah S, Ghosh S, Ooi EE, et al. Early molecular correlates of adverse events following yellow fever vaccination. *JCI. Insight* 2017;2(19).
- [22]. Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F: the how's and what's of vaccine reactogenicity. *NPJ Vaccines* 2019;4:39. [PubMed: 31583123]
- [23]. Chan KR, Wang X, Saron WAA, Gan ES, Tan HC, Mok DZL, et al. Cross-reactive antibodies enhance live attenuated virus infection for increased immunogenicity. *Nat Microbiol* 2016;1(12):16164. [PubMed: 27642668]

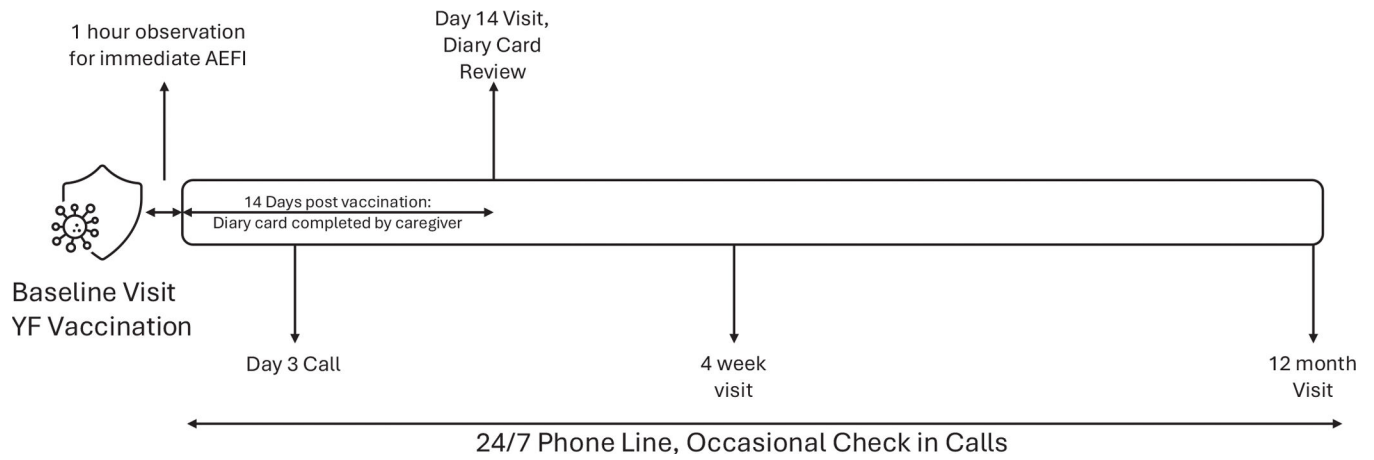


Fig. 1.
Timeline of safety monitoring during fYF trial, Uganda, 2019–2022.

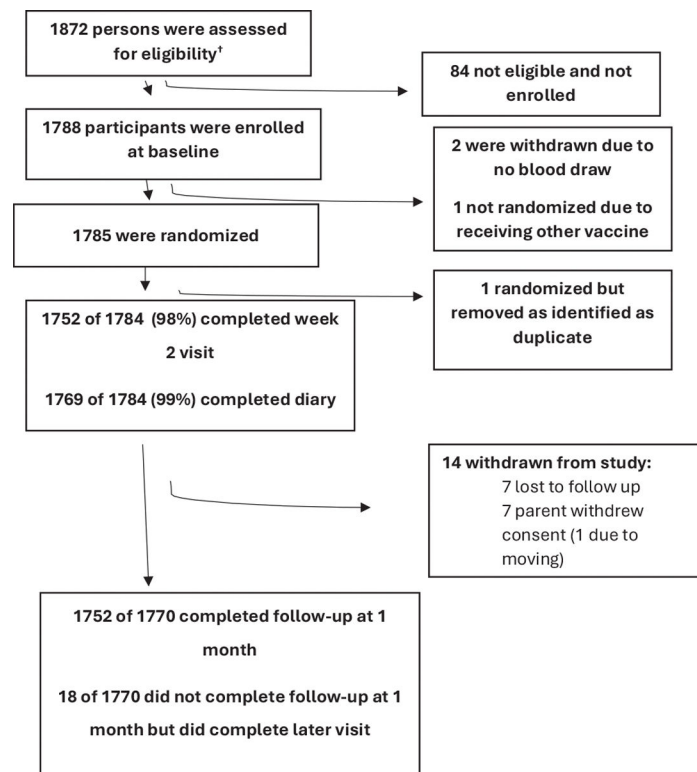


Fig. 2.
Enrollment and follow up of study participants, fYF trial, Uganda, 2019–2022.

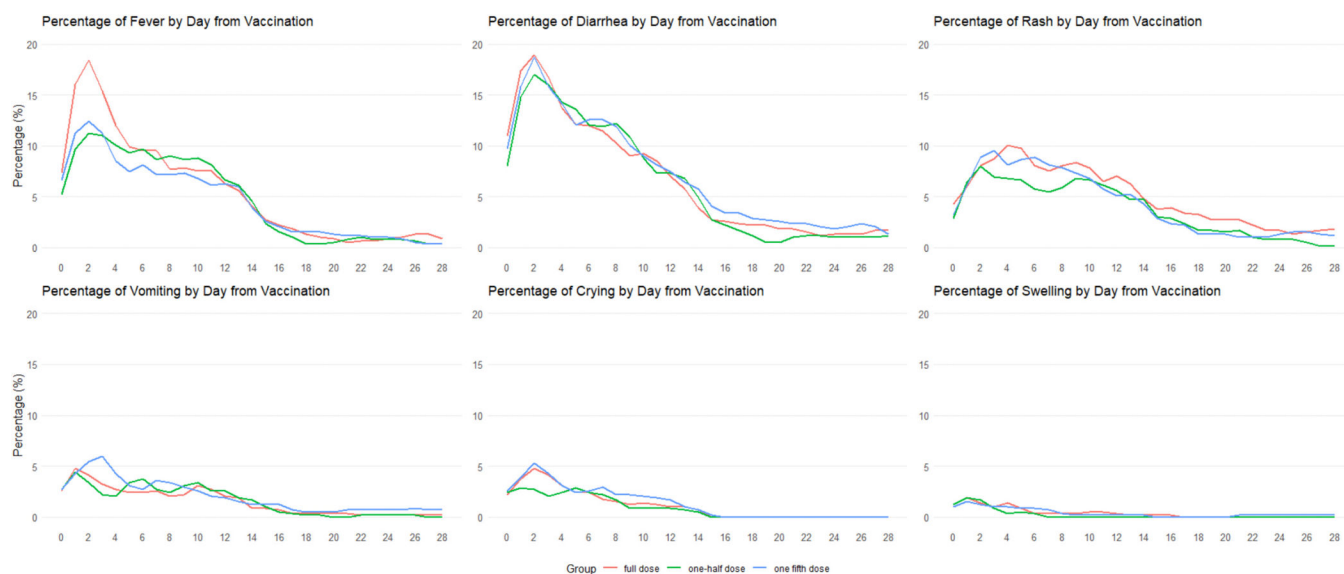


Fig. 3.
Incidence of most common solicited Nonserious adverse events (NSAEs) by arm from 0 to 28 days post vaccination, fYF trial, Uganda, 2019–2022.

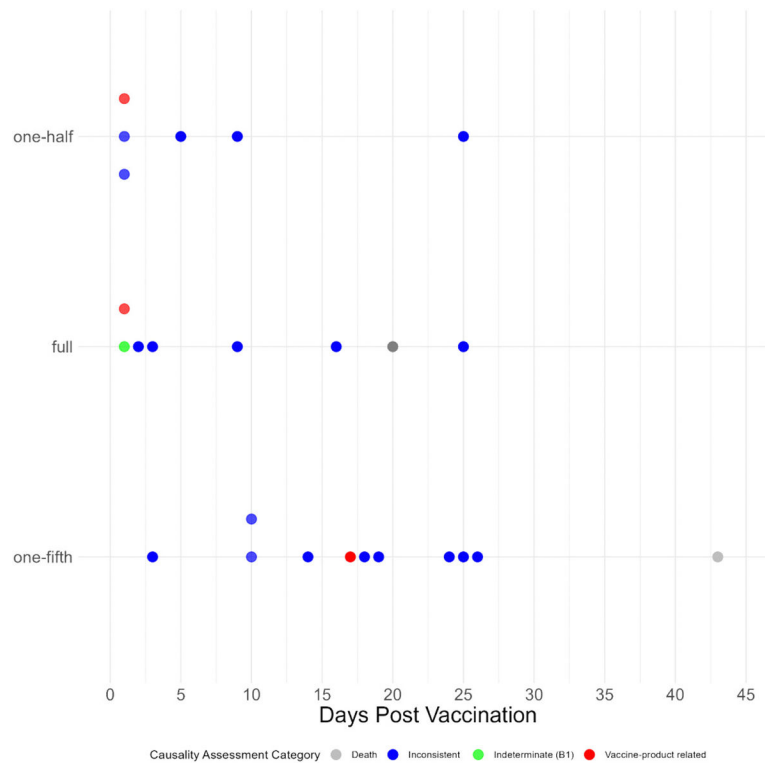


Fig. 4. Distribution of serious adverse events (SAE) by study arm and days post vaccination characterized by causality assessment category, fYF trial, Uganda, 2019–2022.

Table 1

Baseline Characteristics of Participants presented as counts with percentages in parentheses, fYF trial, Uganda, 2019–2022

	Dose arm (number of participants)		
	1/5 (n = 597)	½ (n = 588)	Standard (n = 585)
Characteristic	Number of participants (percent)		
Female	294 (49)	306 (52)	295 (50)
HIV infection	0 (0)	2 (<1)	1 (<1)
Chronic Condition	0 (0)	1 (<1)	2 (<1)
History of receipt of first dose pentavalent * vaccination	596 (100)	586 (100)	582 (99)
History of receipt of first dose measles-containing vaccination	583 (98)	580 (99)	580 (99)

* Pentavalent vaccine containing Diphtheria, Pertussis, Tetanus, Hepatitis B, and *Haemophilus influenzae* type b.

Table 2

Solicited non-serious adverse events count (percentage) by study arm from days 0–28 post vaccination with YF vaccine, fYF trial, Uganda, 2019–2022.

	Dose arm (number of participants)				p-value *
	1/5 (n = 597)	1/2 (n = 588)	Standard (n = 585)	All (n = 1770)	
Symptom	Number of participants reporting symptom (percent)				
Fever	191 (32)	188 (32)	231 (39)	610 (34)	0.007
Diarrhea	207 (35)	200 (34)	201 (34)	608 (34)	0.97
Rash	106 (17)	103 (18)	117 (20)	326 (18)	0.48
Vomiting	89 (15)	83 (14)	86 (15)	256 (15)	0.97
Continuous Crying	56 (9)	44 (7)	45 (8)	145 (8)	0.42
Localized Swelling	18 (3)	13 (2)	21 (4)	52 (3)	0.37
Jaundice	0 (0)	0 (0)	1 (<1)	1 (<1)	0.36
Abscess	0 (0)	1 (<1)	0 (0)	1 (<1)	0.36

* Chi-square test.

Table 3

List of serious adverse events and causality assessment findings, fYF trial, Uganda, 2019–2022.

Dose arm	Description of serious adverse event (SAE)	Final diagnosis	Day post-yellow fever vaccination	AEFI Causality Assessment following review by national AEFI Committee
1/5	Malaria and respiratory tract infection	Malaria	25	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine. Had malaria parasites on blood slide.
1/5	Death	Death	138	Coincidental Underlying or emerging condition(s) or condition(s) caused by exposure to something other than vaccine
1/5	Death	Death	665	Case investigation was not done and no causality assessment was performed since study team was not able to get in touch with the parents
1/5	Malaria	Malaria	18	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine.
1/5	Severe pneumonia, acute gastroenteritis	Severe pneumonia	20	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine. Had pneumonia complicating acute Upper Respiratory Tract Infection
1/5	Febrile seizures	Possible encephalitis	10	Coincidental, underlying, or emerging conditions. Many CNS infections, especially viruses, may cause symptoms of encephalitis.
1/5	Moderate pneumonia, fever, diarrhea	Febrile seizure	19	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine.
1/5	Afebrile seizure	Seizure disorder	3	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine. History of the event not fully obtained. The child was under the care of someone other than parent or grandparent. Was reported to have recovered completely.
1/5	Acute viral infection associated with febrile seizure	Febrile seizure	24	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine.
1/5	Febrile seizures	Seizure	17	Vaccine product related. No prior history of seizure, no fever, no other factor recognizable. Seizure occurred within the expected window of 4–23 days of receiving the vaccine
1/5	Sepsis from generalized skin infection	Steven Johnson's Syndrome (SJS)	221	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine. Had more recently received MR vaccine, which is more frequently associated with SJS.
1/5	Acute watery diarrhea	Acute diarrhea	14	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine.
1/5	Death	Death	43	Causality assessment not done because the investigating team did not get all the necessary information, including the death certificate. However, the history available is suggestive of non – accidental injury
1/5	Superficial burns	Burns	26	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine.
1/2	Asthma/allergic cough	Bronchiolitis	25	Inconsistent causal association / Coincidental. Bronchiolitis was most likely caused by an agent other than the vaccine
1/2	Severe malaria and bacteremia, conjunctivitis	Malaria	1	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine. Had malaria parasites on blood slide.
1/2	Bacterial infection	Upper respiratory tract infection	5	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine. Had Acute Upper Respiratory Tract Infection.
1/2	Seizures	Seizure Disorder	9	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine. Had a previous history of afebrile seizures.

Dose arm	Description of serious adverse event (SAE)	Final diagnosis	Day post-yellow fever vaccination	AEFI Causality Assessment following review by national AEFI Committee
1/2	Viral infection, afebrile seizures	Type 1 hypersensitivity skin reaction	1	Vaccine product related. Type 1 Hypersensitivity. Occurred within 1 h of receiving the vaccine.
1/2	Malaria, Upper Respiratory Tract Infection	Papular Urticaria	1	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine. There are many commoner causes of Urticaria, including insect stings, foods, and drugs
Full	Seizure	Febrile Seizure	1	Indeterminate. Though there was a consistent temporal relation with vaccination, there is no definitive evidence for the vaccine causing febrile convulsions
Full	Death	Death	20	Causality assessment not done since the team did not access the patient or the caretakers. However, the symptoms reported are of an acute febrile illness similar to viscerotropic disease which is a rare complication of Yellow fever vaccine. However, this death occurred 20 days after YF vaccination, outside the usual expected time (within 1 week) for viscerotropic disease.
Full	Febrile seizures	Possible encephalitis	3	Coincidental, underlying or emerging conditions. There are many other cause symptoms of encephalitis.
Full	Acute watery diarrhea associated with seizures	Febrile Seizure	2	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine. Occur in 4 % of the under-five children.
Full	Febrile seizures	Febrile Seizure	1	Vaccine product related. Seizures had a close temporal relation with the vaccine administration, with no other identified cause of fever.
Full	Death following a fall from a height	Death	353	Causality assessment was not done because the father declined. However, it is obvious the child died after a fall from a height, a cause unrelated to the Yellow fever vaccine.
Full	Pneumonia, seizure	Febrile seizure	16	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine. Had previous seizures with fever. The fever occurred on day 16 after vaccination as opposed to 5.
Full	Severe malaria, febrile	Cerebral malaria	9	Inconsistent causal association to immunization; Coincidental/underlying condition.
Full	Sudden unexpected death in childhood	Death	283	Coincidental, underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine
Full	Acute Gastroenteritis with Septicemia	Acute Diarrhea	25	Coincidental, underlying or emerging condition(s) caused by exposure to something other than the vaccine.