

References for Yellow Fever Vaccine: WHO Position on the Use of Fractional Doses, June 2017

References with abstracts cited in the position paper in the order of appearance.

World Health Organization. Vaccines and vaccination against yellow fever. WHO position paper -- June 2013. Wkly Epidemiol Rec. 2013;88(27):269-83.

This article presents the World Health Organizations (WHO) evidence and recommendations for the use of yellow fever (YF) vaccination from "Vaccines and vaccination against yellow fever: WHO Position Paper - June 2013" published in the Weekly Epidemiological Record. This position paper summarizes the WHO position on the use of YF vaccination, in particular that a single dose of YF vaccine is sufficient to confer sustained life-long protective immunity against YF disease. A booster dose is not necessary. The current document replaces the position paper on the use of yellow fever vaccines and vaccination published in 2003. Footnotes to this paper provide a number of core references. In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on diseases and vaccines, and conclude with WHO's current position on the use of vaccines in the global context. This paper reflects the recommendations of WHO's Strategic Advisory Group of Experts (SAGE) on immunization. These recommendations were discussed by SAGE at its April 2013 meeting. Evidence presented at the meeting can be accessed at <http://www.who.int/immunization/sage/previous/en/index.html>.

World Health Organization. Meeting of the Strategic Advisory Group of Experts on immunization, October 2016 - conclusions and recommendations. Wkly Epidemiol Rec. 2016;91(48):561-82.

No abstract available.

Recommendations to assure the quality, safety and efficacy of live attenuated yellow fever vaccines. World Health Organization, Geneva, Switzerland, 2013. Available at http://www.who.int/biologicals/expert_committee/TRS_978_61st_report.pdf

No abstract available.

World Health Organization. Fractional dose yellow fever vaccine as a dose-sparing option for outbreak response, July 2016. Available at: [http://www.who.int/entity/immunization/sage/meetings/2016/october/3 Fractional dose secretariat report full version.pdf](http://www.who.int/entity/immunization/sage/meetings/2016/october/3_Fractional_dose_secretariat_report_full_version.pdf)

No abstract available.

Lopes Ode S, et al. Studies on yellow fever vaccine. III--Dose response in volunteers. J Biol Stand. 1988;16(2):77-82.

Standard and stabilized yellow fever (YF) vaccines were compared on the basis of the serological responses of human volunteers to varying doses of vaccine measured as pfu or LD50. The addition of stabilizer substances to bulk vaccine did not affect the immunogenicity and stabilized vaccine gave a consistently good performance. The vaccine fulfilled WHO recommendations in inducing 100% serological conversion in volunteers given about 200 pfu or 600 LD50.

Roukens AH, et al. Intradermally administered yellow fever vaccine at reduced dose induces a protective immune response: a randomized controlled non-inferiority trial. PLoS One. 2008;3(4):e1993.

BACKGROUND:

Implementation of yellow fever vaccination is currently hampered by limited supply of vaccine. An alternative route of administration with reduced amounts of vaccine but without loss of vaccine efficacy would boost vaccination programmes.

METHODS AND FINDINGS:

A randomized, controlled, non-inferiority trial was conducted in a Dutch university center between August 2005 and February 2007. A total of 155 primary vaccinated and 20 previously vaccinated volunteers participated. Participants were randomly assigned in a 1ratio1 ratio to receive intradermal (i.d.) vaccination with live attenuated yellow fever 17D vaccine at a reduced dose (1/5(th); 0.1 mL) or the conventional subcutaneous (s.c.) vaccination (0.5 mL). Antibody neutralization titers were determined at 2, 4 and 8 weeks and 1 year after vaccination by counting the reduction in virus-induced plaques in the presence of serial serum dilutions. Adverse events were documented in a 3-week diary. Viraemia was measured 5 days after vaccination. From 2 weeks up to one year after vaccination, the maximum serum-dilution at which 80% of the virus plaques were neutralized, which indicates protection against yellow fever, did not differ between those given a reduced i.d. dose or standard s.c. dose of vaccine. In all cases the WHO standard of seroprotection (i.e. 80% virus neutralization) was reached (in 77/77 and 78/78, respectively). Similar results were found in the previously vaccinated individuals. Viraemia was detected in half of the primary vaccinated participants, which was not predictive of serological response. In revaccinees no viraemia was detected.

CONCLUSIONS:

Intradermal administration of one fifth of the amount of yellow fever vaccine administered subcutaneously results in protective seroimmunity in all volunteers. Albeit this vaccination route should enable vaccination of five-times as many individuals at risk for disease, these results should now be confirmed in field studies in areas with potential yellow fever virus transmission to change vaccination policy.

Martins RM, et al. 17DD yellow fever vaccine: a double blind, randomized clinical trial of immunogenicity and safety on a dose-response study. Hum Vaccin Immunother. 2013;9(4):879-88.

OBJECTIVE:

To verify if the Bio-Manguinhos 17DD yellow fever vaccine (17DD-YFV) used in lower doses is as immunogenic and safe as the current formulation.

RESULTS:

Doses from 27,476 IU to 587 IU induced similar seroconversion rates and neutralizing antibodies geometric mean titers (GMTs). Immunity of those who seroconverted to YF was maintained for 10 mo. Reactogenicity was low for all groups.

METHODS:

Young and healthy adult males (n = 900) were recruited and randomized into 6 groups, to receive de-escalating doses of 17DD-YFV, from 27,476 IU to 31 IU. Blood samples were collected before vaccination (for neutralization tests to yellow fever, serology for dengue and clinical chemistry), 3 to 7 d after vaccination (for viremia and clinical chemistry) and 30 d after vaccination (for new yellow fever serology and clinical chemistry). Adverse events diaries were filled out by volunteers during 10 d after vaccination. Volunteers were retested for yellow fever and dengue antibodies 10 mo later. Seropositivity for dengue was found in 87.6% of volunteers before vaccination, but this had no significant influence on conclusions.

CONCLUSION:

In young healthy adults Bio-Manguinhos/Fiocruz yellow fever vaccine can be used in much lower doses than usual. INTERNATIONAL REGISTER: ISRCTN 38082350.

Campi-Azevedo AC, et al. Subdoses of 17DD yellow fever vaccine elicit equivalent virological/immunological kinetics timeline. BMC Infect Dis. 2014;14:391.

BACKGROUND:

The live attenuated 17DD Yellow Fever vaccine is one of the most successful prophylactic interventions for controlling disease expansion ever designed and utilized in larger scale. However, increase on worldwide vaccine demands and manufacturing restrictions urge for more detailed dose sparing studies. The establishment of complementary biomarkers in addition to PRNT and Viremia could support a secure decision-making regarding the use of 17DD YF vaccine subdoses. The present work aimed at comparing the serum chemokine and cytokine kinetics triggered by five subdoses of 17DD YF Vaccine.

METHODS:

Neutralizing antibody titers, viremia, cytokines and chemokines were tested on blood samples obtained from eligible primary vaccinees.

RESULTS AND DISCUSSION:

The results demonstrated that a fifty-fold lower dose of 17DD-YF vaccine (587 IU) is able to trigger similar immunogenicity, as evidenced by significant titers of anti-YF PRNT. However, only subdoses as low as 3,013 IU elicit viremia kinetics with an early peak at five days after primary vaccination equivalent to the current dose (27,476 IU), while other subdoses show a distinct, lower in magnitude and later peak at day 6 post-vaccination. Although the subdose of 587 IU is able to trigger equivalent kinetics of IL-8/CXCL-8 and MCP-1/CCL-2, only the subdose of 3,013 IU is able to trigger similar kinetics of MIG/CXCL-9, pro-inflammatory (TNF, IFN- γ and IL-2) and modulatory cytokines (IL-5 and IL-10).

CONCLUSIONS:

The analysis of serum biomarkers IFN- γ and IL-10, in association to PRNT and viremia, support the recommendation of use of a ten-fold lower subdose (3,013 IU) of 17DD-YF vaccine.

Mihigo R. Feedback from the yellow fever mass vaccination campaign using fractional dose Kinshasa, Democratic Republic of Congo 17-26 August, 2016. Presented at SAGE, 20 October 2016. Available at <http://www.who.int/immunization/sage/meetings/2016/october/Session11-Part2-Feedback-from-the-yellow-fever-mass-vaccination-campaign-using-fractional-dose.pdf>

No abstract available.

World Health Organization. Global Advisory Committee on Vaccine Safety, 30 November - 1 December 2016. Wkly Epidemiol Rec. 2017;92(2):13-20.

No abstract available.

Casey RM, et al. Immune Response Following Reactive Vaccination Campaign Using Fractional Dose Yellow Fever Vaccine — Kinshasa, Democratic Republic of Congo, 2016. 66th Annual Epidemic Intelligence Service (EIS) Conference. Atlanta, GA. April 24–27, 2017. Available at <https://www.cdc.gov/eis/downloads/eis-conference-2017.pdf>

BACKGROUND:

In 2016, several large outbreaks of yellow fever (YF) led to a global YF vaccine shortage. To vaccinate 7.6 million people in Kinshasa in response to an outbreak, fractional (1/5; 0.1 ml) dose of 17DD YF vaccine was provided to children age ≥ 2 years and non-pregnant adults via subcutaneous injection. We assessed the effectiveness of this novel control strategy.

METHODS:

Participants were recruited in four age strata at six vaccination sites. We assessed the presence of YF virus specific neutralizing antibodies from blood samples collected pre vaccination and 28 days post vaccination using the plaque reduction neutralization test (PRNT50). The World Health Organization defines seroprotection as a PRNT50 titer ≥ 10 . The study criteria for immune response were seroconversion (seronegative on pre-vaccination blood to titer ≥ 10 at follow-up), or ≥ 4 fold increase in titer.

RESULTS:

Of 764 participants recruited, 492 have preliminary results available; 483 (98%; 95% confidence interval: 97%–99%) participants were seroprotected against YF at follow-up. Of these, 439 (91%) met criteria for immune response and 44 (9%) had preexisting immunity and did not meet the criteria. Stratified by age group, the proportion seroprotected at follow-up was 97% in 2–5 year olds; 100% in 6–12 year olds; 97% in 13–49 year olds; and 98% in those 50 and older. For the same age groups, the proportions meeting immune response criteria were 79%, 94%, 93% and 88% respectively.

CONCLUSIONS:

In our cohort, fractional dose YF vaccine was highly effective at providing protective immunity. These findings support the use of fractional dose vaccination for outbreak control, which is important to address the ongoing global YF vaccine shortage. Additional studies are needed to assess longer-term immunologic response.

Belmusto-Worn VE, et al. Randomized, double-blind, phase III, pivotal field trial of the comparative immunogenicity, safety, and tolerability of two yellow fever 17D vaccines (Arilvax and YF-VAX) in healthy infants and children in Peru. *Am J Trop Med Hyg.* 2005;72(2):189-97.

We conducted a randomized, double-blind, phase III yellow fever (YF) vaccine trial among 1,107 healthy children in Sullana in northern Peru. The safety and efficacy (by measurement of geometric mean neutralizing antibody titer responses) were determined for two YF vaccines, ARILVAX (n = 738) and YF-VAX(R) (n = 369). Seroconversion rates were higher (94.9%) in ARILVAX than in YF-VAX (90.6%) recipients. The two-sided 95% confidence interval (YF-VAX-ARILVAX) was (-12.8% to -2.5%), indicating that the higher seroconversion rate for Arilvax was significant. Post-vaccination (30-day) mean log₁₀ neutralization indices were found to be similar for both products: 1.32 for ARILVAX and 1.26 for YF-VAX (P = 0.1404, by analysis of variance). A similar number of subjects in each group reported at least one adverse event (AE); 441 (59.8%) for ARILVAX versus 211 (59.9%) for YF-VAX. Most (591; 96.7%) of these were of a mild nature and resolved without treatment. There were no treatment-related serious AEs. This is the first randomized, double-blind comparison of two YF vaccines in a pediatric population; both vaccines were shown to be highly immunogenic and well-tolerated.

Roy Chowdhury P, et al. Immunogenicity of Yellow Fever Vaccine Coadministered With MenAfriVac in Healthy Infants in Ghana and Mali. *Clin Infect Dis.* 2015;61 Suppl 5:S586-93.

BACKGROUND:

Yellow fever (YF) is still a major public health problem in endemic regions of Africa and South America. In Africa, one of the main control strategies is routine vaccination within the Expanded Programme on Immunization (EPI). A new meningococcal A conjugate vaccine (PsA-TT) is about to be introduced in the EPI of countries in the African meningitis belt, and this study reports on the immunogenicity of the YF-17D vaccines in infants when administered concomitantly with measles vaccine and PsA-TT.

METHODS:

Two clinical studies were conducted in Ghana and in Mali among infants who received PsA-TT concomitantly with measles and YF vaccines at 9 months of age. YF neutralizing antibody titers were measured using a microneutralization assay.

RESULTS:

In both studies, the PsA-TT did not adversely affect the immune response to the concomitantly administered YF vaccine at the age of 9 months. The magnitude of the immune response was different between the 2 studies, with higher seroconversion and seroprotection rates found in Mali vs Ghana.

CONCLUSIONS:

Immunogenicity to YF vaccine is unaffected when coadministered with PsA-TT at 9 months of age. Further studies are warranted to better understand the determinants of the immune response to YF vaccine in infancy.

World Health Organization. Eliminating Yellow fever Epidemics (EYE).

<http://www.who.int/csr/disease/yellowfev/eye-strategy/en/>

No abstract available.

WHO Policy Statement: Multi-dose Vial Policy (MDVP). World Health Organization, Geneva, Switzerland, 2014. Available at:

http://apps.who.int/iris/bitstream/10665/135972/1/WHO_IVB_14.07_eng.pdf

All opened WHO-prequalified multi-dose vials of vaccines should be discarded at the end of the immunization session, or within six hours of opening, whichever comes first, UNLESS the vaccine meets all four of the criteria listed below. If the vaccine meets the four criteria, the opened vial can be kept and used for up to 28 days after opening. The criteria are as follows.

1. The vaccine is currently prequalified by WHO.
2. The vaccine is approved for use for up to 28 days after opening the vial, as determined by WHO.†
3. The expiry date of the vaccine has not passed.
4. The vaccine vial has been, and will continue to be, stored at WHO- or manufacturer-recommended temperatures; furthermore, the vaccine vial monitor, if one is attached, is visible on the vaccine label and is not past its discard point, and the vaccine has not been damaged by freezing.

For vaccines that are not prequalified by WHO, independent determinations on preservative efficacy, sterility, presentation and stability may not have been made by a functional national regulatory authority. Consequently, this could mean that the vaccine does not meet the WHO requirements on safety and efficacy, which form the minimum recommended standard for keeping multi-dose vaccine vials opened for more than six hours. Therefore, WHO recommends using non WHO-prequalified

vaccines as soon as possible after opening, and respecting the time limit for using opened vials as indicated by the manufacturer's instructions in the package insert. If this information is not indicated in the package insert, WHO recommends discarding all non WHO-prequalified vaccine products within six hours after opening or at the end of the immunization session, whichever comes first.

This policy statement further outlines conditions under which the MDVP can be implemented safely, including, but not limited to, adherence to good immunization practices.

† Consult each individual vaccine product sheet at the WHO prequalification website, referencing the description "Handling of opened multi-dose vials"

http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html.

World Health Organization. Short-term research priorities for dose-sparing of YF vaccine, September 2016. Available at: http://www.who.int/immunization/sage/meetings/2016/october/5_Short-term_research_priorities_sept26_Final.pdf

No abstract available.

Gershman MD, et al. Viscerotropic disease: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012;30(33):5038-58.

No abstract available.