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Vaccine 24 (2006) 2843–2849
Vaccine
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Neutralizing antibody response to booster vaccination with the 17d yellow fever vaccine

M.J. Hepburn *, M.G. Kortepeter, P.R. Pittman, E.F. Boudreau, J.A. Mangiafico, P.A. Buck, S.L. Norris, E.L. Anderson

Division of Medicine, United States Army Medical Research Institute for Infectious Diseases, 1425 Porter Street, Fort Detrick, MD 21702-5011, United States

Received 11 August 2005; received in revised form 8 December 2005; accepted 23 December 2005
Available online 18 January 2006

Abstract

A retrospective review was conducted of yellow fever vaccination among laboratory workers receiving annual serologic assessment to determine the initial and long-term response after boosting. Patients were divided into three groups based on pre-vaccination serology: Group 1, 1:10; Group 2, 1:20–1:40 and Group 3, >1:40. The percent with ≥four-fold increase in titers after booster vaccination were: 78% (646/829, Group 1), 65% (79/121, Group 2) and 10% (8/79, Group 3) ($p < 0.0001$). The median times to titer failure (<1:40) were 798 days (Group 1), 3340 days (Group 2) and 7709 days (Group 3) ($p < 0.0001$). Pre-vaccination serology influenced the initial and long-term response to yellow fever booster vaccination.
Published by Elsevier Ltd.

Keywords: Yellow fever vaccine; Booster; Neutralizing antibody

1. Introduction

The 17d live, attenuated yellow fever virus vaccine has been very successful at limiting the global impact of yellow fever. However, a resurgence of yellow fever in South America and Africa as well as increasing travel to areas in which yellow fever is endemic [1,2], have necessitated continuing investigation into understanding the immune response to this vaccine. Additional interest has been generated by its use as a chimera virus vaccine to induce an immune response to other flaviviruses, such as Japanese Encephalitis virus [3], dengue virus [4] and West Nile virus [5].

World Health Organization (WHO) guidelines recommend booster yellow fever vaccination every 10 years [6], but this recommendation is not supported by specific clinical evidence. Some studies suggest the yellow fever vaccination may confer immunity for at least 17 [7] or 30–35 years [8]. Protection may be life-long, as there are no known cases of yellow fever infection in patients who have been vaccinated and had an appropriate initial response [2]. The effect of one or more booster vaccinations on the duration of immunity is unknown. Additionally, there are reports of severe infection after vaccination particularly in elderly patients [9], although incidence is rare [10]. Determining the optimal dosing regimens that may minimize boosting would be preferable for the future use of this vaccine.

Prior studies have offered two different possibilities regarding the serologic response to booster vaccination: (1) the existence of pre-formed antibodies in the serum inhibits a strong serologic response to a live, attenuated vaccine or (2) immunologic memory allows for a robust serologic response to vaccination. One hypothesis compatible with both of these explanations is that patients receiving booster vaccination to live, attenuated vaccines with low pre-booster titers would have a strong serologic response, while patients with high pre-booster titers would tend to have a muted response. This explanation has been suggested in prior literature on the yellow fever vaccine [11–13]. These studies were performed

* Corresponding author. Present address: PSC 821, Box 84, FPO, AE 09421, United States. Tel.: +1 44 1980 613 929; fax: +1 44 1980 613 284.
E-mail address: matthew.hepburn@amedd.army.mil (M.J. Hepburn).

0264-410X/$ – see front matter. Published by Elsevier Ltd.
doi:10.1016/j.vaccine.2005.12.055

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
1 APR 2006	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Neutralizing antibody response to booster vaccination with the 17d yellow fever vaccine, Vaccine 24:2843 - 2849	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Hepburn, MJ Kortepeter, MG Pittman, PR Boudreau, EF Mangiafico, JA Buck, PA Norris, SL Anderson, EL	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD	**RPP-05-397**
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

A retrospective review was conducted of yellow fever vaccination among laboratory workers receiving annual serologic assessment to determine the initial and long-term response after boosting. Patients were divided into three groups based on pre-vaccination serology: Group 1, 1:10; Group 2, 1:20-1:40 and Group 3, >1:40. The percent with >/=four-fold increase in titers after booster vaccination were: 78% (646/829, Group 1), 65% (79/121, Group 2) and 10% (8/79, Group 3) (p<0.0001). The median times to titer failure (<1:40) were 798 days (Group 1), 3340 days (Group 2) and 7709 days (Group 3) (p<0.0001).
Pre-vaccination serology influenced the initial and long-term response to yellow fever booster vaccination.

15. SUBJECT TERMS

yellow fever virus, vaccine, booster, neutralizing antibody, vacccination

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**SAR**	**7**	

on limited numbers of patients, without a significant range of pre-booster serologies. A similar phenomena has been described after measles vaccination and booster [6,14]. Generally, a strong amnestic response would be expected after booster vaccination if enough viral replication or antigen is present [12], and this response would be specific to yellow fever. The concept of 'original antigenic sin' has been observed after yellow fever vaccination, in that a strong antibody response to yellow fever occurred when patients who had received the 17d yellow fever vaccine were exposed to another flavivirus vaccine [15]. In these patients, the response to the current antigen is delayed.

To investigate these hypotheses, we conducted a retrospective review of active and archived records in our Special Immunizations Program to assess the initial and long-term serologic response of yellow fever booster vaccination in patients who have been primed and show evidence of pre-booster neutralizing antibodies to yellow fever. We suspected that the aforementioned hypothesis regarding a differential initial response, based on the level of pre-existing antibodies, would be observed and booster vaccination would lead to prolonged and elevated antibody levels.

2. Materials and method

2.1. Patients

Serologic data on participants in the Special Immunizations Program (SIP) at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) were analyzed. This program provides vaccinations to protect laboratory researchers from potential exposures to various infectious diseases studied in the Institute's laboratory containment suites. As part of this program (beginning in the 1960s), at-risk participants received the 17d yellow fever vaccine. To minimize the risk to the researchers and to add an additional measure of protection, neutralizing antibody responses to the vaccine were measured regularly, and booster vaccination given to workers with low titers. If the neutralizing antibody titer decreased below 1:40, participants would receive a booster vaccination. The policy was modified slightly in 1996, so that booster shots were administered if titers fell below 1:20. The annual surveillance of yellow fever titers ended in 2002. Patients routinely had titers measured 28 days after booster vaccination. Serologic results were maintained in a database. Volunteers were also identified if they received another flavivirus vaccine such as Japanese Encephalitis (JE) virus or Tick-borne Encephalitis (TBE) during the study period.

Records were reviewed on 17d yellow fever vaccine recipients between 1976 and 2002. This time period was selected since the method for measuring the serologic response (80% plaque reduction neutralization titers or PRNT) was performed with identical technique. For patients vaccinated prior to SIP entry, no documentation of the date of primary vaccination was available; therefore, the time between primary and booster vaccination was not known. Patients with no pre-vaccination serology, or a pre-vaccination serology of zero were excluded from the analysis. Some patients received a booster vaccination on enrollment even when their pre-vaccination titer was >1:40. Archived records suggested this practice was conducted to ensure immunity for laboratory workers at risk of potential infection from yellow fever. Age, gender and race were recorded on these patients for sub-group analysis. Race was determined by self-classification. The Human Use Committee at USAMRIID approved the study (protocol #FY03-28, approved 18 December 2003).

2.2. PRNT

Patient sera were tested for neutralizing antibody to yellow fever virus (YFV) using a $PRNT_{80}$ as described by Mangiafico et al. [16], but modified for use with the Asibi strain of YFV. Briefly, test sera and controls were initially diluted 1:10 in HBSS containing penicillin and streptomycin and heat inactivated at 56° for 30 min. Serial four-fold dilutions were then prepared, through 10,240 from the 1:10 dilution, in HBSS containing human serum albumin, HEPES, penicillin and streptomycin. An equal volume of YFV, calculated to yield approximately 50–100 pfu/0.1 ml, was added to each serum dilution and the mixture held overnight at 4 °C. The next day mixtures were inoculated into duplicate 23 mm wells (0.1 ml/well) with a confluent layer of LLC-MK_2 cells and placed in a 37 °C incubator with 5% CO_2 for approximately 1 h. Inoculated wells were then overlaid with 1% agar containing nutrient medium, 5% fetal bovine serum, 200 U penicillin/ml and 200 mg streptomycin/ml and placed in a 37° with 5% CO_2 for approximately 72 h. A second overlay, similar to the first but containing neutral red was then added to all wells. Plates were returned to the 37° plus 5% CO_2 incubator and checked daily until visible plaques were countable. The neutralizing antibody titer was expressed as the reciprocal of the highest initial serum dilution that inhibited 80% or greater of the plaque formation compared with the virus control titration. Two-fold antibody titers (1:20, 1:80, etc.) were obtained through interpolation.

2.3. Analysis

Patients were divided into three groups: Group 1 had pre-booster vaccination serologies of 1:10, Group 2 had pre-booster serologies of 1:20 or 1:40 and Group 3 had pre-booster serologies of >1:40. The initial response to boosting was examined by comparing pre-booster and post-booster (within 365 days after vaccination) geometric mean titers (GMT), as well as the post/pre titer ratio. Additional analysis was performed to determine if including only subjects with an initial titer within 35 or 90 days had any impact on the results. Sub-group analysis was also performed to determine if subjects with initial titers within the first 35 or 90 days had different results compared to subjects with later initial

post-vaccination titers. The response rates between groups were compared, with response defined as a four-fold increase in titers.

The overall post-vaccination titers and response rates (four-fold increase in titers) were compared for three demographic characteristics: race (White versus African American), gender and age. Ethnic groups were classified as White or African American, with other groups excluded from the analysis due to low numbers. Age was considered a continuous variable. Sub-group analysis was performed on each pre-vaccination titer group, comparing the aforementioned demographic characteristics. For Group 1, an additional outcome measure was utilized: developing a post-vaccination titer $\geq$1:20 (yes/no, considered a dichotomous variable). Additionally, covariate analysis was utilized to determine if any of the difference in post-vaccination titer and response rates was attributable to demographic characteristics as opposed to pre-vaccination titer.

The long-term response to booster vaccination was examined by comparing all titers, including annual titers, recorded after first boost until administration of a second booster or exit from the program. Failure was defined as titer declining below 1:40 or receipt of an additional booster vaccination. The analysis was repeated using a definition of failure as decline in titers below 1:20 or receiving repeat vaccination. This second analysis was performed to confirm the validity of the data using a different cut-off point, since a cut-off point of 1:20 was utilized in more recent years in our program. Sub-group analysis was conducted to compare differences in vaccine response rates between genders, age groups (in deciles) and ethnic groups.

2.4. Statistical analysis

All titer values were log 10 transformed for analysis. After transformations were applied, the titer variables met assumptions of normality and homogeneity of variance. Analysis of variance (ANOVA) was used to compare the post-serologic response between the three groups, with the Tukey–Kramer test for post hoc pair-wise testing. ANOVA was also used to compare titer response between races, genders and age groups. Chi-square tests and Fisher's exact tests were used to compare response rates to vaccination between groups, as well as between races, genders and age groups. Analysis of covariance (ANCOVA) and logistic regression were performed to determine the effect of a demographic variable on the response to vaccination between different pre-vaccination titer groups. Kaplan–Meier product-limit survival analysis was used to evaluate duration of serologic response to vaccination. Log-rank tests were used to compare rate of titer failure over time between groups. All analyses were conducted using SAS Version 9.1 (SAS Institute Inc., SAS OnlineDoc, Version 9, Cary, NC, 2003).

3. Results

Pre-vaccination and a minimum of one post-vaccination serology were available on 1029 patients and the total number of post-vaccination titers over time was 4796. These were divided into three groups for analysis: 829 patients with pre-booster serologies at 1:10 (Group 1), 121 patients at 1:20–1:40 (Group 2) and 79 patients with a pre-booster serology >1:40 (Group 3). The gender, racial background and mean age of each group are indicated in Table 1. There were differences between groups in the mean age of patients and numbers of males, with Group 1 having a higher percentage of females and a lower mean age than either Groups 2 or 3 ($p < 0.0001$ for all).

3.1. Initial response to booster vaccination

The ratio of post to pre titer was 11.1 (95% CI: 10.0, 12.5) for Group 1, 4.6 (95% CI: 3.7, 5.6) for Group 2 and 1.3 (95% CI: 1.1, 1.5) for Group 3 (Table 2), demonstrating a minimal increase in titers in patients with a high pre-vaccination titer. However, the post-vaccination geometric mean titer in Group 3 (1:203) was significantly higher than Group 2 (1:119, $p = 0.0431$) or Group 1 (1:111, $p = 0.0028$). When assessing response rates (four-fold increase in titers)

Table 1
Demographic information on patients

Variable	Group 1, *n* (%)	Group 2, *n* (%)	Group 3, *n* (%)	Overall, *n* (%)	*p*-Value
Gender					0.0001*
Male	622 (75)	112 (93)	78 (99)	812 (79)	
Female	207 (25)	9 (7)	1 (1)	217 (21)	
Race					0.0701
White	700 (84)	104 (86)	73 (92)	877 (85)	
African American	61 (7)	11 (9)	6 (8)	78 (8)	
Hispanic	30 (4)	3 (2)	0	33 (3)	
Asian	31 (4)	1(1)	0	32 (3)	
Other	7 (1)	2 (2)	0	9 (1)	
Age (mean ± S.D.)	30.4 ± 8.5	39.1 ± 10.4	38.1 ± 11.8	32.0 ± 9.6	<0.0001#

* For gender comparisons, Group 1 was different than Group 2 ($p < 0.0001$) and Group 3 ($p < 0.0001$), whereas Group 2 and Group were not different (p = NS).
\# For age comparisons, Group 1 was different than Group 2 ($p < 0.0001$) and Group 3 ($p < 0.0001$), whereas Group 2 and Group were not different (p = NS).

Table 2
Comparison of pre-booster and post-booster titers within groups

Group	Pre-shot titer			Post-shot titer[a]			Ratio of post to pre		
	Geo. mean	Lower 95% CI	Upper 95% CI	Geo. mean	Lower 95% CI	Upper 95% CI	Geo. mean	Lower 95% CI	Upper 95% CI
1	10.00			100.72	92.62	109.52	10.07	9.26	10.95
2	25.64	24.39	26.95	109.35	94.06	127.13	4.26	3.63	5.01
3	152.19	134.79	171.84	176.83	146.20	213.88	1.16	0.98	1.37
Overall	13.85	13.19	14.54	117.56	106.94	129.23	8.48	7.66	9.38

Most subjects had titers drawn within 90 days after vaccination.
[a] Post-shot tiers were the first available titers within 365 days after the vaccination.

between groups, only 10% (8/79) of patients in Group 3 had a ≥four-fold rise in titers compared to Group 1 (78% (646/829), $p < 0.0001$) or Group 2 (65% (79/121), $p < 0.0001$). The difference between Groups 1 and 2 was statistically significant ($p = 0.002$). Among all patients, 71% (733/1029) had a four-fold rise in titers after vaccination.

A majority of subjects had their post-vaccination titer within 35 days of booster vaccination (Group 1, 604/829 or 73%; Group 2, 67/121 or 55% and Group 3, 33/79 or 42%) and almost all subjects were within 90 days (Group 1, 779/829 or 94%; Group 2, 102/121 or 84% and Group 3, 60/79 or 76%). When comparing %subjects with an initial four-fold rise in titer before versus after 35 and 90 days within groups, there was no statistically significant difference within Groups 1 and 3. For Group 2, the %subjects with a four-fold rise was greater before versus after 35 days (50/67 or 75% versus 29/54 or 54%, $p = 0.02$) and 90 days (71/102 or 70% versus 8/19 or 42%, $p = 0.02$). Additionally, we assessed for difference between Groups 1 and 3 in terms of %subjects with four-fold titer increase, but using cut-offs to only include subjects with initial titers within 35 and 90 days. The results were similar to comparing Groups 1–3 with a cut-off of 365 days (analysis above), as Group 3 was statistically different than Groups 1 and 2 ($p < 0.0001$). The only discrepancy in results when using an early cut-off date was that the difference between Groups 1 and 2 was not statistically significant at 35-day cut-off ($p = 0.53$) but was significant at a 90-day cut-off ($p = 0.045$).

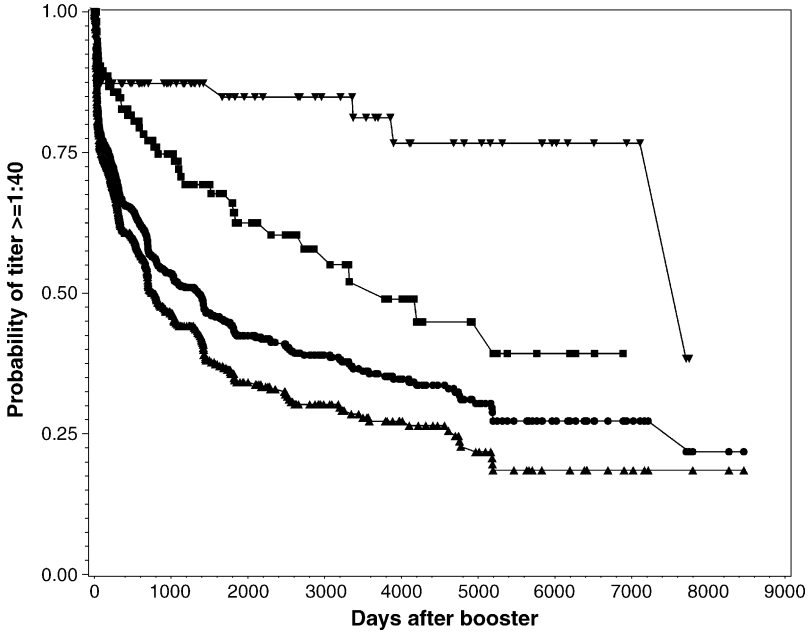

Fig. 1. Response to booster vaccination with the yellow fever vaccine, USAMRIID. Analysis of time from vaccination to loss of titer and/or additional booster given, with cut-off to failure at less than 1:40. (●) All patients ($n = 1029$); (▲) Group 1, pre-booster titer 1:10 ($n = 829$); (■) Group 2, pre-booster titer 1:20–1:40 ($n = 121$) and (▼) Group 3, pre-booster titer >1:40 ($n = 79$).

Percentile	KM estimate of time to loss of titer (in days post-shot)			
	Group 1	Group 2	Group 3	Overall
25	200	774	2854	184
50 (median)	714	3072	7709	1363
75	4204	6172	n/e	7709

Overall, African Americans had a lower mean post-vaccination titer than Whites (1:70 versus 1:124, $p = 0.0015$), as well as a lower percentage of patients achieving a four-fold increase (60% versus 72%, $p = 0.0292$). In analysis within Group 1, African Americans also had lower mean post-vaccination titers (1:54 versus 1:120, $p = 0.0003$), lower percentage four-fold increase in titers (61% versus 80%, $p = 0.0005$) and a lower number with an increase in titer above 1:20 (61% versus 80%, $p = 0.0005$). There were no differences in post-vaccination titers or response rates between males and females ($p =$ NS). Age was not associated with differences in post-vaccination titers ($p =$ NS), but was associated with the percentage of patients with a four-fold increase in titer ($p = 0.0180$). For every year of increasing age, the probability of achieving a four-fold titer response was reduced by 1.7%. An association with age and either post-vaccination titer or four-fold increase in post-vaccination titer was not observed in any sub-group analysis.

ANCOVA and logistic regression tested the influence of demographic characteristics on the observed response to booster between pre-vaccination titer groups. However, when controlling for the demographic characteristic, the differences between pre-vaccination titer groups remained significant, suggesting that demographic differences between pre-vaccination titer groups did not affect the observed differences in post-vaccination response.

3.2. Duration of a positive serology

There was a significant difference in the rate of titer failure among the three groups ($p < 0.0001$, Fig. 1). All subsequent pair-wise comparisons between the groups showed statistical significance. Group 1 showed a significantly different rate of titer failure than both Group 2 ($p < 0.0001$) and Group 3 ($p < 0.0001$). Groups 2 and 3 were also significantly different ($p = 0.0013$). Similar results were obtained when failure was defined as titer declining below 1:20 (data not shown).

Regarding subjects who received another flavivirus vaccine during the follow-up after YF booster, there were only three subjects who received TBE vaccination after YF booster, post-vaccination titer and then had a subsequent YF titer drawn. All three of these subjects had a four-fold rise in YF titers after TBE vaccination. Five subjects received JE virus vaccine after YF booster, and had a subsequent titer measured. Only one subject had a four-fold increase in titers; the remaining four subjects had either a two-fold or no rise in titers.

4. Discussion

Our review of neutralizing antibodies after booster yellow fever vaccination indicated that patients with lower baseline titers exhibited a relatively robust serologic response. In contrast, patients with a high baseline titer demonstrated minimal serologic response, possibly due to pre-formed antibodies. Vaccine recipients with a low pre-boost titer declined below 1:40 within 3 years. Patients with a higher baseline titer maintained a persistently high titer for more than 10 years after booster vaccination. Overall, our data demonstrate that the initial response and the longevity of a high serologic response (>1:40) varies based on their pre-vaccination serology.

The results of this study may be useful in the development of flavivirus chimera vaccines. Chimeras for vaccination against Japanese Encephalitis virus [3], dengue virus [4] and West Nile virus [5] appear to be promising in early studies. Our data would imply that patients with high pre-existing antibody titers against yellow fever virus might have poor responses to those vaccines, as pre-existing serologies could remove the chimera virus prior to the induction of protective immunity. This phenomenon was observed with a vaccinia-vectored hantavirus vaccine [17]. The same may not be true for patients with low pre-existing titers who would be expected to have a robust response, and may not need to be excluded from receiving these chimera vaccine products.

We anticipated that the initial booster response to yellow fever vaccination would be affected by pre-existing immunity. Prior literature supported this hypothesis in limited numbers of patients [12,13,18,19]. The proposed explanation is that pre-formed antibodies facilitate the clearance of the attenuated yellow fever virus before a more robust immune response can be activated. A similar effect has been observed after booster vaccination with the live, attenuated measles vaccine [6,14,20]. It is also possible that cell-mediated immunity quickly disposes of the viral infection before any antibody response can occur. These results imply that since pre-formed antibodies are present in low concentrations, the vaccine virus is allowed to produce a low-level infection, prompting a memory response and an increase in serology. However, we observed that even in patients with a pre-vaccination serology of 1:10 (Group 1), only 78% had a four-fold rise in titers. In some patients, it is possible that even low-level antibodies or perhaps a robust cell-mediated response prevent a serologic response. Additionally, responses would be slightly higher by including only patients with a day 35 post-vaccination titer were included, instead of including all subjects with a titer in the 365 days after vaccination. Alternatively, some patients with low-level pre-vaccination antibody titers may tend have a poor response to vaccination due to host factors beyond our study scope.

We observed that African Americans have a lower response rate to yellow fever boosters, but these results need further study in a racially balanced sample. Racial classifications in medical research have substantial limitations, such as problems with self-classification and racially mixed populations [21–23]. We did not observe a gender effect with booster response within groups or in analysis in which all groups were included. The effect of age on response was observed (older age corresponding to dimin-

ishing response to vaccination), but the effect was not substantial. Although the majority of patients were male overall, the patients in Group 3 (high pre-vaccination titers) were even more predominantly male, but this demographic difference did not affect the response rate differences between pre-vaccination titer groups when covariate analysis was utilized.

Many patients do not maintain a prolonged high titer over time after yellow fever booster vaccination. Our data does not address the question of what level of serology is considered protective, nor is it known. It is plausible that a titer of 1:10 or lower may be protective considering the paucity of cases of yellow fever in vaccinated persons. Additionally, titers may not indicate a linear increase in protection in that any titer above an unknown minimum amount may have an approximately equivalent degree of protection. However, it is also possible that the maintenance of a high titer is more protective, which may be desirable in some populations (laboratory workers).

A limitation of this study is the inability to document the date of primary yellow fever vaccination or if individuals received multiple prior YF vaccinations. It is possible that some patients never received the 17d yellow fever vaccine, and that the yellow fever serology was due to a cross-reactive response to another flavivirus [13,24]. However, the neutralizing antibody response to the yellow fever vaccine is thought to be specific and distinct compared to other flaviviruses [25]. Also, neutralizing antibody tests for yellow fever infection tend to be specific for that organism [26]. Finally, most of the laboratory workers at USAMRIID were either active duty military personnel, or had previously served in the military, and were likely vaccinated once during their military service. It is possible that some of the workers in our study were exposed to yellow fever in the laboratory, thus prompting a boost in their serology, even though personal protective measures were enforced, and no recorded accidents with the yellow fever virus occurred. We do not have examples of patients presenting with an acute illness with an unanticipated four-fold or greater increase in titers over time. Finally, a few patients received vaccination against JE and TBE while following their yellow fever titers, but this small number of subjects would not have a substantial impact on the study results.

Our results indicate that re-vaccination with YF vaccine produces a more pronounced increase in patients with low pre-vaccination serologies. Our data also suggest that most patients will not maintain a titer >1:40 for more than 3–5 years. If a persistent high titer is preferred, booster vaccination more frequently than every 10 years should be considered, except in patients with a high titer already. However, it is unknown whether patients need a titer of 1:40, or even 1:10, to be protected. These findings raise new questions as to whether 10 year boosting is the best strategy for all patients with ongoing risk and potentially provides an opportunity for additional research on optimal dosing schedules.

Acknowledgements

The opinions or assertions contained herein are those of the authors and are not to be construed as official policy or as reflecting the views of the Department of the Army or the Department of Defense. Presented in part: Infectious Diseases Society of America Annual Meeting, Boston MA, October 31–November 2, 2004.

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