# Low-dose vaccination for yellow fever in adults

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## Abstract

*Background*: Yellow fever (YF) vaccine is highly effective with a single dose but vaccine supply is limited. The minimum dose requirements for seroconversion remain unknown.

*Methods*: We conducted a randomized, double-blind, non-inferiority trial in Mbarara, Uganda and Kilifi, Kenya, recruiting 480 adults aged 18 to 59 years, with no history of YF vaccination or infection. Volunteers were randomized to vaccination with a standard dose (13803 international units [IU]), 1000 IU, 500 IU or 250 IU of the Institut Pasteur de Dakar 17D-204 YF vaccine. Seroconversion was defined as a four-fold or greater rise in day 28 post-vaccination antibody titers, measured by 50% plaque reduction neutralization test. Non-inferiority was defined as the lower bound of the 95% confidence interval (CI) for the difference in seroconversion rate between fractional and standard dose being greater than –10% and presented per-protocol (PP) and by intention-to-treat (ITT).

*Results*: The seroconversion rate was 98% (95% CI 94 to 100) at the standard dose. Differences in seroconversion were: -1.9% (95% CI -7.0 to 3.2) and 0.01% (95% CI -5.0 to 5.1) for 1000 IU; -1.8% (95% CI -6.7 to 3.2) and 0.01% (95% CI -5.0 to 5.1) for 500 IU; and -6.7% (95% CI -11.7 to 1.6) and -4.4% (95% CI -9.4 to 0.7) for 250 IU, by PP and ITT, respectively. 111 vaccine-related adverse events were reported: 103 were mild, 7 moderate and 1 severe with no imbalance by group.

*Conclusion*: A dose as low as 500 IU was non-inferior to the standard YF vaccine dose.

*Trial registration:* The trial was registered with ClinicalTrials.gov NCT04059471.


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## Introduction

Yellow fever (YF) is a mosquito-borne viral zoonotic illness endemic in Africa and South America [1]. YF outbreaks are most commonly reported in Africa where over 100,000 severe YF cases, with a case fatality of 20-60%, are estimated to occur annually [2,3].

The 17D live-attenuated YF vaccine is safe and effective; a single dose provides life-long immunity [4]. However, the YF vaccine manufacturing process is laborious, and difficult to scale up rapidly, leading to persistent challenges with vaccine availability [5].

The World Health Organization (WHO) recommends the use of fractional doses as a dose-sparing strategy during outbreaks when there are vaccine shortages [6]. This policy is supported by trials evaluating the immunogenicity and safety of a fifth of a standard dose from each of the four WHO-prequalified vaccine manufacturers in healthy adults, children and individuals infected with HIV [7-10]. However, as the potency of doses can vary substantially by manufacturers and by batch [7], there may be limits on the generalizability of these data.

A dose-finding trial, carried out in Brazil using the 17DD vaccine sub-strain found that a dose of 587 IU resulted in seroconversion in 97.7% (95% CI 92.4-99.2%) of the participants and a dose of 158 IU resulted in seroconversion in 88.5% (95% CI 81.5-93.6) [11]. This study was conducted on young male adults with a mean age of 19.4 years, and hence further data are required.

We conducted a trial to compare the immunogenicity of bespoke titrations at 1000, 500 or 250 IU/dose of the 17D-204 YF vaccine manufactured by the Institut Pasteur de Dakar in Senegal for non-inferiority to the standard vaccine dose (i.e. 13803 IU).

## Methods

*Study design, setting and participants*

This randomized, double-blind, non-inferiority trial was conducted at the KEMRI-Wellcome Trust Research Programme Clinical Trials Facility in Kilifi County, Kenya and the Epicentre Mbarara Research Centre in Mbarara city, Uganda. We held community meetings to present the study design, the rationale of conducting the fractional dosing study, expectations for participation and

77 the possible impact of the data generated from the study. Volunteers were eligible for inclusion if
78 they were ≥18 to <60 years old, either HIV negative on a standard serological screening test or
79 HIV-positive and on treatment and clinically stable with CD4 count >200 [12]; were not pregnant or
80 lactating, had no history of wild-type YF virus infection or vaccination with YF vaccine, and were
81 able to comply with the study procedures [13]. The recruited study participants were randomized to
82 vaccination with: a) full standard dose (13803 IU); b) 1000 IU; c) 500 IU; or d) 250 IU in equal
83 numbers per group. The various dose levels were prepared as per manufacturer's instructions
84 (see Supplementary Methods and Table S1). Computer-generated random numbers with fixed
85 blocks were prepared in advance by an independent firm (DiagnoSearch LifeSciences, Mumbai,
86 India) allocating to a dose in equal allocations for use in the blinded randomization.

87 *Study oversight*

88 The trial was sponsored by the University of Oxford. The trial protocol was reviewed and approved
89 by the Oxford Tropical Research Ethics Committee, the Kenya Medical Research Institute
90 Scientific and Ethics Review Unit, Mbarara University of Science and Technology Research Ethics
91 Committee and the Uganda National Council of Sciences and Technology. Regulatory approval
92 was obtained from the Kenya Pharmacy and Poisons Board, and the Uganda National Drug
93 Authority. All authors contributed to study design and implementation and vouch for the accuracy
94 and completeness of the data and analysis. DK, AJG, BO, PB and GMW wrote the first draft of the
95 manuscript, and all authors contributed to the final manuscript version and decided to publish the
96 paper.

97 *Study procedures and follow-up*

98 All the vaccine doses were administered subcutaneously as 0.5mls at a 45° injection angle using
99 auto-disable syringes with a 25G × 3/4" needle size. For immunogenicity, blood samples were
100 collected at baseline, and at 10 and 28 days after vaccination, then at 1 and 2 years after
101 vaccination. For viremia monitoring, blood samples were collected at baseline and day 10; in
102 addition, participants were randomized for one additional blood sampling visit at either day 2, 3, 4,

5, 6 or 7 (i.e., 80 participants on each day) for assessment of post-vaccination viremia. Blood was processed for serum that was stored at -80°C until assayed.

*Laboratory assessments*

The plaque reduction neutralization test (PRNT) assays for this study were conducted at the WHO-accredited regional YF reference laboratory at the Institut Pasteur de Dakar in Senegal using well-described standardized methods [14,15]. Seroconversion was defined as a four-fold increase of antibody titers achieved in a 50% plaque reduction neuralization test ($PRNT_{50}$) compared to titers prior to vaccination. Post-vaccination viremia was assessed using standard reverse transcriptase polymerase chain reaction (RT-PCR) methods at the WHO-accredited regional YF reference laboratory at the Uganda Virus Research Institute (UVRI), Entebbe, Uganda.

*Sample size estimation*

The study design assumed a 95% seroconversion rate, a 0.025 α for a one-sided test and with 90% power to detect a non-inferiority margin of -10% based on the public health consequence of waning population immunity [16] (see Supplementary Methods). Sample size calculation was performed using *art2bin* on Stata version 15 (StataCorp, College Station,TX) and cross-checked using Power Analysis & Sample Size software (PASS) version 14. Sample size calculation and simulations based on these assumptions yielded a sample size of 100 participants per arm and we increased this by 20% to account for participants lost to follow-up, any participants whose results would be unevaluable and participants with pre-existing antibodies against YF virus at baseline. Thus, we used a total sample size of 480 for the four vaccine dose groups. No adjustment for multiplicity of testing was a-priori specified for outcomes other than the 28-day outcome.

*Statistical analysis*

The primary outcome was non-inferiority of the seroconversion rate of each fractional dose compared to the standard dose at 28 days post-vaccination. Analysis was performed by intention-to-treat (ITT) and per-protocol (PP). Secondary outcomes included assessing non-inferiority of the

proportion of participants who seroconverted using a 90% plaque neuralization reduction ($PRNT_{90}$), describing geometric mean titers (GMT) and geometric mean fold increase in titers (GMFI; i.e., geometric mean of the ratios of post-vaccination titer to pre-vaccination titer) using $PRNT_{50}$ and $PRNT_{90}$, and seroconversion rate using $PRNT_{90}$ in the ITT and the PP study population.

The ITT group was defined as any randomized participant. The PP group was defined as participants who were seronegative for YF at baseline, and had a PRNT result at the day of test. Hence, where data were available for analysis, PP exclusions were made only on the basis of baseline characteristics and not on the basis of post-randomization events.

This study is registered with ClinicalTrials.gov, NCT02991495.

## Results

The study was conducted between 11th November 2019 and 4th April 2022. 518 volunteers were screened, 33 were excluded as they were ineligible, 5 eligible declined to participate, and 480 were enrolled and randomly assigned to a vaccine dose: 120 assigned to 250 IU, 120 assigned to 500 IU, 120 assigned to 1000 IU, and 120 assigned to the standard dose (Figure 1). 479 (~100%) of 480 participants completed day 10 follow-up visit, 465 (97%) completed the 28 days post-vaccination visit and 444 (93%) completed the last study follow-up visit at day 730. The primary ITT analysis included 115 participants in the 250 IU, 117 in the 500 IU, 117 in the 1000 IU, and 116 in the standard dose groups, respectively. Missing outcome values in the ITT and PP population were due to 15 missed visits (i.e. 3% of 480 volunteers), randomly distributed across the four dose groups. Additional exclusions from the PP population were due to pre-vaccination YF antibody positivity (n=35). This exclusion is for a pre-randomization covariate which is not known at the time of randomization, but which complicates the definition of seroconversion (i.e. the primary endpoint). The mean age at enrolment was 39.7 (SD 11.5) years, the majority (296 [62%]) were female, and 38 (8%) were HIV positive at baseline. Baseline characteristics of the participants were similar across the dose groups (Tables 1 and S6), and the participants were considered representative of the general adult population in the study locations (Table S7).

*Immunogenicity*

28 days post-vaccination, seroconversion rates, in terms of $PRNT_{50}$, were above 90% for all groups (Table 2). From day 28 onwards, the consistent pattern was for lowest seroconversion rates in the 250 IU group, and similar seroconversion rates among 500 IU, 1000 IU and the standard dose groups. By contrast, seroconversion rates at 10 days were lower for 500 IU and 1000 IU compared with the standard dose. A similar pattern of results was seen when comparing GMTs (Table 2).

The difference with the standard dose in the seroconversion rate at 28 days was -4.4% (-9.4 to 0.7) for 250 IU, and 0.01% (-5.0 to 5.1) for both 500 IU and 1000 IU by ITT (Figure 2A, S1). Thus, non-inferiority, defined as the lower bound of the 95% CI of the seroconversion rate difference greater than -10% was met for the 250 IU, 500 IU and 1000 IU doses. By PP, differences in seroconversion were: -1.9% (95% CI -7 to 3.2) for 1000IU; -1.8% (95% CI -6.7 to 3.2) for 500 IU; and -6.7% (95% CI -11.7 to 1.6%) for 250 IU (Figure 2B). Hence, the 250 IU dose did not meet non-inferiority criteria on PP analysis at 28 days. Similar conclusions were made using $PRNT_{90}$ in the ITT and the PP population (Tables S2 and S3).

Antibody responses, as shown by GMTs, in all dose groups peaked at 28 days post-vaccination (Figure S2). Similar peak GMTs were observed in the standard dose, 1000 IU and 500 IU dose groups, and lower for the 250 IU group. While the high GMTs were maintained 365 days after vaccination, there was a 4 to 6-fold drop in GMTs by 730 days post-vaccination. The lowest GMTs were recorded 10 days post-vaccination. Similar profiles were observed for GMFIs (Table 2). Compared with $PRNT_{50,}$ the GMTs and GMFIs were consistently lower by $PRNT_{90}$ (Figure S2 and Table S2). Similar observations as for ITT populations were made for PP population (Table S3). Of 480 participants, 12 (2.5%, 95% CI 1.3–4.3) were positive for YF vaccine viremia between days 2–10. One participant was positive on day 4, one on day 5, five on day 6, one on day 7 and 4, one of whom showed very high viremia, on day 10 (Table S4). GMTs of subsequent $PRNT_{50}$ responses were higher in those who were previously viremic (GMT ratios: 28 days=2.1 [95% CI 1.3–3.3], 365 days=2.2 [95% CI 0.9–5.2]; Figure S3). All viremia positive participants were from Mbarara, and all

were among participants receiving fractional doses (Table S5). The risk of post-vaccination viremia was higher in males than females. There was no association with dose nor baseline characteristics (Table S5).

*Safety*

A total of 546 adverse events (AEs) were reported by 274 participants by 28 days post-vaccination. 66 (55%) of 120 participants in the 250 IU group reported 122 AEs, 75 (63%) of 120 participants in the 500 IU group reported 163 AEs, 68 (57%) of 120 participants in the 1000 IU group reported 136 AEs, and 65 (54%) of 120 participants in the standard dose group reported 125 AEs (Table 3). Three (<1%; 1 in 500 IU and 2 in 1000 IU groups) of 480 participants reported AEs classified as severe. The rest reported either mild (244 [51%]) or moderate (89 [19%]) AEs. 30 (25%) of 122 AEs in the 250 IU group, 26 (16%) of 163 AEs in 500 IU group, 29 (21%) of 136 AEs in 1000 IU group, and 26 (21%) of 125 AEs in standard dose group were classified as related to the study vaccine (Table 3). The most common AEs were headache (n=77 [14%]), upper respiratory tract infection (n=44 [8%]), gastritis (n=43 [8%]), dizziness (n=41 [8%]), myalgia (n=28 [5%]), cough (n=21 [4%]), and fatigue (n=20 [4%]) (Table S9). There were 11 serious adverse events reported throughout the study, which were all reported to the ethical and regulatory bodies. They included sinusitis, myocardial infarction, sepsis, malaria, cerebral hemorrhage, umbilical hernia, cerebrovascular accident, hypoglycemia, accidental death, and anemia (Listing S1). Ten of the twelve viremic participants reported an AE and only one (in the 1000 IU group) reported a serious adverse event but recovered without sequelae. The distribution of the AEs was similar across viremia status (Table S8).

## Discussion

The primary endpoint analysis indicates that at 28 days post-vaccination, 500 IU and 1000 IU were non-inferior to standard vaccine dose (13803 IU) with respect to seroconversion rate. The 250 IU dose met non-inferiority criteria when analyzed ITT, with a lower bound for the difference of -9.4% (i.e. just above the delta of -10%), but did not meet non-inferiority when analyzed PP. The ITT

group included volunteers with baseline antibodies to YF virus (n=35), whereas PP excluded this group. This group may cause dilution of the endpoint, given the difficulties of determining seroconversion in them. Hence, we conclude that non-inferiority criteria were shown for 500 IU and not for 250 IU, although the possible reduction in immunogenicity with the latter dose may be considered acceptable in an emergency outbreak response with substantial vaccine shortage. The current recommended minimum is 1000 IU per dose, but this was based on limited data obtained decades ago and most vaccine doses in circulation are substantially in excess of this threshold. Previous data from Brazil (sub-strain 17DD) had indicated that immunogenicity is reduced below 587 IU [11], but was not formally analyzed for non-inferiority, and may not generalize to adults in Africa or vaccines from other sub-strains.

This finding gives further confidence to recommendation to use the one fifth fractional dosing, as currently recommended by WHO for consideration in epidemics, provided that the standard dose in the vaccine used contains 500 IU or higher. Furthermore, vaccine manufacturers may consider it cost effective to reduce the potency of batches released and hence formally expand the vaccine stock that can be produced through existing manufacture facilities. This would have amounted to a 27-fold increase in doses based on the standard dose used in the present study, and for the lowest potency vaccine stock tested in our previous study [7], this would have been a 13-fold increase. However, allowance will need to be made for reductions in potency on storage and hence further manufacturer development processes will be required to determine an appropriate potency threshold for lyophilized doses. To fully realize the potential gains in vaccine stock production would require a re-assessment of the longstanding process of releasing very high potency batches.

As in previous studies [7-9] we identified that lower doses raised significantly lower neutralization titers and lower seroconversion rates at day 10, even though these differences were erased by the peak antibody responses seen at day 28. It is unlikely that this would be important in routine vaccination practice, or in outbreak control given that the intrinsic and extrinsic incubation periods are 5 and 13 days, respectively. However, it may be of consideration in travel medicine, although

seroconversion rate was 61% versus 85% for 500 IU versus a standard dose after 10 days, and this may be judged an acceptable risk given the short duration of the difference [16].

We found that post-vaccination viremia was infrequent, contrasting somewhat higher proportions of viremia seen ranging from 11% in studies in Brazil [17], to 82% in studies in France [18]. Factors explaining the variability in prevalence include the frequency and timing of sampling, prevalence of HIV infection, and the sub-strain and dose of vaccine used.

Limitations of the study include statistical power. As in previous studies, we were powered to establish non-inferiority at a 10% potential reduction in seroconversion rates at 28 days post-vaccination, and this margin was informed by previous modelling studies on requirements for herd immunity [16]. Nevertheless, we cannot exclude lower margins of non-inferiority which may be relevant in some circumstances. Given recommendations to regard one dose as providing life-long immunity, longer-term follow-up to determine the duration of responses is required. Finally, our data may apply only to the 17D-204 vaccine sub-strain used by Institut Pasteur Dakar.

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## Figures and Tables

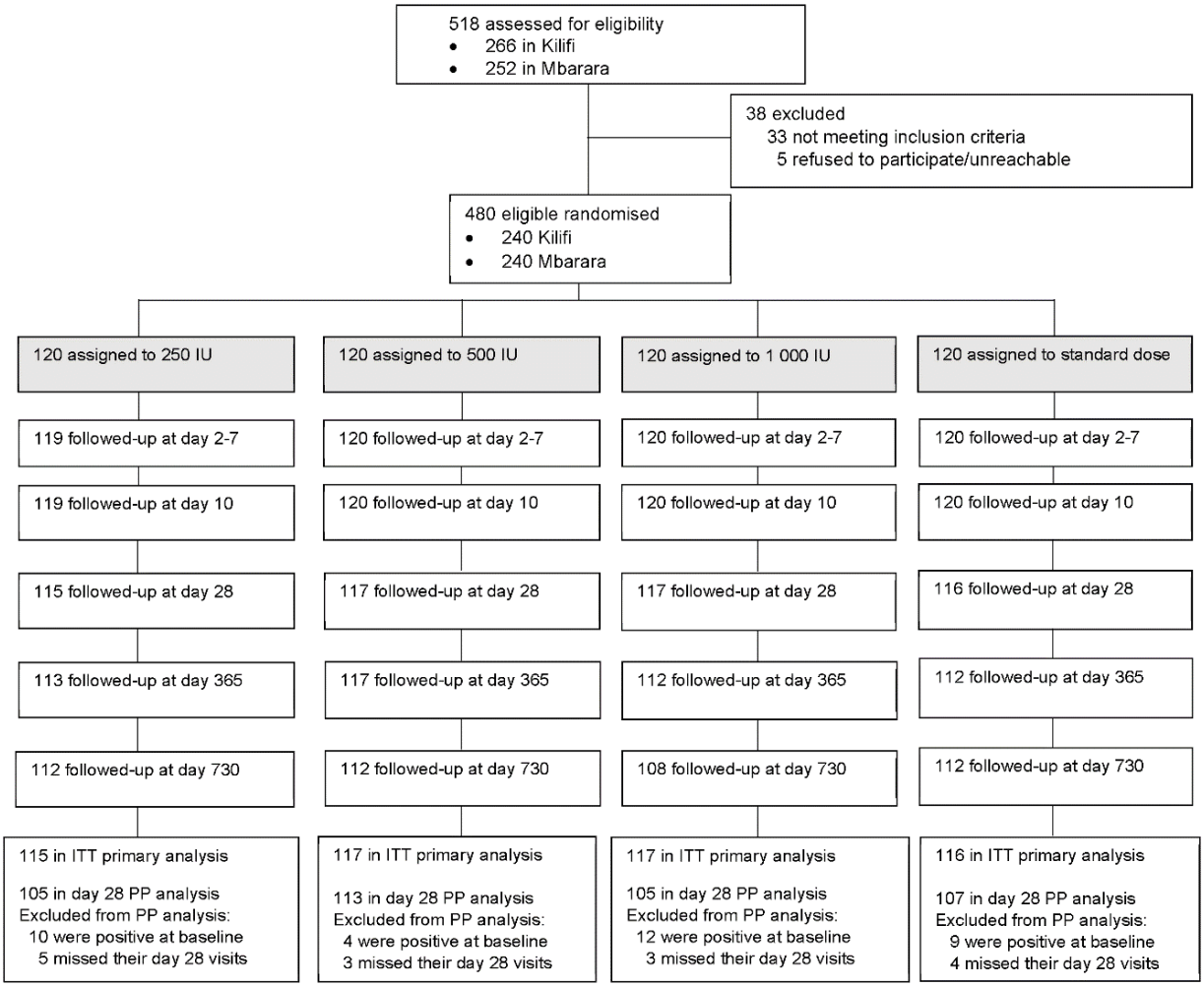
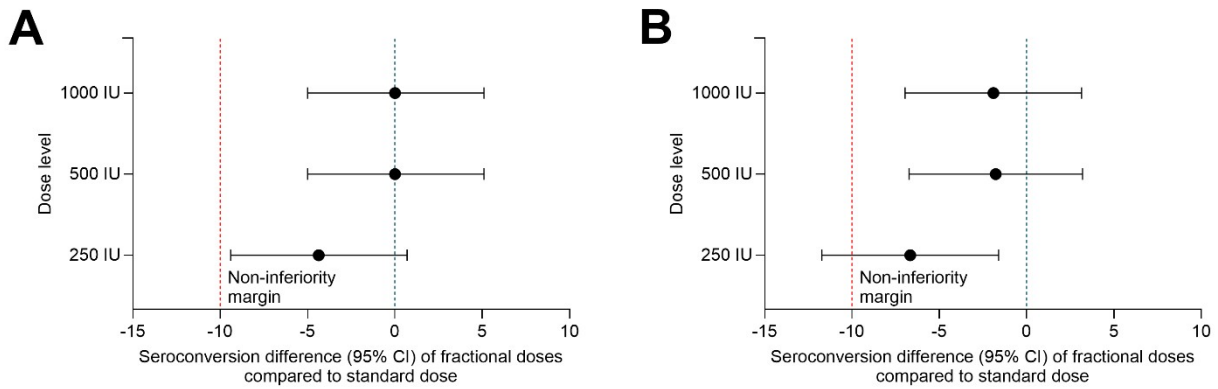



**Figure 1**. Study profile




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318 **Figure 2**. Non-inferiority of seroconversion rate of fractional doses compared with full standard
319 dose of yellow fever vaccine for intention-to-treat (Panel A) and per-protocol (Panel B) population
320 ($PRNT_{50}$) at day 28 after vaccination.

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**Table 1**. Baseline characteristics.[†]

| Characteristic | 250 IU | 500 IU | 1000 IU | Standard dose |
|---|---|---|---|---|
| Number enrolled | 120 | 120 | 120 | 120 |
| Mean age at enrolment (SD), years | 40.2 (11.0) | 38.5 (11.7) | 40.4 (11.6) | 39.8 (11.9) |
| Sex | | | | |
| Female, n (%) | 78 (65%) | 68 (57%) | 71 (59%) | 79 (66%) |
| Male, n (%) | 42 (35%) | 52 (43%) | 49 (41%) | 41 (34%) |
| Temperature, ºC, mean (SD) | 36.4 (0.5) | 36.4 (0.5) | 36.3 (0.4) | 36.4 (0.5) |
| Seropositive for YF at baseline, n (%) | 10 (8%) | 4 (3%) | 12 (10%) | 9 (8%) |
| Reported previous flavivirus infection, n (%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Reported previous medical illness, n (%) | 48 (40%) | 54 (45%) | 44 (36%) | 56 (47%) |
| HIV positive at baseline, n (%)* | 8 (7%) | 12 (10%) | 5 (4%) | 13 (11%) |
| CD4 cell count, median (IQR) | 653 (533, 712) | 654 (428, 884) | 943 (709, 951) | 613 (480, 758) |

Data are mean (SD), median (IQR) or number (percent). *35 were at WHO clinical stage 1, 3 were at WHO clinical stage 2. [†]All participants had complete data for all baseline characteristics.

**Table 2**. Seroconversion rate and geometric mean titer by $PRNT_{50}$ in fractional and standard doses of yellow fever vaccine at days 10, 28, 365 and 730 post-vaccination in the intention-to-treat population.

| Dose level | Total (n) | Seroconversion rate* | | | Geometric mean titer (95% CI)** | Geometric mean titer ratio: fractional ÷ standard (95% CI)** |
|---|---|---|---|---|---|---|
| | | n | % (95% CI)** | Difference (fractional-standard)** | | |
| Day 10 | | | | | | |
| 250 IU | 119 | 60 | 50 (42 to 59) | -34.6 (-48.7 to -20.5) | 20.6 (15.5 to 27.4) | 0.21 (0.13 to 0.33) |
| 500 IU | 120 | 73 | 61 (52 to 69) | -24.2 (-38.2 to -10.1) | 30.1 (22 to 41.3) | 0.3 (0.19 to 0.49) |
| 1000 IU | 120 | 73 | 61 (52 to 69) | -24.2 (-38.2 to -10.1) | 36.1 (26 to 50) | 0.36 (0.22 to 0.59) |
| Standard dose | 120 | 102 | 85 (77 to 90) | Reference | 99.6 (69.1 to 143.7) | Reference |
| Day 28 | | | | | | |
| 250 IU | 115 | 108 | 94 (88 to 97) | -4.36 (-9.4 to 0.7) | 1303 (878 to 1934) | 0.84 (0.52 to 1.35) |
| 500 IU | 117 | 115 | 98 (94 to 100) | 0.01 (-5 to 5.1) | 1773 (1337 to 2352) | 1.14 (0.78 to 1.69) |
| 1000 IU | 117 | 115 | 98 (94 to 100) | 0.01 (-5 to 5.1) | 2182 (1661 to 2865) | 1.41 (0.96 to 2.06) |
| Standard dose | 116 | 114 | 98 (94 to 100) | Reference | 1550 (1183 to 2030) | Reference |
| Day 365 | | | | | | |
| 250 IU | 113 | 104 | 92 (85 to 96) | -7.1 (-12.8 to -1.3) | 1112 (753 to 1641) | 0.88 (0.55 to 1.41) |
| 500 IU | 117 | 114 | 97 (92 to 99) | -1.7 (-7.4 to 4) | 1556 (1148 to 2110) | 1.24 (0.83 to 1.84) |
| 1000 IU | 112 | 109 | 97 (92 to 99) | -1.8 (-7.5 to 4) | 1580 (1182 to 2112) | 1.25 (0.85 to 1.85) |
| Standard dose | 112 | 111 | 99 (95 to 100) | Reference | 1259 (969 to 1636) | Reference |
| Day 730 | | | | | | |
| 250 IU | 112 | 94 | 84 (76 to 90) | -11.6 (-20.6 to -2.6) | 221 (148 to 329) | 0.61 (0.36 to 1.04) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 500 IU | 112 | 104 | 93 (86 to 97) | -2.7 (-11.7 to 6.3) | 440 (299 to 648) | 1.21 (0.72 to 2.05) |
| 1000 IU | 108 | 98 | 91 (84 to 95) | -4.8 (-13.9 to 4.3) | 373 (254 to 549) | 1.03 (0.61 to 1.74) |
| Standard dose | 112 | 107 | 96 (90 to 98) | Reference | 362 (254 to 517) | Reference |

*Seroconversion is defined as a four-fold or greater increase in neutralizing antibody titer at each timepoint from baseline. **The widths of the confidence intervals were not adjusted for multiplicity and may not be used in place of hypothesis testing except for the Day 28 and safety outcomes.

366 **Table 3.** Summary of all adverse events 28 days post-vaccination for all consented participants

| | 250 IU | 500 IU | 1000 IU | Standard dose | Total N=480 |
|---|---|---|---|---|---|
| **Number of AEs reported** | 122 | 163 | 136 | 125 | 546 |
| **Number of subjects with AEs [1]** | 66 | 75 | 68 | 65 | 274 |
| **Number of SAEs reported** | 2 | 0 | 5 | 4 | 11 |
| **Number of subjects with SAEs [1]** | 2 | 0 | 5 | 4 | 11 |
| **Number of AEs by severity*** | | | | | |
| Mild | 92 (75%) | 120 (74%) | 105 (77%) | 98 (78%) | 415 (76%) |
| Moderate | 30 (25%) | 42 (26%) | 29 (21%) | 27 (22%) | 128 (23%) |
| Severe | 0 (0%) | 1 (<1%) | 2 (1%) | 0 (0%) | 3 (<1%) |
| Life-threatening | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Subjects with AEs by severity [2]**** | | | | | |
| Mild | 62 (52%) | 63 (53%) | 60 (50%) | 59 (49%) | 244 (51%) |
| Moderate | 19 (16%) | 31 (26%) | 19 (16%) | 20 (17%) | 89 (19%) |
| Severe | 0 (0%) | 1 (<1%) | 2 (2%) | 0 (0%) | 3 (<1%) |
| Life-threatening | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Number of AEs by relationship to study product*** | | | | | |
| Related | 30 (25%) | 26 (16%) | 29 (21%) | 26 (21%) | 111 (20%) |
| Probably related | 15 (12%) | 25 (15%) | 17 (13%) | 13 (10%) | 70 (13%) |
| Not related | 77 (63%) | 112 (69%) | 90 (66%) | 86 (69%) | 365 (67%) |

367 [1] Subjects who experience one or more AEs or SAEs are counted only once

368 [2] Subjects are counted only once within a particular severity grade or relatedness category

369 *Percentages are based on number of AEs reported for each treatment arm

370 **Percentages are based on N for each treatment arm

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