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Duration of seropositivity following yellow fever vaccination in U.S. military service members

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Abstract

Background: The United States military regularly deploys thousands of service members throughout areas of South America and Africa that are endemic for yellow fever (YF) virus. To determine if booster doses might be needed for service members who are repetitively or continually deployed to YF endemic areas, we evaluated seropositivity among US military personnel receiving a single dose of YF vaccine based on time post-vaccination.

Methods: Serum antibodies were measured using a plaque reduction neutralization test with 50% cutoff in 682 military personnel at 5–39 years post-vaccination. We determined noninferiority of immune response by comparing the proportion seropositive among those vaccinated 10–14 years previously with those vaccinated 5–9 years previously. Noninferiority was supported if the lower-bound of the 2-tailed 95% CI for $p_{10\text{-}14\text{years}} - p_{5\text{-}9\text{years}}$ was ≥−0.10. Additionally, the geometric mean antibody titer (GMT) at various timepoints following vaccination were compared to the GMT at 5–9 years.

Results: The proportion of military service members with detectable neutralizing antibodies 10–14 years after a single dose of YF vaccine (95.8%, 95% CI 91.2–98.1%) was non-inferior to the proportion 5–9 years after vaccination (97.8%, 95% CI 93.7–99.3%). Additionally, GMT among vaccine recipients at 10–14 years post vaccination (99, 95% CI 82–121) was non-inferior to GMT in YF vaccine recipients at 5–9 years post vaccination (115, 95% CI 96–139). The proportion of vaccinees with neutralizing antibodies remained high, and non-inferior, among those vaccinated 15–19 years prior (98.5%, 95%CI 95.5–99.7%). Although the proportion seropositive decreased among vaccinees ≥ 20 years post vaccination, >90% remained seropositive.

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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.

Conclusions: Neutralizing antibodies were present in > 95% of vaccine recipients for at least 19 years after vaccination, suggesting that booster doses every 10 years are not essential for most U.S. military personnel.

Keywords

Yellow fever; Vaccine; Seropositivity; Military

1. Introduction

Yellow fever (YF) virus is a mosquito-borne virus in the genus *Flavivirus*. Clinically, YF disease ranges from a mild, undifferentiated febrile illness to severe disease with jaundice and hemorrhagic manifestations; the case-fatality ratio for severe YF disease is 30–60% [1]. YF virus is endemic to tropical areas of South America and Africa and causes thousands of cases and deaths annually [2,3]. Because there is no specific treatment for YF disease, prevention through personal protection measures and vaccination is critical to lower disease risk and mortality [4]. YF vaccine is a live-attenuated vaccine that was developed in the 1930s [5]. All YF vaccines currently produced are of the 17D or 17DD substrain. The vaccine licensed in the United States is YF-VAX, a 17D-204 substrain vaccine manufactured by sanofi pasteur (Swiftwater, Pennsylvania). For persons for whom vaccination is indicated, a single subcutaneous dose is administered.

Although no human efficacy studies have been performed with YF vaccine, clinical trials have reported that 80% to 100% of vaccinated individuals develop YF virus neutralizing antibodies by 10 days after vaccination [6–8]. Furthermore, most studies found that > 99% of the vaccinated individuals developed neutralizing antibodies by 28 days after vaccination and these antibodies are detectable for years, even decades, following vaccination [2].

From 1965 through 2016, International Health Regulations regarded a single dose of YF vaccine as providing adequate protection for 10 years [9]. The revaccination interval was determined based on published studies from the 1950 s and 1960 s that showed neutralizing antibodies were present in the majority of vaccine recipients for at least 10 years after vaccination [10–12]. Since then, numerous studies have been published on the presence of neutralizing antibodies in adult YF vaccine recipients ≥ 10 years after vaccination [13–24]. Although different techniques and cut off values were used in the studies, most documented a high proportion of vaccine recipients (>80%) with detectable levels of serum neutralizing antibodies up to and beyond 20 years post vaccination [13,16,19,21]. Some of the more recently published studies have reported lower proportions of detectable neutralizing antibodies among adults vaccinated 10 or more years previously; reasons for the difference are not known but could include the use of different assays, cut off values, and vaccines administered [18,23,24].

Based on systematic review of YF vaccine immunogenicity data and information on vaccine failures, the World Health Organization Strategic Advisory Group of Experts (SAGE) on immunization concluded in 2013 that a single dose of YF vaccine was sufficient to provide lasting immunity against YF disease and, therefore, a booster dose was not needed [25]. The following year, the World Health Assembly adopted the recommendation to remove the

booster dose requirement from the International Health Regulations; the revised regulations were enacted in 2016 [26]. The U.S. Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) also determined that a single primary dose of YF vaccine provides long-lasting protection and is adequate for most travelers [27]. However, ACIP currently recommends a booster dose for selected individuals who might not have as robust or sustained immune response to YF vaccine or who are at increased risk for YF disease [28].

The U.S. military regularly deploys thousands of service members throughout areas of South America and Africa that are endemic for YF virus transmission. Because of repeated or continued exposure, a proportion of service members could require a booster dose of YF vaccine to maintain protection. Demonstrating adequate long-term seropositivity would support the use of a single dose of YF vaccine for military personnel, which would decrease cost and conserve resources, negate the impact of the time and schedule interruption needed for revaccination, and possibly reduce adverse events following immunization. We evaluated YF neutralizing antibody titers of U.S. military service members based on time postvaccination, and assessed the impact of selected factors (e.g., age, sex, concomitant vaccines) on titer levels.

2. Methods

The primary objective of this study was to determine if the proportion of military service members who have neutralizing antibodies against YF virus at 10–14 years after a single dose of YF vaccine is non-inferior to the proportion of military service members who have neutralizing antibodies 5–9 years after a single dose of YF vaccine. Secondary objectives were to 1) demonstrate noninferiority of geometric mean titer (GMT) in YF vaccine recipients at 10–14 years post vaccination compared with GMT in YF vaccine recipients at 5–9 years post vaccination; 2) validate the historical estimate of 86% seropositivity rate among YF vaccine recipients at 15–19 years post vaccination; and 3) describe the GMT trends in YF vaccine recipients between 5 and 39 years post vaccination. This study was deemed to be exempt from human protection requirements by Department of Defense (DoD) Institutional Review Board as all samples were anonymized by the DoD Serum Repository prior to sharing with investigators. CDC relied on DoD IRB determination.

Sample size estimates.

The sample size for the primary objective of non-inferiority of seropositivity was calculated using data from five separate studies [10,14,17,29,30]. The data indicated that approximately 93% of vaccinees are seropositive in the 5–9 year time frame and approximately 96% of vaccinees are seropositive in the 10–14 year time frame. We determined that a sample size of 150 individuals per group (or total of 300) was needed to show non-inferiority of seropositivity for the 10–14 year time frame compared to the 5–9 year time frame, with power 88% and size alpha of 5% using a non-inferiority margin of 10% and assuming conservatively that the true underlying seropositivity proportions are equal to 93%. Computations were made using PASS version 11.0.8 (NCSS, LLC, Kaysville, UT). For the secondary objective related to non-inferiority of GMTs, it was assumed that the sample size

needed to show non-inferiority of GMTs between those vaccinated 10–14 years compared to those vaccinated 5–9 years previously was less than that needed to show non-inferiority of the seropositivity. This assumption was made due to the lack of specific GMT data for YF vaccine recipients and calculation from other studies that have found smaller sample sizes are needed for assessing the non-inferiority of GMTs versus seropositivity. For the objective related to seropositivity rates at 15–19 years following vaccination, data from previous studies suggested that the proportion of vaccinees seroprotected 15–19 years post vaccination would be approximately 86% [11,15,16]. A sample size of 200 was expected to estimate a seropositivity rate of 86% with a 95% confidence interval of 81%–90% (i.e., precision approximately ± 4.5%).

Specimen/data acquisition.

All serum specimens used in this study were obtained from existing samples stored in the DoD Serum Repository. The Armed Forces Health Surveillance Branch manages the repository, which contains archived sera collected from military members, at the following time points: 1) upon commencement of military service, 2) every 2 years for routine HIV-1 antibody screening unless more frequent screenings are clinically indicated, and 3) before and after operational deployments. As of September 2012, the repository had sera for 578,000 service members who received at least one dose of YF vaccine, with the serum sample obtained > 9 years following their last dose. A total of 740 serum specimens (aliquot of 0.5 mL) were randomly selected from unique service members who previously received only one dose of YF vaccine during one of the following time intervals: 5–9 years (n = 150), 10–14 years (n = 150), 15–19 years (n = 200), 20–29 years (n = 120), and 30–39 years (n = 120) post vaccination. Only one sample was sought per person to avoid correlation between results and ensure adequate variability and representativeness of the data. For each specimen, data requested included: time since YF vaccination, subject age at time of sample collection, sex, service component, and vaccinations received within 30 days of YF vaccination.

Specimen testing.

Serum specimens were frozen during transport and storage until testing at CDC. Each specimen was tested by a 50% plaque reduction neutralization test ($PRNT_{50}$) for neutralizing antibodies against YF virus using a standardized protocol as previously described [31]. The $PRNT_{50}$ is the reciprocal of the highest serum dilution at which 50% of the virus is inhibited. Titers measured by PRNT are believed to be reliable markers of vaccine efficacy [1,4]. In this analysis, titers ≥ 10 were considered seropositive. Laboratory personnel were blinded to the time at which the subject previous received YF vaccination.

Data analysis.

If time since YF vaccination, subject age at time of sample collection, sex, and vaccinations received within 30 days of YF vaccination were missing for any specimen, the test results for these specimens (n = 58) were excluded from the final data analysis. Specimens were categorized according to the time period between the YF vaccine dose and specimen collection. Categorical variables are presented as frequencies and proportions and compared using 95% confidence intervals (95% CI) for the difference of proportions. Continuous

variables are presented using median and range or GMT with 95% CI, and comparisons of GMTs are based on ratios and 95% CI. Titers < 10 were assigned a value of 5 for GMT calculations. To determine if the immunologic response at ≥ 10 years was no worse than that before 10 years, noninferiority was evaluated [32] with the primary comparison being the proportion (p) of participants seropositive in the group vaccinated 10–14 years previously ($p_{10\text{-}14\text{years}}$) with that of the group vaccinated 5–9 years previously ($p_{5\text{-}9\text{years}}$). Noninferiority was supported if the lower-bound of the 2-tailed 95% CI for $p_{10\text{-}14\text{years}} - p_{5\text{-}9\text{years}}$ was ≥ −0.10. Margin of 10% was utilized as this is relatively standard in vaccine trials but also to ensure herd immunity with at least 80% seropositivity at 10–14 years post-vaccination based on the seropositivity estimate of 93% at 5–9 years post vaccination [10,14,17,29,33]. A secondary immunogenicity assessment was made by comparing the GMT at 10–14 years following YF vaccination with the GMT at 5–9 years following vaccination. Noninferiority was defined as the lower bound of the two-tailed 95% CI of the GMT ratio in 10–14 years post vaccination group to 5–9 years post vaccination group > 1/1.5, which for titers would typically be within one fold and not considered to be different [31]. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and R version 3.0 (www.r-project.org).

3. Results

A total of 682 specimens were included in the analysis, representing the following time intervals following primary YF vaccination: 5–9 years (136), 10–14 years (144), 15–19 years (193), 20–29 years (111), and 30–39 years (98). In all time interval groups, >85% of service members were male and the overall median age at the time of vaccination was 22 years (range 18–51). The median age at vaccination decreased with increasing number of years since vaccination (Table 1). Overall, 364 (53%) of service members were administered YF vaccine alone. The proportion of service members administered YF vaccine alone was significantly lower among those vaccinated 5–9 years ago compared to those vaccinated 15–39 years previously. Very few service members (23, 3%) received another live vaccine in the 30 days prior to YF vaccination.

Overall, a total of 652/682 (95.6%) service members were seropositive for YF. The proportion seropositive among those vaccinated 10–14 years (95.8%) or 15–19 years (98.5%) previously was non-inferior to that among those vaccinated 5–9 years previously (97.8%) (Table 2). The lowest proportion seropositive was seen among persons vaccinated 20–29 years prior to specimen collection (91.0%). GMTs for the 10–14 and 15–19 year groups also were non-inferior to the 5–9 year group (Figure). The GMTs also were lowest among persons vaccinated 20–29 years prior to specimen collection (Figure). (See Fig. 1)

The proportions of service members seropositive by YF administrated alone or in combination with other vaccines were not statistically significantly different overall (96.4% vs 94.7%, p = 0.26) or by years since vaccination (Table 3). Only one (4%) of the 23 service members who received another live vaccine in the 30 days prior to YF vaccination was seronegative.

4. Discussion

This is one of the largest studies to investigate the duration of immunity following a single dose of YF vaccine in adults. We found that seropositivity and antibody titers measured 10–19 years following a single dose of YF vaccine were noninferior to those measured 5–9 years following a single dose. These results suggest that booster doses every 10 years are not necessary for most U.S. military personnel and provides additional evidence of the robust duration of immunity among healthy adults following a single dose. >90% of vaccinees had detectable neutralizing antibodies all at time points up to 39 years post-vaccination, but the proportion with detectable antibodies were significantly lower ≥ 20 years following vaccination compared to the proportion at 5–9 years.

There are several publications that report on the immune response following YF vaccine in adults [13–24]. In the first 5 years post-vaccination, seropositivity has been consistently reported to be > 90%. Although different techniques and cut off values were used in the studies, most have documented a high proportion of vaccine recipients (>80%) with detectable levels of serum neutralizing antibodies up to and beyond 20 years post vaccination [13,16,19,21]. Interestingly, two studies saw higher rates of seropositivity 30 to 35 years post-vaccination compared to rates at 10 to 20 years post vaccination [19,21]. In our study, the seropositivity rate among YF vaccine recipients at 15–19 years post vaccination (98.5%, 95% CI 95.5%, 99.7%) was higher than the historical estimate of 86%. We also saw slightly higher GMTs at 30–39 years post-vaccination compared to those at 20–29 years post-vaccination. The specific reason for this difference is not known but could be due to differences in the potency of YF vaccines products that have been administered overtime [1]. It is also possible that persons in this group may have been revaccinated at some point. While specimens were only included from service members whose records indicated that they previously received only one dose of YF vaccine, it is possible that some records may have been incomplete.

In contrast to our findings, a few more recently published studies have reported lower proportions of detectable neutralizing antibodies among adults vaccinated 10 or more years previously [18,23,24]. Data from a cohort of 651 adults in Brazil found that 93% of vaccine recipients were seropositive at 30 days postvaccination compared to 85% at 12 or more years postvaccination. Interestingly, lower rates of seropositivity (76%) were seen in persons who were 5–9 years postvaccination [18]. The authors noted the difference in their results compared to other studies and suggested these differences might be the result of variation in the immune response to specific vaccine strains (i.e., 17DD vs 17D-204) or to preexisting immunity or natural boosting in endemic areas compared to nonendemic areas as was seen in a separate study comparing the immune response to YF vaccination. A second Brazilian cohort reported seropositivity of 90% at 5–9 years postvaccination, but a decrease to 71% (39/55) among those vaccinated ≥ 10 years previously [23]. A cross-sectional analysis of 17D vaccinees living in a nonendemic area (Portland, Oregon) reported decreased seropositivity even among vaccinees at 3–12 years previously (28/37; 76%) and only 67% (22/32) for those vaccinated > 12 years [24]. This study used $PRNT_{90}$ to quantify antibody titers, which may explain some of the difference from our study, which used the more sensitive $PRNT_{50}$.

There have been additional immunogenicity studies published among children receiving a YF vaccine, but these have reported widely variable short-term and long-term seropositvity rates [34–38]. One potential explanation for the varying immune responses seen in the pediatric studies could be the age at which the children received their vaccine. Younger age groups might be expected to have a less robust initial immune response, potential immunologic interference from maternal antibodies among infants, or more concomitant infections leading to decreased immune response. However, a *meta*-analysis of the immunologic response at 1-month post-vaccination among children did not find differences in the proportion positive for those < 9 months or < 12 month when compared to older children [27]. Additional hypotheses for the variation in immune response in pediatric studies include differences in underlying degree of immune activation (immune microenvironment), vaccine substrains used, vaccine handling, specimen handling, and assays used.

Although all recent studies reporting YF vaccine immunogenicity data used PRNT or microneutralization test for the detection of neutralizing antibodies against YF virus, the percent plaque reduction cut-off used and the definition of seropositivity varied by study, making the findings difficult to compare. Many of these reports are also limited by low numbers of participants, and therefore lacked power for robust inference. Several other factors may have impacted the seropositivity rates reported in these studies, including differences in vaccines or vaccine formulations, documentation of vaccination (receipt of vaccination or accurate documentation of date of vaccination), ages at vaccination, and potential for having received additional doses of YF vaccine. Notably, there have not been apparent differences between studies undertaken in endemic and non-endemic countries.

There are multiple limitations of this analysis. First, this cohort included only military service members, who were mostly young, healthy adult men; therefore, these findings are not generalizable to the larger population of travelers and may have impacted the duration of immunity observed as males have been found in other studies to develop slightly higher titers following YF vaccination than females [39–42]. Additionally, military service members might have been exposed to YF virus during service deployments, resulting in a natural boosting response. Unfortunately, complete data on deployments to YF endemic countries were not available and therefore we were unable to account for potential reexposure to YF virus, which could have positively influenced the seropositivity rate. Because some individuals (<1%) do not respond or seroconvert following YF vaccination, the absence of detectable neutralizing antibodies among some service members may reflect primary vaccination failure, not waning immunity over time. Although most military members likely received YF-VAX, which was licensed in the US in 1978, some of the service members in the 30–39 years cohort likely received the YF vaccine manufactured by National Drug Company. The two vaccines differ slightly in amount of virus in a dose, which might have contributed to some of the variation in titers we observed over time [1]. Finally, it is unknown if the absence of detectable neutralizing antibodies represents an absence of protective immunity against wild-type YF disease or what amount of antibody might be needed to protect someone against developing a symptomatic infection or viremia.

In our study, neutralizing antibodies were present in > 90% of vaccine recipients for at least 39 years after vaccination. When compared to 5–9 years post-vaccination, seropositivity rates and GMTs at 10–19 years post-vaccination were non-inferior, suggesting that booster doses every 10 years are not necessary for most U.S. military personnel. Overall, these data support WHO recommendations to remove booster dose requirement for YF vaccination. However, additional research is needed to determine what constitutes protective immunity against YF virus infection and the durability of immunity elicited by YF vaccine [43]. Continued improvement of YF disease surveillance and laboratory testing is crucial to detect potential vaccine failures and identify increases in YF disease activity in areas where booster doses of YF vaccine are no longer being administered. Future studies should be carefully conceived to ensure that studies are sufficiently powered to detect genuine differences, should they exist, and to allow for comparability of results.

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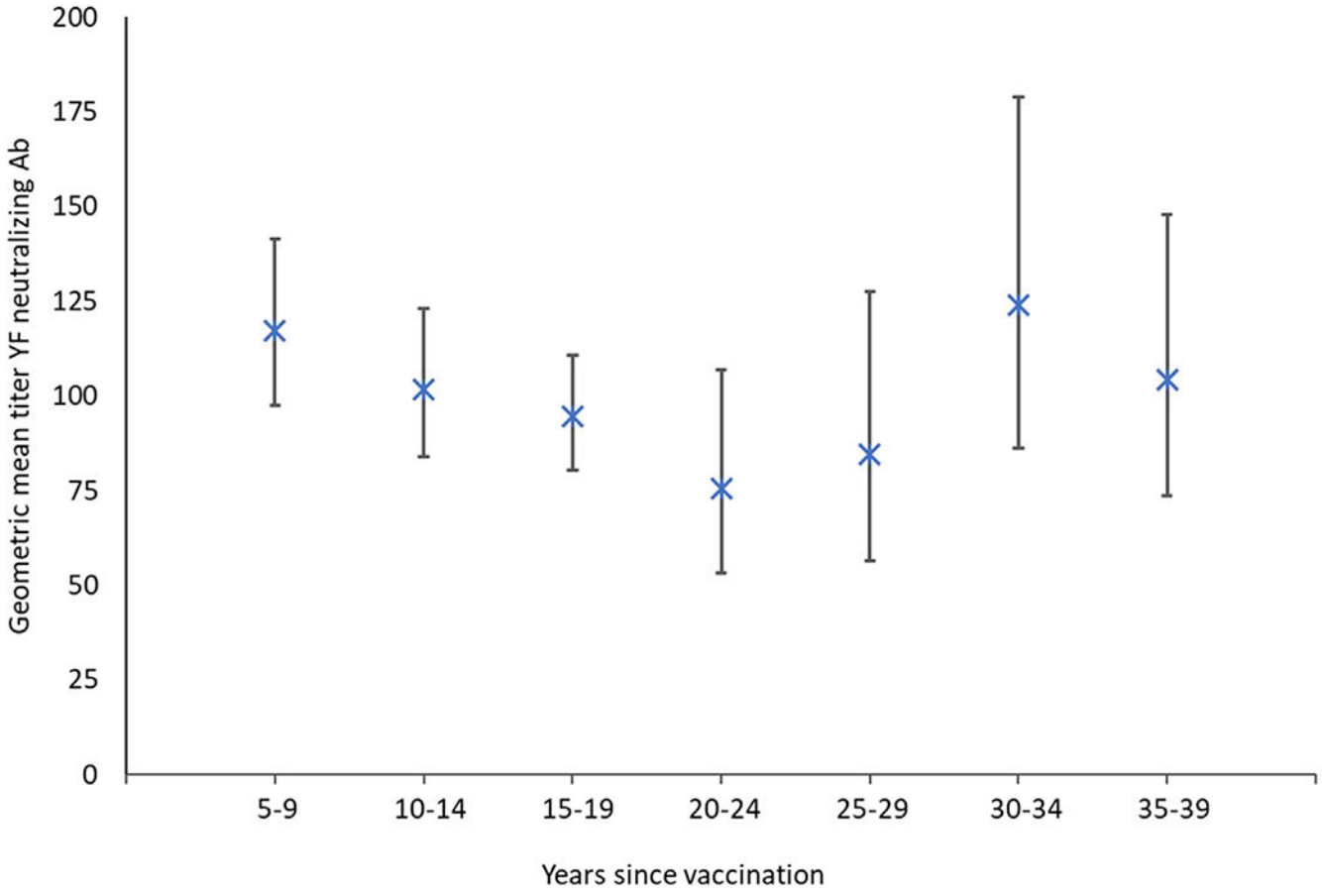

Fig. 1.

Yellow fever neutralizing antibody titers[a] by years since vaccination among U.S. military service members. [a] Geometric mean and 95% confidence intervals. As measured by 50% plaque reduction neutralization test. [b] Non-inferiority to 5–9 year group not supported. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Characteristics of service members with serum tested for yellow fever neutralizing antibodies by years since vaccination.

Years since vaccination	Total	Male		Median age at vaccination (range)		YF Alone [a]	
	No.	No.	(%)			No.	(%)
5–9	136	117	(86)	24	(18–51)	50	(37)
10–14	144	123	(85)	24	(18–45)	60	(42)
15–19	193	167	(87)	23	(18–49)	120	(62) [b]
20–29	111	96	(86)	22	(18–35) [b]	71	(64) [b]
30–39	98	90	(92)	19	(18–29) [b]	63	(64) [b]
Total	682	593	(87)	22	(18–51)	364	(53)

[a] Yellow fever vaccination given without other concomitant vaccinations

[b] Significantly different than 5–9 year group

Table 2

Proportion of U.S. military service members with yellow fever neutralizing antibodies[a] by years since vaccination.

Years since vaccination	Positive $PRNT_{50}$/tested	Proportion positive	95% CI	Δ proportion positive	Exact 95% CI for Δ	GMT[b]	95% CI
5–9	133/136	97.8	93.7, 99.3	ref		115	96, 139
10–14	138/144	95.8	91.2, 98.1	−2.0	−7.0, 2.7	99	82, 121
15–19	190/193	98.5	95.5, 99.5	0.7	−2.8, 5.0	96	82, 114
20–29	101/111	91.0	84.2, 95.0	−6.8	−14.0, −1.0[c]	83	63, 109[c]
30–39	90/98	91.8	84.7, 95.8	−6.0	−13.4, −0.3[c]	108	82, 144

[a] As measured by 50% plaque reduction neutralization test. The $PRNT_{50}$ is the reciprocal of the highest serum dilution at which 50% of the virus is inhibited.

[b] Geometric mean titer

[c] Non-inferiority to 5–9 year group not supported

Table 3

Proportion of U.S. military service members with yellow fever neutralizing antibodies[a] by years since vaccination and vaccine administration.

Years since vaccination	YF Alone (N = 364)			YF in Combination (N = 318)		
	Positive $PRNT_{50}$/tested	Proportion positive	95% CI	Positive $PRNT_{50}$/tested	Proportion positive [b]	95% CI
5–9	50/50	100.0	92.9, 100	83/86	96.5	90.2, 98.8
10–14	58/60	96.7	88.6, 99.1	80/84	95.2	88.4, 98.1
15–19	118/120	98.3	94.1, 99.5	72/73	98.6	92.6, 99.9
20–29	65/71	91.6	82.8, 96.1	36/40	90.0	76.9, 96.0
30–39	60/63	95.2	86.9, 98.4	30/35	85.7	70.6, 93.7

[a] As measured by 50% plaque reduction neutralization test. The $PRNT_{50}$ is the reciprocal of the highest serum dilution at which 50% of the virus is inhibited.

[b] None were significantly different than the YF alone group by Fisher's exact test.