Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Duration of post-vaccination immunity to yellow fever in volunteers eight years after a dose-response study

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ARTICLE INFO

Article history:
Received 13 March 2018
Received in revised form 4 May 2018
Accepted 7 May 2018
Available online xxxx

Keywords:
Yellow fever vaccine
Immunogenicity
Dose-response study
Duration of immunity
Fractionated vaccine

ABSTRACT

In 2009, Bio-Manguinhos conducted a dose-response study with the yellow fever vaccine, administering the vaccine in the usual mean dose of 27,476 IU (full dose, reference) and in tapered doses (10,447 IU, 3013 IU, 587 IU, 158 IU, and 31 IU) by the usual subcutaneous route and usual volume (0.5 mL). Tapered doses were obtained by dilution in the manufacturer's laboratory, and the test batches presented industrial quality. Doses down to 587 IU showed similar immunogenicity to the full dose (27,476, reference), while the 158 IU and 31 IU doses displayed lower immunogenicity. Seropositivity was maintained at 10 months, except in the group that received the 31 IU dose. The current study aims to determine whether yellow fever seropositivity was maintained eight years after YF vaccination in non-revaccinated individuals. According to the current study's results, seropositivity was maintained in 85% of 318 participants and was similar across groups. The findings support the use of the yellow fever vaccine in fractional doses during outbreaks, but each fractional dose should have at least 587 IU. This study also supports the minimum dose required by WHO, 1000 IU.

Clinical trials registration: Clinicaltrials.gov NCT 03338231.

1. Background

There is a global shortage of yellow fever (YF) vaccine, and the problem of vaccine stockpile depletion is recurrent due to a combination of limited production capacity and expanding circulation of the YF virus, with increasing risk of YF urbanization or reurbanization in several countries. An estimated 450 million doses are needed to achieve >80% coverage in YF-affected areas, while current annual YF vaccine production is only 80 million doses [1,2]. The situation will become even more dramatic if yellow fever spreads to Asia [3].

In 2016, 7509 suspected and 1080 laboratory-confirmed cases of yellow fever, with 171 deaths, were reported to WHO during outbreaks in six countries, including two urban outbreaks, in Angola and Democratic Republic of Congo (DRC). Yellow fever vaccine stockpiles were depleted. To deal with this challenge, WHO proposed to fractionate the YF vaccine doses to address the emergency in Angola and DRC in 2016 [4]. In August 2016, over 7 million people received 1/5 of the 17DD YF vaccine in Kinshasa, and the epidemic was rapidly controlled [5,6]. Previous dose-response studies were the basis for the WHO recommendation to administer 0.1 mL rather than 0.5 mL, by the usual route (SC or IM). However, due to lack of information on duration of immunity following reduced doses and lack of studies on reduced doses in children and pregnant women, this strategy was only recommended in emergency situations [7].

In Brazil, following YF outbreaks in Greater Metropolitan São Paulo and Rio de Janeiro, a mass vaccination campaign with 1/5 (0.1 mL) of the dose was launched in February 2018. Information on duration of immunity from reduced (diluted or fractional) doses is crucial, considering the possible need to revaccinate these individuals.

Unpredictable YF outbreaks suddenly increase the demand for the vaccine, and production targeted to routine vaccination may not meet the needs for mass vaccination. There are currently only four WHO-prequalified YF vaccine manufacturers, of which only

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https://doi.org/10.1016/j.vaccine.2018.05.041
0264-410X/

two are large-scale producers. In addition, YF vaccine is produced with traditional labor-intensive methods and is rather inexpensive, so it tends not to attract new producers. Alternative vaccines employing more modern technologies have not been developed to date, although they are the object of active research efforts.

In response to the need to increase production by diluting the vaccine, in 1988 Bio-Manguinhos conducted a 17DD YF vaccine dose-response study in adults, with very high seroconversion rates using doses from 2000 PFU (plaque-forming units) to 200 PFU and lower seroconversion rates below this dose. However, the small number of participants in the study arms precluded the adoption of reduced doses of YF vaccine based on these findings [8].

Following the YF vaccine shortage in the 2008 epidemic in Brazil, in 2009 Bio-Manguinhos conducted a randomized dose-response study with the 17DD YF vaccine administered in the usual mean dose of 27,476 IU (full dose, reference) and in tapered doses of 10,447 IU, 3013 IU, 587 IU, 158 IU, and 31 IU, by the usual subcutaneous route and with the usual volume (0.5 mL). Tapered doses were obtained by dilution in the manufacturer's laboratory, and the test batches presented industrial quality. Doses down to 587 IU showed similar immunogenicity to the full dose, whereas the lowest doses, 158 IU and 31 IU, were less immunogenic. Moreover, seropositivity of volunteers who had seroconverted and had not been revaccinated was maintained for at least 10 months, except in the 31 IU dose group [9]. Thirty days after vaccination, in the groups that received doses of 587 IU or greater, only 2.2% of 509 participants failed to seroconvert, and after 10 months, 2.0% more reverted from seropositive to seronegative. Therefore, 4.2% of the initial cohort that received doses of 587 UI or greater were revaccinated because they were seronegative at 30 days or 10 months. In the 158 IU dose and 31 IU dose groups, 13.5% and 43.9%, respectively, were revaccinated for this same reason.

A complementary study in a subset of volunteers from the previous study evaluated the cellular immune response to the YF vaccine and concluded that doses $\geq$3013 IU showed immune responses equivalent to that of the standard mean dose of 27,476 IU [10].

The objective of this study was to evaluate the duration of immunity eight years after administration of reduced doses of the 17DD YF vaccine in the dose-response study in 2009, by measuring neutralizing antibody levels, with a view towards supporting the use of fractionated doses.

2. Methods

2.1. Study design

This was a cohort study in healthy young adult males (military recruits) who had received the 17DD YF vaccine during the dose-response study in 2009 [5]. The target group consisted of participants who were seronegative before vaccination in the dose-response study in 2009 and had not been revaccinated. Participants that were YF-seronegative at 30 days and 10 months after vaccination were revaccinated with the standard dose and were not included in the current study. Participants that had gone on military missions or travelled or lived in YF endemic areas since 2009 were analyzed separately.

Participants were contacted by telephone or home visit, and blood samples were collected at Fiocruz, or if necessary at home or in a safe place, following informed consent.

Participants were asked at least twice if they had been revaccinated, during the initial phone call and in the face-to-face interview when the blood sample was taken. They were also asked to confirm that they had participated in the dose-response study in 2009 and about travels on military missions or to YF-endemic areas.

The study was conducted from March 2017 to September 2017, approximately eight years after the dose-response study.

2.2. Laboratory methods

Serology for YF neutralization was performed in all participants, according to the methods described in the dose-response study of 2009 [9], using the same cut-off for seropositivity: >2.7 log10 mIU/mL (501.2 mUI/mL), or about 1/20 in dilution.

2.3. Statistical analysis

Statistical analysis of neutralizing antibodies was performed, first blindly, by comparison of groups by chi-square or Fisher's exact test, as indicated, or by analysis of variance of log10 titers. After unblinding the codes, each vaccine-dose group's seroprotection rate and neutralizing antibody level were compared to those of the reference group. Volunteers who had travelled or lived in YF-endemic areas or had participated in military missions to endemic areas were analyzed separately. The statistical analyses used SPSS v.20 and WinPepi v. 11. Neutralizing antibody levels are presented in log10 mIU/mL, and geometric mean titers are presented with 95% CI.

2.4. Ethical approval and good clinical practices

The study protocol and final report were approved by the Institutional Review Board of the Evandro Chagas National Institute of Infectious Diseases and by an independent data safety monitoring committee. All the procedures complied with the Declaration of Helsinki, the Brazilian Code of Research Ethics, the Good Clinical Practices: Document of the Americas and the International Conference on Harmonization. The identification and revaccination of individuals that were YF-seronegative eight years after initial vaccination were clear benefits for participants.

2.5. Results and comments

Fig. 1 summarizes the study inclusion steps. 318 participants were eligible according to the study protocol. The lower number of participants in the lowest dose group reflects the high number of primary vaccine seroconversion failures in that group in the dose-response study in 2009 (i.e., with fewer eligible participants for follow-up).

From a total of 370 participants that were included in the 2017 follow-up study, 51 were later found to be ineligible. One other participant was excluded because of a marked rise in antibody levels in 2017, suggesting that he had received a booster dose. Therefore, data from 318 individuals were available for analysis.

The geometric mean titers were similar between the dose groups before vaccination, at one month, and at 10 months after vaccination, but differed substantially at eight years after vaccination (Table 1). From here on, we present only the results at eight years after vaccination.

The difference in seropositivity rates between groups are large but statistically non-significant compared to the reference dose (27,476 IU). A high proportion of participants were seropositive, with no consistent pattern according to vaccine dose (Table 2).

Geometric mean titers were much higher in the 31 IU group, and the discrepancy persisted when the 5% trimmed means were considered in order to reduce the impact of outliers (data not shown). In any case, the lower limits of the 95% CI were above the cut-off of 2.7 log10 mIU/mL (501.2 mIU/mL) in all the groups (Table 3). The scatterplot of log10 neutralizing antibody titers by

Please cite this article in press as: de Menezes Martins R et al. Duration of post-vaccination immunity to yellow fever in volunteers eight years after a dose-response study. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.041