



Published in final edited form as:

Vaccine. 2024 September 17; 42(22): 126197. doi:10.1016/j.vaccine.2024.126197.

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

Rebecca M. Casey^{a,*}, Marjorie Sserunga Najjengo^b, Irene Lubega^b, Arthur B. Sekiziyivu^b, Ellon Twinomuhwezi-Oyet^b, Winfred Nansozi Nakato^b, Courtney N. Sciarratta^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: In 2016, the World Health Organization recommended that a fractional dose of yellow fever (YF) vaccine could be used in persons 2 years of age or older in response to an emergency that resulted in a global shortage of available YF vaccine. However, this recommendation did not extend to the youngest age group licensed for YF vaccine because there were no published data on the use or safety of fractional dose YF vaccination in children aged 9–23 months. We conducted a single-blind randomized controlled trial, comparing the

*Corresponding author at: U.S. Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329, USA. lyn6@cdc.gov (R.M. Casey).

Authors' contributions

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Ethical approval

The protocol was approved by the Uganda Virus Research Institute Ethics Committee and the Uganda National Council for Science and Technology. 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.

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.

CRedit authorship contribution statement

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

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.

immunogenicity and safety of fractional one-fifth and one-half doses of Bio-Manguinhos 17DD YF vaccine with full dose in children aged 9–23 months old in Uganda. In this paper, we present the interim analysis on safety.

Methods: Children aged 9–23 months presenting for routine well-child services were recruited for inclusion at one of three study sites. We collected data during March 26, 2019–August 31, 2020, on all adverse events following immunization (AEFI) during active surveillance for 28 days post-vaccination using multiple collection tools including a diary card with an objective measurement of fever. An independent team from the Uganda national AEFI Committee investigated and classified serious AEFI (SAE) according to Brighton Collaboration Criteria.

Results: Among 1053 enrolled children, 672 (64%) were reported to have a non-serious AEFI (NSAE) and 17 (2%) were reported to have a SAE. The most common AEFI were diarrhoea, fever, and rash, each reported by 355 (34%), 338 (33%), and 188 (18%) participants, respectively. Among 17 participants with SAE, eight were reported to have had seizures and five were hospitalised for seizures or other causes (respiratory symptoms, gastrointestinal illness, malaria). Four SAEs (deaths) occurred >28 days after vaccination. There were no reported cases of pre-specified or vaccine-related SAEs. We observed no significant difference in frequency or severity of adverse events among the study groups.

Conclusions: Using comprehensive active surveillance monitoring, we did not identify any unexpected safety concerns among children aged <2 years receiving YF vaccination, including with the fractional doses. Although we identified a high number of both serious and non-serious AEFI, none were determined to be causally related to YF vaccination. These results provide evidence for the safety of fractional dose YF vaccination among children aged 9–23 months.

Keywords

Yellow fever vaccination; Adverse events following immunization; AEFI; SAE; Prospective active surveillance; Fractional dose yellow fever vaccination; Uganda

1. Introduction

Yellow fever (YF) virus is estimated to cause 200,000 cases of disease and 30,000 deaths globally each year, with 90% occurring in Africa [1]. Vaccination with one of the four World Health Organization (WHO) prequalified live attenuated YF virus vaccines derived from the 17D strain is the most effective way of preventing YF and a single full (0.5 ml) dose of YF vaccine provides long-lasting protection evidenced by the detection of neutralizing antibodies and memory T cells, up to 60 years following vaccination and probably for life [2–4]. WHO recommends routine YF vaccination for all people aged ≥9 months in endemic countries as well as mass vaccination campaigns for YF prevention and control. Over half a billion doses of the 17D vaccine have been successfully used worldwide since its introduction >90 years ago, and the vaccine is considered safe and effective [3].

In recent years large YF outbreaks in central Africa and elsewhere precipitously exhausted the global supply of YF vaccine [5]. This put many populations at risk and increased the potential for international spread. Due to the global vaccine shortage to respond to YF outbreaks and based on the available efficacy and safety evidence from three clinical trials

on fractional doses [6–9], the World Health Organization (WHO) recommended in 2016 that a fractional dose of YF vaccine should be considered in adults and children ≥ 2 years of age during outbreak response when the current vaccine supply is insufficient [5]. However, data on the safety of the fractional dose are limited. Of the available data considered for the WHO fractional dose recommendation, all were in persons ≥ 2 years of age, and only one of the four papers included an assessment of safety of a fractional dose administered via the usual subcutaneous route, with follow-up limited to 3–10 days. Since there was a lack of published data for the efficacy and safety of the fractional dose YF vaccines in children < 2 years of age, this age group was still recommended to receive the full-dose YF vaccination. Therefore, WHO advised that studies on the safety and reactogenicity of the fractional and full-dose YF vaccine among children aged 9–23 months are a research priority.

Adverse events following immunization (AEFI) with YF vaccination are usually mild, such as headache, myalgia and low-grade fever [5,10]. Serious adverse events (SAE) related to YF vaccination are rare, including YF vaccine-associated viscerotropic disease (YEL-AVD) (0.25–0.4 cases per 100,000 vaccine doses) and YF vaccine-associated neurotropic disease (YEL-AND) (0.25–0.8 cases per 100,000 vaccine doses) [3,11–14]. Severe hypersensitivity reactions, like anaphylaxis, are estimated to occur in 0.8 per 100,000 vaccinations [3]. Within the limited study data available [6,15,16], there were no differences in reported minor adverse effects following vaccination with full and fractional YF vaccine doses. However, much of the assumption about the safety of the fractional dose YF vaccination has been based on passive surveillance in campaign settings. During a fractional dose campaign of ~ 7.9 million non-pregnant persons aged ≥ 2 years in the Democratic Republic of the Congo, no safety signals were identified by passive surveillance.

We conducted a randomized clinical trial comparing the full dose (0.5 ml) vs. fractional dose of one-half (0.25 ml) and one-fifth dose (0.1 ml) of YF vaccination in children aged 9–23 months in Uganda. In this paper, we present interim data on the safety profile of the fractional and full dose YF 17DD vaccine in children aged 9–23 months. We created a robust pharmacovigilance plan consistent with WHO guidelines on AEFI surveillance and these data add to the extensive track record on the safety of YF vaccine. The safety profile is described for both pre-specified and unspecified AEFI.

2. Methods

2.1. Study participants and design

We conducted a single-blind randomized controlled trial comparing the safety of fractional one-fifth and one-half doses of Bio-Manguinhos 17DD YF vaccine with full dose in children aged 9–23 months old in Uganda. Uganda was chosen as the study location because YF vaccination was not yet introduced into this country's routine immunization program. Three vaccination sites (two urban, one rural) were selected to capture economically diverse catchment populations and for logistic feasibility. These three large health facilities provide other routine vaccinations through the Ministry of Health of Uganda's Expanded Programme on Immunization. Beginning on March 26, 2019, we approached caregivers of children aged 9–23 months presenting for routine well-child services for potential inclusion in the study. Healthy children living in the catchment area were eligible for inclusion

unless they reported 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. Children with asymptomatic HIV infection were eligible unless there was a record of a blood test demonstrating a CD4+ T-lymphocyte count lower than 26% of total lymphocytes on their medical record. We excluded children who received rubella-containing vaccine on the same day, based on the potential for interference with immunological response [17]. Parents or caregivers provided verbal consent for basic initial screening, and we also obtained written informed consent for more in-depth second screening and enrolment. If the parent or caregiver was illiterate, we conducted the consent procedures verbally in the presence of a literate witness.

2.2. Study oversight

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 Ethics Committee and the Uganda National Council for Science and Technology. 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.

2.3. Baseline visit and vaccination

Demographic characteristics and general health information, including vaccination history, were collected for each participant. A medical doctor examined the study participants, and if the physical examination was abnormal, the child was referred to the paediatric clinic for further evaluation. The findings from the paediatric assessment were used to determine whether the child could be included in the study.

Enrolled children were randomly assigned to one of three vaccination groups to receive the Bio-Manguinhos 17DD YF vaccine administered subcutaneously: one-fifth fractional dose (0.1 ml), one-half fractional dose (0.25 ml) or full dose (0.5 ml). We performed randomization by block randomization using computer-generated random numbers with individual assignments placed in sealed and numbered envelopes. The envelopes were opened sequentially for each child enrolled. The parent/caregiver did not know the dose given. Study staff members administered a subcutaneous dose of the 17DD YF vaccine according to the assigned dose from Lot 184VFA027A. According to vaccine potency data, one fifth of a dose of the batch had 3388 IU per dose, which is above the minimum vaccine potency (1000 IU per dose) set by the WHO [18].

Following vaccination, staff monitored the children for 1 h for any immediate AEFI. Emergency adrenaline kits were available to treat anaphylaxis. During the observation period, the staff also trained the parent/caregiver on the completion of a standardized diary card to record the presence, onset, and duration of any symptoms and how to measure and record the child's temperature twice per day for two weeks after vaccination. Parents/caregivers received detailed instructions on how to use the provided thermometer for taking and recording temperatures. The pre-specified symptoms and signs included generalized conditions (fever, seizures, rashes, persistent crying for ≥ 3 h), local reactions

(pain, swelling), gastrointestinal symptoms (vomiting, diarrhoea), bleeding, jaundice, or neurological changes (lethargy, obtundation). Parents/caregivers also received a study participation card with a 24-h continuously monitored study telephone line in case of questions or to report any AEFI.

2.4. Follow-up procedures

We collected the data by phone and in-person visits on all illnesses encountered by the study participants during the first 28 days post-vaccination.

First, three days (day 3 follow-up) after the enrolment visit, study staff called parents/caregivers to answer any outstanding questions, document the presence of AEFI and troubleshoot any challenges with using the diary card or thermometer.

Next, in-person visits took place at 14–17 days (week 2 follow-up) and 28–42 days (1-month follow-up) after vaccination. During these visits, the detailed data regarding AEFIs were collected including onset and duration of symptoms. Children had a physical examination at the health centre, and parents/caregivers answered questions about the period since their last visit including the receipt of medical care and other vaccinations. Study staff reminded parents/caregivers about their scheduled follow-up by telephone before each visit date.

We developed standard operating procedures for diagnostic work-up and clinical management of potential AEFI and conducted active monitoring of AEFI, using Brighton Collaboration Criteria [19] and WHO guidelines for YF AEFI surveillance [20]. Study staff received training in AEFI diagnostic and management procedures. We collected additional data about the participants who had an AEFI regarding the presenting complaint(s), other symptoms, duration, management, and outcome. An SAE was defined as hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, seizures, or any life-threatening illness including a list of pre-specified conditions (anaphylactic shock, cranial nerve abnormalities, encephalitis/encephalopathy, myelitis, acute disseminated encephalomyelitis, Guillain-Barré Syndrome, renal failure, liver failure, rhabdomyolysis, septicaemia, thrombocytopenia) occurring within 0–28 days post-vaccination. A non-serious adverse event (NSAE) was defined as any other adverse event occurring 0–28 days post-vaccination. All SAEs were investigated, including any death regardless of time interval since vaccination, by an independent investigation team, and included medical record review using standardized chart abstraction forms followed by review by the national AEFI Committee for causality assessment.

2.5. Statistical analysis

We conducted the AEFI evaluation concurrently with the immunogenicity evaluation and included the data collected from March 26, 2019–August 31, 2020. Data collected using paper forms at the study sites were scanned and securely faxed to a central DataFax server at the Infectious Disease Institute (IDI) in Kampala. We used R software, version 3.6.2 (R Foundation for Statistical Computing) for descriptive analysis and determined means and ranges for continuous variables. We summarized categorical variables as counts and

percentages and compared the proportion of participants with AEFI according to the dosing group using Chi-square and Fisher's exact tests. No imputation was made for missing data.

2.6. Sample size

The sample size was calculated based on the immunogenicity evaluation. We determined that a sample size of 596 per arm would provide 90% power (with alpha 0.05) to conclude non-inferiority with a 5% margin in seroconversion among fractional YF vaccine recipients compared to full dose recipients when the true seroconversion proportions are the same in the two arms. This was based on an estimated rate of seroconversion of 93% and an attrition rate of 25%. This calculation is based on a z statistic for the difference between two proportions using a pooled variance estimate with a continuity correction.

3. Results

3.1. Participants

Of the 1085 participants screened, 1053 met the eligibility criteria and were enrolled. 1052 children received YF vaccination; 1051 (99.8%) completed the day 3 follow-up call; 1026 (97%) completed the week 2 follow-up visit; 1035 (98%) completed a diary card, and 1005 (95%) completed the 1-month follow-up visit (Fig. 1). One child was enrolled but excluded before the randomization due to failed baseline blood draw.

Of 1053 enrolled participants, 529 (50%) were female (Table 1). Three (0.2%) participants were reported to have HIV infection; none were reported to have any other chronic medical condition. Overall, 99% and 98% of participants had a history of receiving the first dose of pentavalent vaccine (penta1) and the first dose of measles-containing vaccine (MCV1), respectively. Of all enrolled children, 173 children had received same-day measles vaccination. The median age of participants (12.5 months) and mean weight for height [2] (17) were similar across the randomization arms. None of the children had an immediate serious or non-serious adverse reaction following the YF vaccination.

3.2. Follow-up

3.2.1. Day 3—Of 1051 (99.8%) enrolled participants for whom day 3 telephone calls were completed, 984 (94%) were completed on day 3 post-vaccination. Of these 1051 participants, 202 (19%) parents/caregivers reported their child had an AEFI. Five (<1%) parents/caregivers reported problems completing the diary card and one parent/caregiver (<1%) reported a faulty thermometer.

3.2.2. Week 2—Among 1026 (97%) enrolled participants who completed the week 2 follow-up visit; 1004 (98%) completed a week 2 visit within the visit window (12–17 days post-vaccination), 200 (19%) children had reported illness after vaccination, and 103 (10%) children received medical care. Reported illnesses included malaria, respiratory tract infections, conjunctivitis, gastrointestinal illness (diarrhoea, vomiting, appetite loss) and rash.

Among 1035 participants with a completed diary card, the most common AEFI (Table 2) were diarrhoea ($n = 355$; 34%), fever ($n = 338$; 33%) and rash ($n = 188$; 18%). Less commonly reported across all groups were vomiting ($n = 153$; 15%), continuous crying ($n = 90$; <1%), localized swelling ($n = 28$; <1%), and seizure ($n = 10$; <1%). We observed no significant difference in the frequency of AEFI among dose arms.

Overall, the time from vaccination to symptom onset was a mean of 3 days (range 0–14 days) for diarrhoea and a mean of 5 days (range 0–28 days) for rash, with a mean duration of 4 days (range 0–33 days) and 5 days (range 0–30 days) for each, respectively. Among the 338 children with a recorded history of fever on the diary card, the mean number of days between vaccination and onset of fever was 4 days (range 0–15 days) and the mean duration of the fever was 3 days (range 0–17 days) (Fig. 2). The timing and duration of fever were also similar across groups. Three children were reported to have been hospitalised with a mean duration of 3 days (range 2–4 days) after vaccination. One child had received a measles vaccination in the period after receiving the YF vaccination, but no AEFI were reported for this child.

3.2.3. Week 4—Staff completed an interim call 4–7 days before the week 4 follow-up visit for 997 (95%) of all enrolled participants. During the interim call, 27 (3%) parents/caregivers reported their child had an AEFI since their last visit. At the week 4 visit, 35 (3%) children had reported illnesses, including malaria, respiratory tract infections, gastrointestinal illness (vomiting), and rash. Among the 13 (1%) children referred for medical care, 4 children were hospitalised for a mean duration of 3 days (range 2–4 days). Six children had received other vaccinations since the YF vaccination (four measles-rubella, one measles, and one hepatitis B).

Overall, the total number of AEFI reported for all participants was 806 (789 NSAEs, 17SAEs), and 672 (64%) parents/caregivers reported that their child had at least one NSAE. Among the 17 participants with SAEs, eight were reported to have seizures and five were reported to be hospitalised for seizures or other causes (respiratory symptoms, gastrointestinal illness, or malaria) (Table 3). Based on the assessment by the AEFI Committee, none were determined to be causally related to YF vaccination. There were no reported cases of pre-specified SAEs. Additional descriptions of SAEs will be discussed in a separate publication in the future.

4. Discussion

This is the first published safety study evaluating the use of fractional doses of the Bio-Manguinhos 17DD YF vaccination among children aged <2 years. In this trial using active surveillance monitoring, we did not identify any unexpected safety concerns among children aged <2 years receiving YF vaccination, for both fractional and full doses. NSAEs during the 28 days after YF vaccination were common with 672 (64%) parents/caregivers reporting that their child had an NSAE; this rate is comparable to results of a randomized trial of four YF vaccines as standard and fractional doses conducted in Uganda and Kenya among adults, during which 48–63% of the participants in each group reporting at least one AEFI [21]. The reported frequency of NSAEs in this study is higher than the rates

reported from passive AEFI surveillance, which was the basis for previous assumptions on the safety of fractional YF vaccination. The higher frequency of AEFI reported in this study is expected given the known limitations including under-reporting of passive surveillance. A post-campaign review of medical records in two hospitals in one health zone in DRC following a subnational YF vaccination campaign earlier in 2016 found that passive YF AEFI surveillance had failed to identify half of all AEFI that were identified through active surveillance, including two serious AEFI [22]. Similarly, a report on AEFI during preventive mass YF vaccination campaigns in eight West African countries found lower rates of AEFI (2952 NSAEs and 164 SAEs reported for 38 million YF vaccine doses administered [23]) than those observed in post-marketing surveillance in other settings [24] and studies on travellers [25].

Among the children in this study, the most frequently reported AEFI were diarrhoea (34%) and fever (33%). Most AEFI were mild, occurred within the 14 days post-vaccination and often resolved within a week, as referenced in the literature [26–28]. However, some symptoms such as diarrhoea persisted for 30 days or more. Post-vaccination diarrhoea observed in this study is inconsistent with the previous reports on AEFI after YF vaccination, where generally the most commonly cited AEFI after YF vaccination are headache, fatigue and fever [9]. This also has been observed among adult YF vaccine recipients in a clinical trial in Uganda with frequencies of 22.2%, 13.7% and 9.0% of headache, fatigue, and fever, respectively [21]. The young age of the participants might explain the differences in the frequency and types of AEFI reported in our study. History of headache or fatigue would be more difficult to discern in children <2 years than among adults. Furthermore, it is important to also consider the background prevalence of diarrhoea and fever in the Ugandan setting. While the frequency of diarrhoea reported by parents/caregivers in this study was higher than what has been reported as the background prevalence of diarrhoea in Kampala district (12%) [29] and is also higher than the 20% prevalence of diarrhoea among children aged <5years reported in the Uganda Demographic and Health Survey (DHS) 2016, our study population includes age groups that may be most vulnerable to diarrhoea [30]. Of note, the background prevalence of diarrhoea is reported to be higher elsewhere in Uganda (40.8% in Agago District, 41.3% in Adjumani Refugee Camp in West Nile, and 40.3% in Sembabule District [31–35]). Additionally, 32.9% of the children aged 12–23 months in Uganda are reported to have a fever in the preceding 2 weeks [36] as other fever-causing infectious diseases are prevalent in the Ugandan setting such as malaria [37], and respiratory tract infections [32,38]. Notably, in our study, 173 children received measles vaccination on the same day and six children had received other vaccinations after YF vaccination by the time of the week 4 follow-up. This may also have had an impact on both the frequency and nature of the AEFI since AEFI vary by antigen and tend to be more frequently reported in persons who received other vaccines simultaneously [12,39].

It has been argued that lower doses of live flavivirus vaccines can result in a negative impact on safety [40] because viraemia of the vaccine virus does not correlate with the dose [41]. However, similar to other studies [9,21,42,43], we found there was a similar number of AEFI across dose arms and fractional-dose vaccination did not elicit more SAEs than full dose vaccination. Similarly, a recent systematic review and meta-analysis of the safety of

fractional dose YF vaccination found that mild AEFI did not differ across doses and no SAEs were reported in any study arm [42]. While the limited sample size in this clinical trial does not allow definitive conclusions on the frequency of all SAEs, especially for rare events, it is reassuring that the national AEFI Committee concluded none of the SAEs in this study were causally related to the YF vaccine.

This analysis has some limitations. Firstly, the study was powered to assess dose differences in immunogenicity, not specifically for capturing AEFI data, especially SAEs. Secondly, we did not include a matched control group to compare the outcomes among unvaccinated persons. Thirdly, since all events were reported by parents/caregivers without objective assessment by healthcare workers, there was potential for under- or over-reporting. Finally, these data represent an interim analysis only, and although we do not expect substantial changes, the final data are still pending.

In conclusion, in this trial using robust active surveillance monitoring, we did not identify any unexpected safety concerns among children aged <2 years receiving YF vaccination, including when the vaccine was given in fractional doses. We identified a high number of both serious and non-serious AEFI, but none were determined to be causally related to YF vaccination. These results provide evidence for the safety of fractional dose YF vaccination among children aged 9–23 months. However, more data on the use of fractional dose YF vaccination from active surveillance systems in other contexts would be beneficial to better understand the prevalence of AEFI after YF vaccination.

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.

References

- [1]. U.S. Centers for Disease Control and Prevention. Global Health - Newsroom -Yellow Fever [Internet] [cited 2021 Feb 13]; Available from: <https://www.cdc.gov/globalhealth/newsroom/topics/yellowfever/index.html>; 2021.
- [2]. Staples JE, Monath TP, Gershman MDBA. Yellow fever vaccines. In: Plotkin SA, Orenstein WA, Offit PA, Edwards KM, editors. Vaccines. Philadelphia: Elsevier Saunders; 2018. p. 1181–267.
- [3]. World Health Organization. WHO | WHO position paper on vaccines and vaccination against yellow fever. WHO; 2013.
- [4]. Staples JE, Bocchini JA, Rubin L, Fischer M, Centers for Disease Control and Prevention (CDC). Yellow Fever Vaccine Booster Doses: Recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR Morb Mortal Wkly Rep [Internet] 2015;64(23):647–50 [cited 2020 Mar 31] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26086636><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4584737>. [PubMed: 26086636]

- [5]. World Health Organization. Fractional dose yellow fever vaccine as a dose-sparing option for outbreak response WHO Secretariat information paper [Internet] [cited 2020 Mar 31] Available from: <http://www.who.int>; 2016.
- [6]. Roukens AH, Vossen AC, Bredenbeek PJ, van Dissel JT, Visser LG. Intradermally administered yellow fever vaccine at reduced dose induces a protective immune response: a randomized controlled non-inferiority trial. PLoS One [Internet] 2008;3 (4) [cited 2021 Feb 13] Available from: <https://pubmed.ncbi.nlm.nih.gov/PMC2297511/>.
- [7]. Lopes Ode S, Guimarães SS de CR. Studies on yellow fever vaccine. III–Dose response in volunteers. J Biol Stand 1988;16(2):77–82. [PubMed: 3372545]
- [8]. Campi-Azevedo AC, de Almeida Estevam P, Coelho-dos-Reis JG, et al. Subdoses of 17DD yellow fever vaccine elicit equivalent virological/immunological kinetics timeline. BMC Infect Dis [Internet] 2014;14(1) [cited 2021 Feb 13] Available from: <https://pubmed.ncbi.nlm.nih.gov/25022840/>.
- [9]. Martins RM, Maia MDLS, Farias RHG, et al. 17DD yellow fever vaccine: A double blind, randomized clinical trial of immunogenicity and safety on a dose-response study. Hum Vaccines Immunother [Internet] 2013;9(4):879–88 [cited 2021 Feb 13] Available from: <https://pubmed.ncbi.nlm.nih.gov/23364472/>.
- [10]. Staples JE, Gershman M, FMC for DC and P (CDC). Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MWR Recomm Rep 2010;59(RR-7):1–27. P 20671663.
- [11]. Lindsey NP, Rabe IB, Miller ER, Fischer M, Staples JE. Adverse event reports following yellow fever vaccination, 2007–13. J Travel Med 2016;23(5).
- [12]. Lindsey NP, Schroeder BA, Miller ER, et al. Adverse event reports following yellow fever vaccination. Vaccine [Internet] 2008;26(48):6077–82 [cited 2020 Mar 31] Available from, <http://www.ncbi.nlm.nih.gov/pubmed/18809449>. [PubMed: 18809449]
- [13]. Khromava AY, Eidex RB, Weld LH, et al. Yellow fever vaccine: An updated assessment of advanced age as a risk factor for serious adverse events. Vaccine [Internet] 2005;23(25):3256–63 [cited 2020 Mar 31] Available from, <http://www.ncbi.nlm.nih.gov/pubmed/15837230>. [PubMed: 15837230]
- [14]. Thomas RE. Yellow fever vaccine-associated viscerotropic disease: current perspectives. Drug Des Devel Ther [Internet] 2016;10:3345 [cited 2021 Oct 10] Available from: <https://pubmed.ncbi.nlm.nih.gov/PMC5066857/>.
- [15]. Martins RM, Maia MDLS, Farias RHG, et al. 17DD yellow fever vaccine: a double blind, randomized clinical trial of immunogenicity and safety on a dose-response study. Hum Vaccines Immunother [Internet] 2013;9(4):879–88 [cited 2021 Oct 10] Available from: <https://pubmed.ncbi.nlm.nih.gov/23364472/>.
- [16]. Freestone DS, Ferris RD, Weinberg AL, Kelly A. Stabilized 17D strain yellow fever vaccine: dose response studies, clinical reactions and effects on hepatic function. J Biol Stand 1977;5(3):181–6. [PubMed: 893464]
- [17]. Nascimento Silva JR, Camacho LAB, Siqueira MM, et al. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps and rubella. Vaccine [Internet] 2011;29(37):6327–34 [cited 2020 Mar 31] Available from, <http://www.ncbi.nlm.nih.gov/pubmed/21640779>. [PubMed: 21640779]
- [18]. Barrett ADT. Fractional dosing of Yellow fever vaccines: review of vaccine potency & stability information, available evidence, and evidence gaps. 2024.
- [19]. Gershman MD, Staples JE, Bentsi-Enchill AD, et al. Viscerotropic disease: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2012;30(33):5038–58. [PubMed: 22561144]
- [20]. World Health Organization. Surveillance of adverse events following immunization against yellow fever [Internet] [cited 2021 Feb 13]; Available from: https://www.who.int/csr/resources/publications/HSE_GAR_ERL_2010_1ENw.pdf; 2010.
- [21]. Juan-Giner A, Kimathi D, Grantz KH, et al. Immunogenicity and safety of fractional doses of yellow fever vaccines: a randomised, double-blind, non-inferiority trial. Lancet [Internet]

- 2021;397(10269):119–27 [cited 2021 Oct 6] Available from: <http://www.thelancet.com/article/S0140673620325204/fulltext>. [PubMed: 33422245]
- [22]. Otshudiema JO, Ndakala NG, Loko ML, et al. *Notes from the Field*: Adverse Events Following a Mass Yellow Fever Immunization Campaign — Kongo Central Province, Democratic Republic of the Congo, September 2016. *MMWR Morb Mortal Wkly Rep* [Internet] 2017;66(12):343–4 [cited 2021 Feb 13] Available from: <http://www.cdc.gov/mmwr/volumes/66/wr/mm6612a7.htm>. [PubMed: 28358792]
- [23]. World Health Organization. Yellow fever mass vaccination campaigns using fractional dose [Internet] [cited 2021 Oct 13]; Available from: <https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/yellow-fever-vaccines/campaigns>; 2021.
- [24]. Martins RDM, Leal MDLF, Homma A. Serious adverse events associated with yellow fever vaccine. *Hum Vaccin Immunother* 2015;11(9):2183–7. [PubMed: 26090855]
- [25]. Breugelmans JG, Lewis RF, Agbenu E, et al. Adverse events following yellow fever preventive vaccination campaigns in eight African countries from 2007 to 2010. *Vaccine* [Internet] 2013;31(14):1819–29 [cited 2020 Mar 31] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23395587>. [PubMed: 23395587]
- [26]. Department of Health and Aged Care | Surveillance of adverse events following immunisation: Australia, 2000–2002 [Internet] [cited 2022 Aug 3]; Available from: <https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-pubs-cdi-2003-cdi2703-htm-cdi2703a.htm>; 2022.
- [27]. Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)—United States, 1991–2001. *MMWR Surveill Summ* [Internet] 2003 Jan 24;52(1): 1–24 [cited 2022 Aug 3] Available from: <https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5201a1.htm>.
- [28]. Biscayart C, Carrega MEP, Sagradini S, et al. Yellow fever vaccine-associated adverse events following extensive immunization in Argentina. *Vaccine* [Internet] 2014;32(11):1266–72 [cited 2022 Aug 3] Available from: <https://europepmc.org/article/med/24456625>. [PubMed: 24456625]
- [29]. Tumwine JK, Kekitiinwa A, Nabukeera N, Akiyoshi DE, Rich SM, Widmer G, et al. *Cryptosporidium parum* in children with diarrhea in Mulago Hospital, Kampala, Uganda. *Am J Trop Med Hyg* 2003;68(6):710–5. p. Jun. [PubMed: 12887032]
- [30]. 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):1–9. 201 [Internet] 2020 [cited 2021 Oct 10] Available from: 10.1186/s12879-020-4770-0.
- [31]. Nambuusi BB, Ssempiira J, Makumbi FE, Kasasa SVP. Associations and contribution of childhood diseases to fever risk among children less than five years in Uganda. *J Glob Heal Reports* [Internet] 2020;4. Available from: <https://www.joghr.org/article/13072-associations-and-contribution-of-childhood-diseases-to-fever-risk-among-children-less-than-five-years-in-uganda>.
- [32]. Mbonye AK. Prevalence of childhood illnesses and care-seeking practices in rural Uganda. *Sci World J* [Internet] 2003;3:721–30 [cited 2021 Oct 10] Available from: <https://pubmed.ncbi.nlm.nih.gov/12941972/>.
- [33]. 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. 2019.
- [34]. Risk Factors for Diarrhoea and Upper Respiratory Tract Infections among Children in a Rural Area of Uganda on JSTOR [Internet] [cited 2021 Oct 10]; Available from: <https://www.jstor.org/stable/23499009>; 2021.
- [35]. AGN Izale. Prevalence and factors associated with diarrhoea among children under five years in Nyumanzi Refugee Settlement Camp Adjumani District, Uganda [cited 2021 Oct 10]; Available from: <http://makir.mak.ac.ug/handle/10570/5705>; 2015.
- [36]. Uganda Bureau of Statistics. Uganda Demographic and Health Survey 2016 [Internet] [cited 2021 Jan 31] Available from: www.DHSprogram.com; 2018.
- [37]. UGANDA. Malaria Indicator survey. 2018.
- [38]. Soremekun S, Kasteng F, Lingam R, et al. Variation in the quality and out-of-pocket cost of treatment for childhood malaria, diarrhoea, and pneumonia: Community and facility based care

in rural Uganda. PLoS One [Internet] 2018;13(11): e0200543 [cited 2021 Oct 10] Available from: 10.1371/journal.pone.0200543. [PubMed: 30475808]

- [39]. Nazareth A, Nazareth Lara A, Takesaki Miyaji K, Yaqub Ibrahim K, Heloisa Lopes M, Marli Christovam Sartori A. Adverse events following yellow fever vaccination in immunocompromised persons. 2021. 10.1590/S1678-9946202163013 [cited 2021 Oct 10];Available from:.
- [40]. Sanchez V, Gimenez S, Tomlinson B, et al. Innate and adaptive cellular immunity in flavivirus-naïve human recipients of a live-attenuated dengue serotype 3 vaccine produced in Vero cells (VDV3). Vaccine 2006;24(23):4914–26. [PubMed: 16632108]
- [41]. Monath TP, Guirakhoo F, Nichols R, et al. Chimeric live, attenuated vaccine against Japanese encephalitis (ChimeriVax-JE): phase 2 clinical trials for safety and immunogenicity, effect of vaccine dose and schedule, and memory response to challenge with inactivated Japanese encephalitis antigen. J Infect Dis [Internet] 2003;188(8):1213–30 [cited 2021 Oct 10] Available from: <https://academic.oup.com/jid/article/188/8/1213/895814>. [PubMed: 14551893]
- [42]. Nnaji CA, Shey MS, Adetokunboh OO, Wiysonge CS. Immunogenicity and safety of fractional dose yellow fever vaccination: a systematic review and meta-analysis [internet]. Vaccine 2020;38(6):1291–301 [cited 2021 Oct 10] Available from: <https://pubmed.ncbi.nlm.nih.gov/31859201/>. [PubMed: 31859201]
- [43]. Roukens AHE, Visser LG. Fractional-dose yellow fever vaccination: an expert review [internet]. J Travel Med 2019;26(6) [cited 2021 Oct 10] Available from: <https://pubmed.ncbi.nlm.nih.gov/30937437/>.



Fig. 1.
Enrollment and Follow-up of Study Participants — The Fractional Dose Yellow Fever AEFI Study, Uganda, 2019–2020.

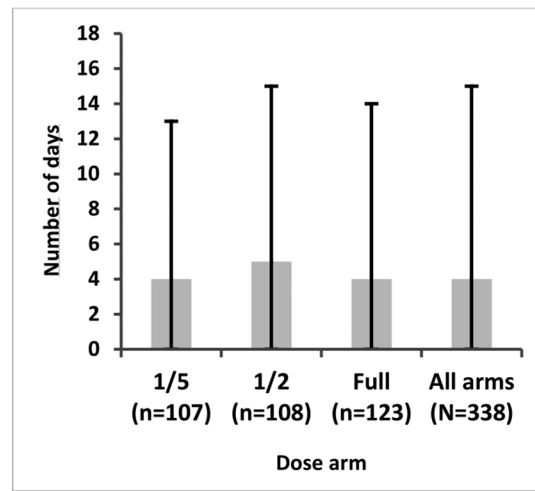
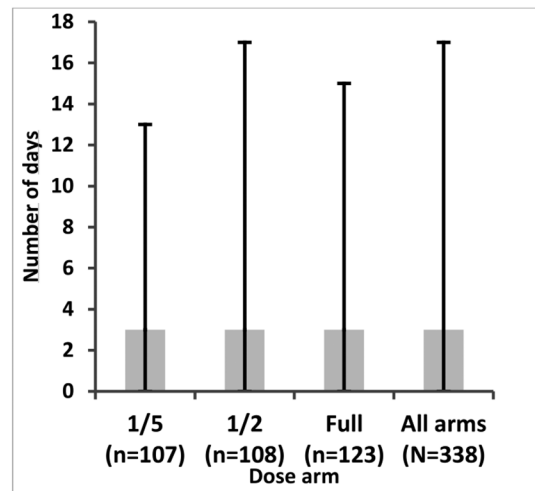
(A) Number of days from vaccination to fever (mean and range)**(B) Duration of fever (mean and range)**

Fig. 2.
Description of fever among participants with completed diary card — The Fractional Dose Yellow Fever AEFI Study Uganda 2019–2020.

Table 1

Characteristics of the enrolled participants[†] according to vaccination dose arm — The Fractional Dose Yellow Fever AEFI Study, Uganda 2019–2020.

	1/5 dose (n = 354)	½ dose (n = 351)	Full dose (n = 347)
<i>Number of participants (percent)</i>			
Female	172 (49)	188 (54)	169 (49)
HIV infection	0 (0)	2 (<1)	1 (<1)
Chronic condition	0 (0)	0 (0)	0 (0)
History of receipt of first dose pentavalent [^] vaccination *	353 (100)	348 (99)	345 (99)
History of receipt of first dose measles-containing vaccination *	346 (98)	342 (97)	340 (98)

[†] n = 1052; 1 participant enrolled, but not randomized due to failed blood draw.

[^] Pentavalent vaccine containing Diphtheria, Pertussis, Tetanus, Hepatitis b and *Haemophilus influenzae* type b.

* Of 1051 children with available vaccination history.

Table 2

Frequency of non-serious AEFI within 2 weeks of vaccination according to vaccination dose arm reported using diary cards — The Fractional Dose Yellow Fever AEFI Study Uganda 2019–2020.

Symptom	Dose arm (number of participants)				<i>P</i> -value *
	1/5 dose (<i>n</i> = 349)	½ dose (<i>n</i> = 344)	Full (<i>n</i> = 342)	All arms (<i>N</i> = 1035)	
	<i>Number of participants reporting symptom (percent [95% CI **])</i>				
Diarrhoea	112 (32 [27–37])	129 (38 [32–43])	114 (33 [28–39])	355 (34 [31–37])	0.3
Fever	107 (31 [26–36])	108 (31 [27–37])	123 (36 [31–41])	338 (33 [30–36])	0.3
Rash	59 (17 [13–21])	55 (16 [12–20])	74 (22 [17–26])	188 (18 [16–21])	0.1
Vomiting	52 (15 [11–19])	52 (15 [12–19])	49 (14 [11–19])	153 (15 [13–17])	0.96
Continuous crying	34 (10 [7–13])	27 (8 [5–11])	29 (8 [6–12])	90 (<1 [0.07–0.1])	0.7
Localized swelling	9 (3 [1–5])	8 (2 [1–5])	11 (3 [2–6])	28 (<1 [0.02–0.04])	0.8

* Chi-square test.

** 95% confidence interval.

Table 3

Description of serious adverse event (SAE), final diagnosis and characterization of serious AEFI category of causality assessment by the national AEFI committee — The Fractional Dose Yellow Fever AEFI Study, 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
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.
	Seizure	Febrile Convulsion	1	Vaccine product related reaction. However, there was a coincidental underlying condition other than vaccine i.e., dysentery and high fever which may cause febrile seizures.
	Seizure	Febrile Seizure	2	Coincidental, underlying or emerging condition caused by exposure to something other than vaccine. Febrile seizures are frequent children under five years up to 4%.
	Seizure	Possible Encephalitis	3	Coincidental, underlying or emerging conditions. There are many other causes of encephalitis
	Fevers, diarrhoea, Hospitalization	Malaria	9	Inconsistent causal association to immunization; Coincidental/ underlying condition.
	Death	N/A	36	Causality assessment not done, study team and investigators were unable to reach parent/caretaker after this event.
	Death	Sudden Unexplained Death in childhood	283	Inconsistent causal association / coincidental. Child was living under adverse social conditions (caretakers other than parents) and received MR vaccine about 3 months prior.
1/2	Malaria symptoms, Hospitalization	Malaria	1	Inconsistent causal association / coincidental. Blood slide confirmed presence of malaria parasites as the cause of fever.
	Seizure, Hospitalization	Acute Upper Respiratory Tract Infection	5	Inconsistent causal association / coincidental. However, there is a possibility of a vaccine related reaction as per published literature.
	Seizure	Seizure Disorder	9	Inconsistent causal association / coincidental. However, there is a possibility of a vaccine related reaction as per published literature.
	Respiratory symptoms	Bronchiolitis	25	Inconsistent causal association / coincidental. Bronchiolitis was most likely caused by an agent other than the vaccine
1/5	Seizure	N/A	1	Causality assessment not done, during investigations parent informed team event did not happen, was checked on the diary card in error.
	Seizure	Possible Encephalitis	10	Coincidental, underlying, or emerging conditions. Many CNS infections, especially viruses, may cause symptoms of encephalitis.
	Fever, Hospitalization	Malaria	18	Inconsistent causal association / coincidental. Blood slide confirmed presence of malaria parasites as the cause of fever.
	Malaria symptoms Hospitalization	Malaria	25	Inconsistent causal association / coincidental. Blood slide confirmed presence of malaria parasites as the cause of fever.
	Death	Sudden Death	138	Inconsistent causal association / coincidental. There are numerous causes associated with sudden death. Child also received MR vaccine 8 days before death.
	Death	Steven-Johnson Syndrome (SJS)	221	Inconsistent causal association to immunization. There are many precipitators of SJS, child had recently received MR vaccine hence more probable cause.