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Duration of post-vaccination immunity against yellow fever in adults

Collaborative group for studies on yellow fever vaccines[1]

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ABSTRACT

Introduction: Available scientific evidence to recommend or to advise against booster doses of yellow fever vaccine (YFV) is inconclusive. A study to estimate the seropositivity rate and geometric mean titres (GMT) of adults with varied times of vaccination was aimed to provide elements to revise the need and the timing of revaccination.

Methods: Adults from the cities of Rio de Janeiro and Alfenas located in non-endemic areas in the Southeast of Brazil, who had one dose of YFV, were tested for YF neutralising antibodies and dengue IgG. Time (in years) since vaccination was based on immunisation cards and other reliable records.

Results: From 2011 to 2012 we recruited 691 subjects (73% males), aged 18–83 years. Time since vaccination ranged from 30 days to 18 years. Seropositivity rates (95%C.I.) and GMT (International Units/mL; 95%C.I.) decreased with time since vaccination: 93% (88–96%), 8.8 (7.0–10.9) IU/mL for newly vaccinated; 94% (88–97), 3.0 (2.5–3.6) IU/mL after 1–4 years; 83% (74–90), 2.2 (1.7–2.8) IU/mL after 5–9 years; 76% (68–83), 1.7 (1.4–2.0) IU/mL after 10–11 years; and 85% (80–90), 2.1 (1.7–2.5) IU/mL after 12 years or more. YF seropositivity rates were not affected by previous dengue infection.

Conclusions: Eventhough serological correlates of protection for yellow fever are unknown, seronegativity in vaccinated subjects may indicate primary immunisation failure, or waning of immunity to levels below the protection threshold. Immunogenicity of YFV under routine conditions of immunisation services is likely to be lower than in controlled studies. Moreover, infants and toddlers, who comprise the main target group in YF endemic regions, and populations with high HIV infection rates, respond to YFV with lower antibody levels. In those settings one booster dose, preferably sooner than currently recommended, seems to be necessary to ensure longer protection for all vaccinees.

1. Introduction

Yellow fever is an acute arboviral disease with clinical presentations that include mild forms with a sudden onset of febrile symptoms and severe forms with over 30% lethality, and also asymptomatic infections [1]. Yellow fever is one of the diseases requiring immediate report to the World Health Organization (WHO) under International Health Regulations [2].

In Brazil, most cases of yellow fever occur among adult males conducting occupational, tourism, or leisure activities in forested areas, where they become exposed to infected mosquitoes, mainly the wild species *Haemagogus janthinomys*. Although disease transmission in urban areas have not been reported in Brazil since 1942, sporadic outbreaks of yellow fever transmitted by jungle vectors in the southern and southeastern regions of the country, close to urban zones where *Aedes aegypti* is abundant, poses a threat of re-urbanisation of the disease [3].

There is no specific treatment for yellow fever. Disease prevention relies on current commercially available vaccines, which are highly immunogenic and safe. Immunisation is recommended to unvaccinated residents and travellers to and from at-risk areas, aged ≥9 months [3,4].

Despite the lack of efficacy studies on yellow fever vaccines, vaccine effectiveness is evidenced by the dramatic reduction of disease incidence following mass vaccination. The duration of vaccine-induced immunity in primo-vaccinated adults appears to last for decades [5]. Previous recommendations [6] of revaccination have been revised by WHO experts in 2013 [5] and a systematic review of scientific evidence available until June 2012 [7]. The International Health Regulations have been ammended in May 2014 to stipulate that a single dose of the yellow fever vaccine is valid for the duration of the vaccinee's life [2].

Data on the long-term immunity induced by yellow fever vaccine, which should guide vaccination policy are still scarce. Therefore, this study aimed to assess the level of neutralising antibodies persisting after years of primovaccination against yellow fever in adults. Moreover, the study evaluated the immune

[1] The research group is described in Appendix A.

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status of adults over 1 year post-vaccination compared with those at 30 days post-vaccination using neutralising antibodies as humoral immune response biomarkers.

2. Methods

This cross-sectional study was designed to assess and compare the rate of seropositivity and the geometric mean titres (GMT) of yellow fever neutralising antibodies persisting in primo-vaccinated adults. The time since vaccination was grouped in arbitrary categories to determine the length of time that it takes for the immune response to decline and warrant the need for revaccination. Study subjects were grouped according to the length of time since vaccination as follows: 30–45 days, 1–4 years, 5–9 years, 10–11 years, and 12 years or more. In the 30–45 days vaccination subgroup, the presence of neutralising antibodies was also assessed prior to immunisation. The immune response in this newly vaccinated subgroup provided the reference to assess the variation of antibody levels over time. For the comparison subgroups, 1 year was thought to be the minimum time since vaccination, to disclose substantial decline antibody titres. In addition, the effects of anti-dengue IgG antibodies on the humoral immune status of yellow fever-vaccinated adults were also evaluated.

The study population comprised adult volunteers of both genders serving in the Army in the city of Rio de Janeiro, in addition to civilian volunteers from the "Oswaldo Cruz" Foundation (FIOCRUZ; Manguinhos campus, Rio de Janeiro) and from health centres in the municipality of Alfenas, state of Minas Gerais. All subjects either had received a single dose of the yellow fever vaccine 17DD at least 1 year before (confirmed in immunisation records) or had never been vaccinated (Fig. 1). Rio de Janeiro residents are advised to take the yellow fever vaccine only if they travel to endemic areas. The municipality of Alfenas is located in Minas Gerais, which is a large state in southeast Brazil where vaccination against yellow fever is recommended at the age of 9 months. In the Alfenas region, there are no recorded cases of yellow fever. In Brazil, infections by flaviviruses other than dengue and yellow fever have been reported, with minor public health significance.

Aliquots (5 mL) of peripheral blood were collected to measure anti-yellow fever neutralising antibodies and anti-dengue IgG antibodies. Vaccinated subjects were divided into subgroups according to the time elapsed since their last vaccination and were submitted to serological tests to quantify yellow fever antibody titres. A military subgroup with no history of yellow fever vaccination was tested for yellow fever antibodies immediately before routine vaccination required for military personnel involved in missions in the forest. It followed standard immunisation procedures for the general population, which have not undergone major changes in the last decades. The procedures followed in this study were limited to the application of questionnaires inquiring about sociodemographic data and personal medical history, in addition to blood collection for serological tests to determine the maximum antibody levels that the vaccination could achieve. This newly vaccinated subgroup provided the reference for comparison with other subgroups who were vaccinated for longer periods.

Specimens were collected after a signed informed consent was obtained from each participant, and the data collected were handled so as to protect confidentiality. The study protocol was approved by the Research Ethics Committee of the Evandro Chagas Clinical Research Institute at FIOCRUZ (Opinion No. 040/2011).

2.1. Eligibility criteria

Subjects with proof of vaccination (in vaccination card or medical records) and who agreed to the terms of the study were eligible to participate in the study. Exclusion criteria included the following: contraindications for yellow fever vaccine (e.g., pregnancy, permanent or transient immunosuppression, severe adverse reactions following previous vaccination, and severe allergy to chicken eggs), individuals who reported 2 or more previous vaccine doses (even if proof of vaccination could not be provided), lack of proof of prior vaccination, and residence in or travel to risk areas (which have been defined by the Health Surveillance Department of the Ministry of Health) until the time of the study.

The rationale for inclusion of subjects with a documented single dose of yellow fever vaccine and no potential exposure to natural infections was to avoid interference of booster on antibody levels induced by one dose. Cases with uncertain potential exposure to infection were not included. In addition, military personnel who participated in missions to endemic areas or who had been immunised more than once were excluded from the study.

2.2. Laboratory tests

The yellow fever neutralising antibody titres were quantified by $PRNT_{50}$ using 20 μL of heat inactivated (56 °C for 30 min) serum as described by Simões and colleagues [8] in the Laboratory of Viral Technology of Bio-Manguinhos (LATEV/BIO, in Rio de Janeiro). In each set of tests, a standard serum prepared in house was included as positive control (called M7/100). This serum from Rhesus monkeys (*Macaca mulatta*) vaccinated against YF had been calibrated against an international reference serum from WHO and was known to contain 1115 IU/mL. Antibody concentration in IU/mL was calculated relative to the antibody content in the international reference (quotient of 1115 IU/mL and the dilution corresponding to the 50% endpoint of the reference is multiplied by the dilution equivalent to the 50% of each serum sample).

Yellow fever antibody titres (in IU/mL) were classified as follows: titres $\geq 2.9 \log_{10}$ IU/mL or reciprocal of the dilution ≥ 50 indicated positive serology; titres $<2.5 \log_{10}$ IU/mL or reciprocal of the dilution <5 indicated negative serology; titres $\geq$ 2.5 and $<2.9 \log_{10}$ IU/mL or reciprocal of the dilution ≥ 5 and <50 indicated undetermined serology.

The serum samples were also tested for the presence of IgG by ELISA to confirm the presence of anti-yellow fever antibodies in sera from vaccinated subjects according to previously described methods [9]. Serological tests (IgG) for dengue were performed at the Flavivirus Laboratory of the Oswaldo Cruz Institute (Rio de Janeiro) using PANBIO dengue IgG indirect Elisa (Brisbane, Australia) [10]. Dengue is a flavivirus with widespread circulation in Brazil. Neutralising antibody response to YF vaccine is highly specific with no or low-titre antibodies to other flavivirus, but evidence for interference by naturally acquired heterologous flavivirus immunity with 17D vaccine in humans is conflicting [11].

2.3. Statistical analysis

The response variable of interest was the serum neutralising antibody titres (in IU/mL), which were converted to $\log_{10}$ values and categorised. The co-variables of interest were age (in years), gender, presence of anti-dengue virus antibodies, prior vaccination, history of severe illness (hospitalisation, disease sequelae, and disability), comorbidity and medications used at the time of blood collection. The rate of seropositivity and the geometric mean antibody titres, along with the corresponding 95% confidence intervals (CI), were estimated for each subgroup of time since vaccination.

In the multivariate analysis, the immune response (indicated by $\log_{10}$ of titres in the multiple regression model and seropositivity in the logistic regression model) was modelled as a function of the time (in months) elapsed since vaccination as a continuous variable and categories: 30–45 days, 1–9 years, 10–11 years, and $\geq$12 years