Fractional dose yellow fever vaccine as a dose-sparing option for outbreak response

WHO Secretariat information paper

20 JULY 2016

World Health Organization

This document was produced by the
Department of Immunization, Vaccines and Biologicals

Table of content

1. Preamble

This document is a summary of the World Health Organization (WHO) secretariat paper in response to the Yellow fever (YF) outbreak in Africa 2016, which has been discussed with YF experts and has been reviewed by WHO's Strategic Advisory Group of Experts (SAGE) on Immunization. The development of this paper was led by the WHO Initiative for Vaccine Research gathering inputs to specific sections from the Pandemic and Epidemic diseases, Essential Medicines, and Immunization Vaccines and Biologicals departments of WHO. The Secretariat paper benefited from input by SAGE and the proposed recommendations were vetted by SAGE. This document will be further updated as additional data become available. A full review on the use of YF vaccine fractionate dose will be conducted by SAGE in October 2016.

2. Introduction

Ongoing YF outbreaks are sharply increasing the demand for YF vaccine, exhausting the global stockpile and putting at risk the immunization of endemic populations. With the campaigns planned, there is now shortage of vaccine, which could increase further if expansion of outbreaks would require additional immunization campaigns at large scale. Hence, there is a need to assess immediate opportunities to increase availability of vaccine in response to ongoing outbreaks that deplete available supplies. This secretariat paper reviews the existing evidence on dose-sparing strategies through fractional dosing of YF vaccine as an immediate and short-term option in response to eventual large scale campaign needs, and makes recommendations for fractional dose vaccination in case of imminent need. This is not intended to serve as longer-term strategy nor to replace established routine immunization practices. Once an outbreak threatens supply capacities, e.g. spreading into highly populated areas, suggestions from this paper shall be considered to support efforts to introduce fractional vaccine dose use.

3. Background

YF is a mosquito-borne viral disease of humans, which can be asymptomatic or cause a wide spectrum of disease, from mild symptoms to severe illness with bleeding, jaundice and, ultimately, death[i]. Wild-type YF virus induces lifelong protection against subsequent infection. YF is endemic in countries in the tropical regions of Africa and South America. The vast majority of reported cases and deaths (>90%) occur in sub-Saharan Africa, where YF is a major public health problem occurring in epidemic patterns. Based on data from 2013 from African countries, analysis suggest a burden of 84 000 – 170 000 severe cases and 29 000 – 60 000 deaths due to YF. Due to the existence of an enzootic sylvatic transmission cycle among non-human primates, the disease cannot be eradicated. However, prevention through vaccination can limit the morbidity and mortality of the disease. There are two immunization strategies: 1) delivery of YF vaccine in endemic settings via routine childhood immunization programs, and 2) mass

---

[i] Vaccines and vaccination against yellow fever WHO Position Paper – June 2013. WER. No. 27, 2013, 88, 269–284. http://www.who.int/wer/2013/wer8827.pdf?ua=1, accessed June 2016

vaccination campaigns to catch-up on immunization in unvaccinated cohorts not eligible for routine immunization or in response to an outbreak of the disease.

Although YF vaccination is very effective, where implementation of immunization recommendation was suboptimal or even non-existent in some countries, the disease has recurred, leading to major outbreaks in countries where the disease was considered to be under control or disappeared.

By definition, YF outbreaks may constitute one or more cases. Currently, YF outbreaks are ongoing in Africa (Angola, Democratic Republic of Congo (DRC) and Uganda) as well as in South America (Brazil, Colombia, and Peru). As of 7 June, 2945 suspected cases and 329 deaths have been reported from Angola. Of these, 819 cases and 108 deaths were laboratory confirmed. In DRC, 57 cases were confirmed as of 7 June, of which 51 are imported from Angola, 6 are autochthonous (2 Kinshasa, 1 Kwango, 1 Congo Central; and 2 from the Northern provinces (not related to this outbreak)). In Uganda, as of 7 June, a total of 68 suspected cases including 7 confirmed cases were reported. The most recent situation report is available on the WHO website.[ii] Imported cases among unvaccinated individuals have been reported from China (n=11), Morocco (1 suspected case) and Kenya (n=2 cases).

4. International Health Regulations

YF is the only disease specified in the International Health Regulations (IHR (2005)) for which countries may require proof of vaccination from travellers as a condition of entry under certain circumstances and may take certain measures if an arriving passenger is not in possession of such a certificate. WHO publishes a list of countries with risk of YF transmission and countries requiring YF vaccination, which has been updated in February 2016[iii]. However, in practice, the vaccination requirements are unevenly applied, and for example many international workers in Angola were not vaccinated at the start of the outbreaks. To interrupt the international spread, it is urgent and essential that the IHR (2005) is reinforced by requiring travellers to present YF vaccination certificates. The feasibility of implementing this measure at land crossings remains a challenge, and may not be logistically feasible given the porous borders at land crossings.

Annexes 6 and 7 to the IHR (2005) indicate that YF vaccine used must be approved by WHO. Also, Annex 7 was amended in 2014[iv] to indicate that a single dose of the vaccine is enough to confer immunity for life, and that validity of vaccination certificates extends to the life of person vaccinated. Starting on 11 July 2016, this amendment enters into force, and all countries must abide by this new requirement[v].

An Emergency Committee (EC) regarding YF was convened by the Director-General under the International Health Regulations (2005) (IHR 2005) on 19 May 2016. The WHO Director-General accepted the Committee's assessment that the current YF situation is serious and of great concern and

---

[ii] WHO Yellow Fever situation report. http://www.who.int/emergencies/yellow-fever/situation-reports/26-may-2016/en/, accessed June 2016
[iii] http://www.who.int/ith/2016-ith-annex1.pdf?ua=1, accessed June 2016
[iv] World Health Assembly Resolution WHA 67.13
[v] http://www.who.int/ith/annex7-ihr.pdf?ua=1, accessed June 2016

requires intensified control measures, and urged Member States to enforce the YF vaccination requirement for travellers to and from Angola and the Democratic Republic of the Congo in accordance with the IHR (2005), as per the Annex 7 of the IHR (2005)[vi].

Recognizing the limited international supply of YF vaccines, the Committee advised the immediate application of the policy of 1 lifetime dose of YF vaccine[iv] and the rapid evaluation of YF vaccine dose-sparing strategies by the WHO SAGE. This briefing note is prepared to inform SAGE in case of an emergency in which SAGE will be asked to provide their feedback on dose-sparing options. A formal evaluation by SAGE is envisaged for October 2016.

Fractional dose administration of YF vaccine, as discussed in this paper, should not be considered equivalent to full dose vaccination, and until further data have been generated it does not constitute a sufficient dose of YF vaccination in the sense of the IHR.

5. Vector control measures

The incidence of YF is increasing, especially due to infection in metropolitan areas with growing human population densities and urban environments that provide mosquitos with various oviposition sites. Increased urbanization in particular among poorer parts of the population without access to proper water supply and to basic health services as well an increase of international travel both have the potential to further contribute to increased densities of *Aedes aegypti*.

There are no specific data available on vector control measures used in the context of implementing YF vaccination. However, well implemented vector control programmes using existing tools and strategies have been found to be effective in reducing the transmission of Aedes-borne diseases (WHO Vector Control Advisory Group 2016), and can therefore contribute to risk reduction. Improving the quality and extent of implementation of vector control interventions can ensure improved impact against Aedes-borne diseases such as YF.

In particular in a low resource context, country commitment, intersectoral collaboration and capacity building for entomological surveillance, as well as sustained effective control and a rapid outbreak response is critical success factors to strengthen vector control measures.

Interventions that bear the potential to reduce the risk of YF virus transmission include targeted residual spraying on Aedes mosquito resting sites; space spraying inside houses where Aedes mosquito rest and bite; larval control through source reduction and larvicide; and personal protection measures using appropriate repellent and clothing. Furthermore, aggressive promotion and implementation of vector control measures and appropriate personal protective measures can reduce the risk of exposure to circulating YF virus.

[vi] http://www.who.int/mediacentre/news/statements/2016/ec-yellow-fever/en/, accessed May 2016

6. Yellow fever vaccine characteristics

YF vaccines are recommended to be given as a single dose (0.5 ml) injected subcutaneously (SC) or intramuscularly (IM). The evidence in this briefing note is mostly derived from SC route of administration. Healthy individuals rarely fail to develop neutralizing antibodies after vaccination. Clinical trials have found that 80%–100% of vaccine recipients develop protective levels of neutralizing antibodies within 10 days and 99% do so within 30 days. Protection appears to last for life. Limited data suggest that seroconversion is somewhat lower in children below 2 years of age, but the clinical relevance of this is uncertain.[vii] No evidence on potential differences in immunogenicity and efficacy between SC and IM administration could be retrieved.

All the current commercially available YF vaccines are live attenuated viral vaccines from the 17D lineage. According to current WHO recommendations on quality, safety and efficacy of live attenuated YF vaccines[viii] the immunizing dose recommended for use should not be less than 3.0 $\log_{10}$ i.e. 1000 international units (IU). The release specifications should be approved by the National Regulatory Authorities (NRA).

There are two YF sub-strains in use currently for manufacture of YF vaccine, namely YF 17DD and YF 17D-204. YF 17D-213 is a derivative of 204, but differs significantly as it has gained a glycosylation site in the E protein. 17D-204 is used by Sanofi, and Institut Pasteur Dakar (at different passage levels), 17D-213 is used by Federal State Unitary Entreprise of Chumakov Institute, and 17DD is used by Bio-Manguinhos, Brazil.[viii] Therefore, extrapolation of clinical trial data between different products, in particular of different sub-strains, should be done with caution.

7. Fractional Yellow fever vaccine immunogenicity when administration through subcutaneous, intramuscular or intradermal fractional dose

Two recent reviews on dose-sparing strategies were considered. (1) A review of the evidence for a dose-sparing strategy for YF vaccine by ID administration was conducted by the Program for Appropriate Technology in Health (PATH) in 2013. In summary, the authors of this report consider that this approach could be implemented in the short to medium term, as long as clinical evidence for non-inferiority, safety, and dose levels has been generated. It could also be useful in public health emergencies when there might be an acute shortage of YF vaccine. (2) A systematic review by WHO of recent evidence on the fractional dose administration through normal route (SC/IM) and ID administration of YF vaccine. Since the review of PATH additional scientific data were generated by Martins et al (2013) and Campi-Azevedo et al (2014). The WHO search strategy is outlined in Annex 1.

[vii] Gotuzzo E. et al., Efficacy and duration of immunity after yellow fever vaccination: systematic review on the need for a booster every 10 years. Am J Trop Med Hyg 2013

[viii] WHO TRS 978 Annex 5 http://www.who.int/biologicals/expert_committee/TRS_978_61st_report.pdf, accessed May 2016

While Lopes et al dates from 1988, there are two recent vaccine trials studying safety and immunological non-inferiority: Roukens et al (2008) studying the ID administration of YF vaccine, and Martins et al (2013) and Campi-Azevedo et al (2014) studying IM/SC vaccine administration (same cohort, but different analysis). All studies demonstrated seroconversion and geometric mean titers (GMT). Both fractional dose via IM/SC and ID delivery showed similar immunogenicity as full dose.

The following table summarizes their findings.

Table 1: Publications assessing immunogenicity of the use of fractional dose via usual route of delivery or ID delivery.*

Characteristics	**Study #1** Lopes O et al. 1988 (5)	**Study #2** Roukens AH et al. 2008 (6)	**Study #3** Martins RM et al. 2013 (7)	**Study #4** Campi-Azevedo AC et al. 2014) (8)
Study site	Rio de Janeiro, Brazil	The Netherlands	Rio de Janeiro, Brazil	Rio de Janeiro, Brazil
Dose-sparing approach and route of delivery	Fractional dose, IM/SC	Fractional dose, ID vaccination	Fractional dose, IM/SC	Fractional dose, IM/SC
YF vaccine	All YF vaccines came from the same seed lot which complied with WHO min requirements for biological substances (1976)	All administered vaccines originated from Stamaril, Lot # Y5597, Sanofi Pasteur, France.	Experimental products by Bio-Manguinhos having 6 different viral particle concentrations in IU/dose.	Bio-Manguinhos, same vaccine recipients and study #3
Subdose	$1/5^{th}$ of 1000 PFU	$1/5^{th}$ of full dose (which was 3.5×10^4 PFU)	Full dose of 27,476 IU (NIBSC reference)and five lower alternative formulations (31IU, 158IU, 587IU, 3013IU, 10447IU)	Full dose of 27,476 IU (NIBSC reference)and five lower alternative formulations (31IU, 158IU, 587IU, 3013IU, 10447IU)
Sample Size	259 healthy males	175 participants, healthy adults of 18 years and older (up to 70, mean age 25-27)	749 healthy, adult, army males, not previously vaccinated against YF, mean age 19.4Y; around 90% of subjects were seropositivity for Dengue virus and 12-23% for YF at baseline (the latter excluded from PP analysis)	749 healthy, adult, army males, not previously vaccinated against YF; mean age 19.4 years
Study design	Volunteers were allocated to each vaccine group in the order in which they reported for inoculation	Randomized controlled trial to test for immunological non-inferiority. Participants received ID vaccination 0.1 ml or SC vaccination 0.5ml. 155 were primary vaccinated participants (primovaccinees), 20 revaccinees	A double blind, randomized clinical trial to test for immunological non-inferiority.	Randomized control trial. Compared kinetics of biomarkers (serum chemokine and cytokine) triggered by the full dose and the five lower alternative subdoses of currently used doses of 17DD YF vaccine.
Follow up period	28d	1 yr	10 mos	1 yr
Data collection	The amount of PFU and LD_{50} requiring seroconversion were assessed by 8 different varying doses of vaccine. Blood samples were obtained before and 28 days after vaccination. No peak time.	Virus neutralization 80% and virus RNA were evaluated to assess the vaccine efficacy. Primovaccinees: Blood samples were collected before vaccination, 4 wks and 8 wks after vaccination. Revaccinees: Blood samples were collected before vaccination, 5d and 2 wks and 1 yr after vaccination.	PRNT 50%, viral RNA, and GMTs were evaluated to assess the vaccine efficacy. The occurrence of adverse events were evaluated among volunteers who recorded them on their diaries during the first 10 d after vaccination. No peak time.	PRNT, virus RNA, chemokines and cytokines were evaluated to assess the vaccine efficacy as follows: PRNT80%: Day 0, 30, 365 RT-PCR: Day 3, 4, 5, 6, 7 Chemokines & Cytokines: Day 0, 3, 4, 5, 6, 7, 15, 30
Vaccine Efficacy (defined as seroconversion and immune response titres)	The inoculation of 200-500 PFU induced seroconversion in 100% of participants. The amount is much lower than the minimum required standard by WHO of 1,000 PFU.	From 2 wks to 1 yr after vaccination, the max. serum-dilution (1:16) at which 80% of virus plaques were neutralized did not differ between those given a reduced ID or standard SCs dose. In all cases the WHO standard of seroprotection was reached.	Seroconversion: 97% (except fractions lower than 587 IU). The duration of immunity had no statistically significant difference among groups except 31 IU group.	A less than $1/46^{th}$-fold dose of YF vaccine (587 IU) is able to trigger similar immunogenicity, as evidenced by significant titers of anti-YF PRNT. Analysis of serum biomarkers in association to PRNT and viremia, support 10-fold lower subdose (3,013 IU) of 17DD-YF vaccine.
Vaccine Safety	No description	Redness, swelling and itching were reported more by ID group. 3 SC part. rated events as severe.	No serious adverse events were reported from all groups.	No description
Other aspects		No difference in immunogenicity observed between females and males,	Doses below 587 IU (158 and 31IU) were inferior to full dose; viraemia unrelated to vaccine dose	
Limitations		Small sample size, no stratification by age, modified PRNT).	Small non-representative population, and narrow age range	Small non-representative population, and narrow age range

*For risk of bias assessments, see Annex 3. Unit of potency presented as in the publication.

<u>Intradermal administration of a fractional dose</u>

Roukens et al. demonstrated that ID of 17D-204 YF vaccine with 1/5th of 0.5ml (full dose) could induce the same immunogenicity as the SCs delivery of a full dose. (6) Within this randomized control trial, participants received 0.1 ml (1/5th of full dose) ID or 0.5ml SC. From 2 weeks to 1 year after vaccination, the maximal serum-dilution at which 80% of virus plaques were neutralized (e.g. neutralizing antibody titers) did not differ between vaccinees given a reduced ID or standard SC dose. In all cases the WHO standard of seroprotection was reached (See GRADE table 2, Annex 2).

<u>Fractional dose using the normal route of SC administration</u>

Lopes O et al. showed that seroconversion occurred following administration of 17DD YF vaccine in 100% of the participants in 28 days which is 1/5th to 1/2 of the WHO required dose; but the vaccine was based on older vaccine formulations of the product and therefore of limited interest. The recent randomized controlled trial assessing fractional dosing via regular route of administration using 17DD YF vaccine produced by Bio-Manguinhos (Martins et al., 2013; Campi-Azevedo et al., 2014) are of greater interest. Martins showed that even a 46x dilution resulted in equivalent humoral response as the full dose. Seroconversion occurred in 97% of the participants at 30 days at 1/46th of full dose (Martins RM et al), and neutralizing antibody titres achieved equivalent titres to the full dose. Campi-Azevedo et al. did further investigation into viraemia and chemokine and cytokine responses. Viremia pattern was equivalent to full dose down to a dilution of 1/9 (3013 IU), whereas the 1/46 dilution (587 IU) showed a somewhat reduced and delayed viraemia peak. For the 1/46 dilution, slight differences were also seen in relation to pro-inflammatory cytokines, while serum cytokines were equivalent to the full dose (8).

It should be noted that the Martins/Campi-Azevedo study used vaccine of high potency of above 10000 IU (27,476 IU), and hence even the nine-fold dilution contained three times more IU than the lower threshold recommended by WHO. A considerable range of potency in routine vaccine batches has been reported from all manufacturers (WHO informal consultation of the minimum potency specifications for YF vaccines, 2007) ranging from 1995 log10 IU to 2511886 log10 IU/dose (a more than 1000-fold difference). Hence interpretation of non-inferiority results seen with fractional doses need to be normalized by the actual vaccine potency expressed in IU.

In summary, the above findings are encouraging and document the potential of fractional dosing (see GRADE table 1, Annex 2). Based on the data from Martins and Campi-Azevedo, a fraction dose containing about 3000 IU could be considered equivalent to a full dose and should be considered as preferential dose volume for fractional vaccine doses. Below this value (about 3000-600 IU), protective, but possibly less than life-long protection need to be assumed. Dose fractioning below a potency of about 1000 IU/dose is not advisable, to leave a safety margin to 600 IU below which the humoral immune response was inferior to higher potency doses.

The limitations to the evidence available are the following:

- Study populations are likely different from the populations living in YF endemic areas, both in relation to *flavivirus* exposure and genetic background.

- SC immunization data are only available from one manufacturer using YF 17DD vaccine.
- Children and immunocompromised populations (and women for the fractional dosing (IM/SC) are not included in the studies to evaluate immunogenicity and safety in these subpopulations.
- Long-term duration of immunity beyond one year is unknown with a dose-sparing approach.

Actual doses of YF virus particles in each lot of all prequalified companies are different and vary across lots and stage of expiry, which is important to address if considering the use of a fractional dose.

8. Yellow fever vaccine safety when administered as a fractional dose

The most common systemic side effects after full dose YF vaccine include headache, asthenia, myalgia, malaise, fever, rash and chills. Urticaria is uncommon. Allergic reactions are extremely rare, occurring at an incidence of less than 1 per million, with reactions occurring principally in persons with known egg sensitivity[ix]. In clinical trials, non-serious adverse events were reported by 25% of vaccinees receiving a full dose of YF vaccine. Serious adverse events following immunization (AEFI) with a full dose of YF vaccine are rare (1 by 2 million people vaccinated in preventive campaigns).

Serious adverse events related to vaccination include YF vaccine-associated viscerotropic disease, neurological diseases, and severe hypersensitive reactions. The available data suggest that the incidence of acute viscerotropic disease following YF vaccination ranges from 0 to 0.21 cases per 100 000 vaccine doses in regions where YF is endemic, and from 0.09 to 0.4 cases per 100 000 doses in populations not exposed to the virus. Neurological (or neurotropic) disease is estimated to occur with a frequency of 0.8 cases per 100 000 vaccine doses administered. [i,x,xi]

The available data on adverse reactions after fractional doses of YF vaccine are limited to the studies described before and the number of persons vaccinated is too low to appropriately assess the rate of rare but serious adverse events (SAE). A recent study[xii] to compare the immunogenicity and safety for 5 alternative formulations for YF vaccine, with lower concentrations of viral particles reported no SAE attributable to the vaccine. It is, however, difficult to draw conclusions on SAE with this small sample size. Headache and fatigue were the most frequent symptoms, being reported by more than 1/5th of volunteers. Among 749 volunteers in the study, over 15% reported fever ≥ 37.5°C and 2% ≥ 39°C. Pain, arthralgia, pruritus and nausea were also reported. There were no differences in the frequency of common adverse events, with exception of pain, found more frequently with the full dose vaccine.

[ix] Vaccines, SIXTH EDITION, STANLEY A. PLOTKIN
[x] Detection and investigation of serious adverse events following yellow fever vaccination. Guidance from an informal consultation of experts. 18–19 November 2008. Geneva, Switzerland
[xi] Risk of yellow fever vaccine-associated viscerotropic disease among the elderly: a systematic review. Rafferty et al Vaccine 2013, 31(49):5789-805
[xii] 17DD yellow fever vaccine A double blind, randomized clinical trial of immunogenicity and safety on a dose-response study Reinaldo M. Martins et al

In another study[xiii], in 155 primary vaccinated participants, ID vaccination evoked redness and swelling at the site of inoculation more frequently and for a significantly longer period than after subcutaneous vaccination. Itching at the site of injection was also reported more by ID vaccinated. The subcutaneously primovaccinated participants reported significantly longer pain at the site of injection and also myalgia compared to the fractional dose. The severity of adverse events due to vaccination, which was reported on a 4-level scale (−, +/−, +, ++), did not reveal a difference in experienced discomfort (both local and systemic) between the ID and SC group.

It has been argued that lower doses of live *flavivirus* vaccines might be associated with deleterious safety effects[xiv]. This is primarily based on the observation that viraemia of the vaccine virus does not correlate with infectious dose[xv]. A common explanation is that high virus replication compensates for a small inoculum. However, Campi-Azevedo et al. showed that viraemia intensity stays the same throughout all fractional doses steps down to 3,000 IU, and does not increase and is of the same duration at lower doses. Furthermore, a direct correlation of lower doses of YF vaccine with increased reactogenicity or SAE's has not been described and there is absence of data indicating an increase of severe side effects (viscerotropic complications) when using a fractional dose. Active surveillance systems to report and respond to AEFIs is recommended during the introduction of YF vaccines in fractional doses.

9. Considerations related to regulatory approval

The recommendations on fractionate dose administration of YF vaccine discussed in this paper constitute an off-label use of the vaccine. Similarly, vaccine administration via ID route is an off-label use of the vaccine. Exploring other potential strategies on the dose optimization to increase supply or surge capacity is of critical importance. Risk management of the proposed use of a fractional dose should be addressed as well as all implications on a short and long term basis that require clinical, regulatory and programmatic assessments. Regulatory strategies are lengthy and may be promising in the medium- or long-term but cannot be considered as solutions in the short term for off-license and emergency use.

Considering that available data are restricted to specific manufacturers and their specific viruses, and variability of the manufacturing process leading to different vaccine titers, extrapolation to all YF vaccines requires careful consideration. Product specific data are needed to support the regulatory approval and consequent prequalification of the new dose. Dose reduction efforts must be accompanied with relevant stability data and clinical data.

[xiii] Intradermally Administered Yellow Fever Vaccine at Reduced Dose Induces a Protective Immune Response: A Randomized Controlled Non-Inferiority Trial. Anna H. Roukens et al Plos One. 2008; 3(4): e1993

[xiv] Innate and adaptive cellular immunity in flavivirus-naive human recipients of a live-attenuated dengue serotype 3 vaccine produced in Vero cells (VDV3). Sanchez V. et al, Vaccine 2006

[xv] Chimeric live, attenuated vaccine against Japanese encephalitis (ChimeriVax-JE): phase 2 clinical trials for safety and immunogenicity, effect of vaccine dose and schedule, and memory response to challenge with inactivated Japanese Encephalitis Antigen. Monath TP et al., Journal of Infectious Diseases 2003.

As a medium-term strategy to increased vaccine supply, exploration of the introduction of an upper potency limit should be considered by manufacturers and regulators. This approach is already practiced by one manufacturer. If the manufacturer needs to change the target potency during manufacturing, then they need to demonstrate to the NRA and later PQ, that there is no impact of this change in the quality and efficacy of the vaccine, as well as no impact on shelf-life of the vaccine.

In relation to the rubber seal of multi dose vials and its resistance to multiple punctures, no specific prequalification guidelines are available. At national level, ISO or pharmacopeia standards are being applied. No direct evidence could be retrieved on the durability of the rubber seal when applying more punctures than indicated per multidose vial. Also, measures to appropriately monitor any programmatic issues in practice should be included in campaigns as a precautionary measure. Currently, efforts on fraction dose use with IPV vaccine are ongoing in India. These may provide lessons learnt on practical aspects of fraction dose use with 10 dose vials.

10.   Programmatic considerations

Members of the WHO Immunization Practices Advisory Committee (IPAC) provided insight to the following programmatic considerations via an informal consultation.

The four WHO prequalified YF vaccines are currently available in 2, 5, 10, and 20 multidose vials that need to be reconstituted with excipient diluent (water or saline, depending on manufacturer). Before reconstitution, the lyophilized vaccine can be stored at 2-8 °C for a period of up to 2 or 3 years (see Table 2). Due to the limited heat stability of YF vaccine after reconstitution, opened multi-dose vials of YF vaccine must be kept between +2°C and +8°C, and must be discarded at the end of the immunization session, or within six hours of opening, whichever comes first. All WHO prequalified YF vaccines are attached with a vaccine vial monitor type 14 (VVM 14), which means the vaccines can withstand cumulative exposure to 37°C for up to a period 14 days and still retain potency.

Table 2: WHO Prequalified YF vaccines and their characteristics[xvi]

Manufacturer	Vial Size (doses)	VVM type	Shelf Life (months)	Indicated storage Temperature	Cold chain volume (cm^3 per dose)
Sanofi Pasteur	10	14	36	2-8 C	2.46
Bio-Manguinhos	5	14	24	2-8 C	6.31
	10	14	36	2-8 C	2.96
	50 (currently not available)	14	24	2-8 C	0.63
Chumakov Institute	2 (very limited for travellers)	14	24	2-8 C	7.2
	5	14	24	2-8 C	6.0
	10	14	24	2-8 C	3.6
Institute Pasteur Dakar	5	14	36	2-8 C	2.8
	10	14	36	2-8 C	1.4
	20 (upon request)	14	36	2-8 C	0.7

Administered as a full dose, YF vaccines are injected as a single dose (0.5 ml) either SC or IM. All YF vaccines come with a vaccine vial monitor Type 14 (VVM 14).

According to current practice, administration of YF vaccines through preventive mass vaccination campaigns is recommended for target groups in areas at risk of YF where there is low vaccination coverage. Vaccination should be provided to everyone aged ≥ 9 months, in any area with reported cases. Noting that YF vaccine is a live attenuated viral vaccine, a risk-benefit assessment should be undertaken for all pregnant and lactating women[xvii]. YF vaccine can be administered simultaneously with other vaccines.

Fractional-dose vaccine administration
For ease of implementation, a dose-sparing approach for YF vaccine should preferentially keep the same mode of delivery as routinely used vaccine in the country using traditional injection equipment. Diluting the vaccine with a larger volume than recommended by the manufacturer while maintaining a 0.5ml dose to achieve dose sparing is not advised due to programmatic and safety concerns. A fractional dose approach should consist of administration of a volume of not less than 0.1 ml using the standard SC or IM route of administration. Administering a smaller volume of vaccine leads to difficulty in administration such as oozing/loss of volume at injection site, difficulty in availability of appropriately graduated auto-disable (AD) syringes, etc.

[xvi] Adapted from https://extranet.who.int/gavi/PQ_Web/, accessed June 2016
[xvii] WHO Position Paper June 2013: Vaccines and vaccination against yellow fever (available at http://www.who.int/wer/2013/wer8827.pdf?ua=1, accessed June 2016)

If fractional dosing of YF is to be adopted, it is recommended that the dose is administered using the same technique to which vaccinators are accustomed in their daily practice. Most of the injections provided through the immunization programmes are administered IM or SC. For more information on experience in the routine immunization programme with delivering vaccines ID see Annex 5. For Stamaril ® (Sanofi), a country may opt to administer the vaccine via ID route, which is off-label, if experienced in the administering via this route. Otherwise, the Sanofi vaccine should also be administered by the SC route.

Wastage
Since opened vials of YF vaccine should be typically discarded no later than 6 hours (50 dose vial requires discarding after only 4 hours) after opening or at the end of the immunization session (whichever comes earlier), fractional dose administration could theoretically increase wastage. Data for YF mass vaccination campaigns, indicate a 5% wastage rate (similar to measles and rubella vaccine campaigns that have similar handling characteristics) for 10 or 20 dose vials. This is significantly smaller than the indicative wastage rates for routine immunization. As 2 and 50 dose vials are not available and 5 dose immunization are reserved for routine immunization, typically 10 dose vials are considered for use in vaccination campaigns.

Based on this, it could be expected that the administration of YF vaccination through wide age range campaign could result in an effective use of the multi-dose vials, even the larger presentations, if the following aspects are considered:
- Different vial presentation in densely populated/urban and rural settings: larger vials to be used in densely populated or urban settings.
- Different vial presentation for different age groups: some of the countries at risk have very young populations; for instance, Angola's population, is one of the youngest in the African continent, with nearly half of the population under 15 years of age. School (primary and secondary) based vaccination could target large number of children and support the use of larger vials.
- Timely reconstitution of the vaccine, based on the availability of the requisite number of patients.
- Training: for this aspect see section below.

Global supply of injections devices
Implementation of fractional dose use of vaccines would entail a multifold increase of injection devices with a smaller volume compared to the full dose. Dose fractioning strategies have to be therefore based on sufficient availability of suitable injection devices..

WHO is exploring availability of vaccines with various manufacturers for potential use in emergency campaigns.

Vaccine management and handling
Currently, the vial presentations of WHO prequalified YF vaccines are 2, 5, 10 and 20 doses. If used in a ½ dose approach, this essentially equates to the equivalent of 4, 10, 20 and 40 dose vials, and for a 1/5th

fractional-dose approach (0.1ml) to the equivalent of 10, 25, 50 and 100 dose vials. Clearly from a practical standpoint, and given their availability and information secured to date on the stopper, 10 dose vials are the best-available choice for mass campaigns (rapid consumption).

Multiple countries' experiences with implementation of wide age-range supplementary immunization activities demonstrates that administration of YF vaccination with multi dose vials - even of larger presentation - could be effective if the aspects noted under wastage above are considered.

Since most opened vials of YF vaccine should be discarded 6 hours after opening or at the end of the immunization session (whichever comes first), use of fractional dose administration could increase wastage levels if the vaccine presentation is large. This is also borne out by estimations used for measles and rubella supplemental immunization activities, a lyophilised vaccine with similar handling characteristics post-reconstitution as YF vaccine.

The question of whether multiple septum piercings affects the integrity of the septum may need to be considered. YF vaccine contains no preservative and there is a potential risk of increased contamination if vials are repeatedly used (punctured) over the course of an immunization session. The use of lower dose vials would limit the number of punctures and might reduce the risk of contamination. [xviii]

Communication strategy
The development of a funded communication strategy and proper messaging on the new delivery approach (or technology) would be crucial to ensure health worker and community acceptance. This strategy would need to be developed by the Ministry of Health with adequate lead time, and would need to clearly justify and explain the updated approach adopted for mass vaccination. It is essential that the health workforce and general population do not equate fractional dosing with achieving partial efficacy, as this could damage the credibility of the immunization programme well beyond YF vaccination.

Increased pain and swelling due to ID administration is a real risk, which as a consequence may lead to lower public acceptance, decreased trust and therefore lower coverage in certain communities. These risks can be addressed by adequate training but programme communications of what to expect are key to community acceptance. As a consequence, the communication strategy should include a component on crisis management and an effective response to adverse events that may occur following vaccination.

Health worker capacity building and training
All health personnel affected by the new strategy would need to be identified in order to be properly informed and adequately trained, particularly as this would be an "off label" use of the vaccine. Health workers will need to be properly informed on this aspect and more generally be trained on aspects related to YF mass vaccination campaigns[xix]. Depending on the administration technique chosen (ID or

---

[xviii] PATH is currently planning to conduct this type of testing for IPV vials (ID fIPV delivery) and potentially it could expand the testing to include yellow fever vials .

[xix] http://apps.who.int/iris/bitstream/10665/156053/1/WHO_HSE_PED_CED_2015.1_eng.pdf?ua=1&ua=1, accessed June 2016

SC), appropriate training materials or guidance will have to be developed, which should also include all relevant aspects on safety and vaccine management, specifically adapted for the vaccine/manufacturer of choice and to the injection device to be used. Training is needed for health workers to identify how to calibrate the correct dose, as similar type syringes may have more than one interpretable scale. If different syringes are supplied over time, this may create future confusion in the programme. Training and job aides should include all relevant aspects on vaccine handling, vaccination strategy and programme safety. Proper recording of vaccinations and monitoring should also be included in the training.

Adequate and sustained supervision would be essential for the successful implementation and monitoring of this approach and the activities should be properly included in the budget. As with any newly-introduced, unfamiliar practice, post-training support will be important and there will be a need to revise supervision instruments (tally sheets, monitoring forms may need to be adjusted) and develop feedback mechanisms. Supervision activities following initial training would need to be adequately planned and budgeted.

11.   Surveillance and monitoring

Surveillance
When administering vaccination as a fractional dose within a campaign, individual vaccination records need to be established to allow for assessment of duration of protection, effectiveness, tracking of break-through cases and fractional dose vaccine safety (in particular rare SAE following immunization, such as neurotropic and viscerotropic disease) according to age and pending on how close to expiry date the vials are.

A YF Laboratory Network (YFLN) has been developed in the African Region on the backbone of the already existing Global Measles-Rubella Laboratory Network (GMRLN). Currently, 24 National YF laboratories have been established in 21 Member States of the African Region, mainly in countries at risk for YF outbreaks. These National Laboratories have been established predominantly in already existing National Measles-Rubella Laboratories to benefit from the investments made by WHO to establish these MR laboratories. Investments were made in capacity building (including training in conducting IgM testing, QA/QC, biosafety, laboratory management) as well as provision of essential equipment (ELISA washer and reader, automatic pipettes).

According to the YF case definition the diagnostic of a suspected case has to be confirmed by a positive genome detection (PCR) or the detection of YF specific IgM that negative for other flaviviruses (e.g., dengue, West Nile, or Zika viruses) through plaque reduction neutralization test (PRNT). Of note, YF specific IgM antibodies that are formed in response to infection with YF virus or YF vaccine virus cannot be differentiated with currently available rapid diagnostic tests. Furthermore, YF IgM can persist for

years following receipt of YF vaccine and therefore all suspect cases of YF vaccine should be asked about their previous history of YF vaccination in order to appropriately interpret the results.

WHO is working closely together with the Global Specialized Laboratory for YF at the Arbovirus laboratory, CDC-Fort Collins, who routinely provides the network with essential reagents to conduct YF IgM testing using a protocol developed by them and rolled out throughout the global laboratory network (LabNet). They also play a role in upgrading the expertise of individual laboratories and conduct referral testing, as well as quality assurance. A Regional Reference Laboratory for the African Region has been established at the Institut Pasteur of Dakar, Senegal. They provide confirmation of the results from national laboratories and further characterization of virus strains (IgM, IgG, virus isolation, molecular detection and characterization, virus neutralization) and QA/QC. This multi-tiered structure mimics both GMRLN and GPLN (Global Polio LabNet) in all aspects.

As part of the WHO guidance to the YFLN, WHO published a laboratory manual for YF diagnosis[xx]. Throughout the last 15 years, WHO has organized several laboratory-training workshops to strengthen skills of the YF laboratory staff. Furthermore, annual YFLN meetings are conducted jointly with polio and measles networks to mutually benefit from each other's experience and highlight the integrated LabNet approach WHO is striving for.

Currently, efforts are underway to strengthen laboratory capacity for YF testing in countries not previously dealing with YF transmission, and considerations are made to establish additional RRLs to relieve the workload of IP Dakar.

The integrated approach of YF with polio and measles is also reflected in the integrated approach to YF surveillance.

Monitoring

A new guideline entitled Planning and Implementing High Quality Supplementary Immunization Activities for Measles-Rubella and other Injectable Vaccines has recently been developed.[xxi] While this guideline uses measles-rubella vaccine as the example, the principles of campaign planning, implementation and monitoring can be applied to a mass vaccination campaign using YF vaccine. The new guidelines are intended for use by immunization programme managers and their partners and provide tools for use before (i.e., readiness assessment), during (i.e., rapid convenience monitoring) and after (i.e., rapid convenience monitoring and mopping up and coverage surveys) the campaign.

Recording vaccinations administered during campaigns on a vaccination card/home-based record is essential for the valid verification of immunization coverage during post- campaigns surveys, and for establishing the total number of vaccine doses received by a child at school entry (where school enrolment screening policies exist). In particular for fractional dose use, personalized registries may prove useful when considering the need for with revaccination of full dose. Although the use of

---

[xx] http://apps.who.int/immunization_monitoring/Manual_YF.pdf?ua=1, accessed June 2016
[xxi] http://www.who.int/immunization/diseases/measles/SIA-Field-Guide-revised.pdf?ua=1, accessed June 2016

immunization cards can increase the campaign cost and workload, appropriate recording of every vaccination, fractional or full dose, (including those given during campaigns) is recommended by WHO.[xxii] Training and supervision will need to constantly reinforce this issue because in many countries cards are not marked during Measles or Measles/Rubella Supplemental Immunization Activities or polio national immunization days. It is worth noting that a recorded receipt of a fractional dose does not qualify as YF certificate as per IHR.

12.　　Ethical considerations

In emergencies the international community has a collective duty of care to ensure that effective affordable measures are available to those most in need. The duty of care principle demands that effective vaccinations against disease threats should be available to those at risk. Emergencies often require rapid decision-making under uncertainty and unconventional measures, but ethical principles need to be adhered to even in these situations.

In the face of shortages, usually one strategy is prioritization among different population groups. The second is to use a "dose-sparing" approach in order to cover as much of the population as possible, of which the feasibility has been demonstrated by Wu et al. Both options could also be combined. The best of these options should be chosen based on a rigorous public health and ethical analysis.

There are a number of ethical issues that arise when choosing a «dose-sparing» approach:

Risk-benefit considerations
First, the risk of harm to populations and individuals needs to be analyzed («first do no harm principle»). These risks and possible mitigating actions to minimize them should be explicitly discussed. Second, there should be robust evidence for benefit, i.e. for the non-inferiority in comparison to the full dose. In addition, the "dose-sparing" strategy should be considered based on robust evidence for its benefit.

The obligation to produce and share data
In public health emergencies there is an ethical duty to produce and rapidly share all relevant data. The use of lower doses of vaccine as an emergency measure places an ethical obligation to learn as much as possible as quickly as possible. Even if the « dose-sparing » approach is not designed as a research project, research components should be embedded to use this opportunity to gain new knowledge. Ideally, protocols should be submitted for pre-approval now, so that final ethics review can be expedited.

Distributive Justice & Equity
Unless there is scientific necessity and evidence for doing so (e.g. based on safety or futility), the immunization programmes should not discriminate against any groups. Special measures should be taken to facilitate the access of vulnerable groups, such as children and pregnant women.

[xxii] WHO Immunization, Vaccines and Biologicals: Home based records (available at http://www.who.int/immunization/monitoring_surveillance/routine/homebasedrecords/en/, accessed June 2016)

Transparency, trust, public engagement

The vaccination strategy should be well communicated by the national policy-makers to the public health officials, the public and the media. Special effort should be made to ensure that media understand well the rationale for the dose sparing and become real partners in disseminating the messages of the vaccine programmes. Public engagement will facilitate uptake and trust in the programme.

Informed consent

During mass vaccination campaigns, consent is normally presumed (implicit consent), with a possibility to opt-out. This means that information about the vaccine is disseminated widely in an accessible format, and it is ensured that the public knows that they can opt out of vaccination, if they so wish. If mass vaccination campaigns are being planned with the lower dose vaccine, it is an ethical requirement to provide minimum additional information: i.e. that a lower than usual dose will be used but that it is considered as safe and effective as the normal dose.

13. Recommendations

1. The use of YF fractional dose vaccination should be considered in response to an emergency situation in which current vaccine supply is insufficient. Fractional dose vaccination should be used for vaccination campaigns in response to an outbreak or in settings where the extension of the outbreak is imminent and should not be used for routine immunization. As soon as the vaccine supply situation normalizes, fractional dose should be replaced by full dose vaccination. Fractional dose vaccination is an off-label use of the product.

2. Under no circumstances should YF vaccine be reconstituted in different volume of diluent as recommended by the manufacturer, and no efforts should be undertaken to otherwise dilute the vaccine.

3. When YF vaccine is administered in fractional dose, preference should be given to the administration of the vaccine according to standard route, i.e. SC or IM. The minimal dose administered **should preferentially contain 3000 IU/dose, but no less than 1000 IU/dose and the minimum volume of administration should be not less than 0.1 ml**.

4. **The dose fractioning (e.g., ½ or 1/5th) should be done considering the potency of the vaccine batch, the shortage of supply and availability of suitable injection devices**.

5. In the absence of data on the use of fractional dose in young children, children below the age of 2 years should preferentially be offered a full dose of vaccine (i.e. 3000 IU or higher) during emergency campaigns.

6. Different expansion scenarios for YF vaccine fractional dose administration should be considered in view of the anticipated risk of the spread of the disease, and shortage in vaccine supply. Actual potencies of available vaccines need to be considered to meet potency levels as discussed before:

   a.   1/2 dose of Biomanguinhos vaccine administered SC.

   b.   Should the shortage of vaccine exceed the use of ½ dose, use of a 1/5th dose of Biomanguinhos vaccine administered SC could be considered.

   c.   If the shortage even exceeds this fractional dose supply, all WHO prequalified vaccines could be administered as ½ or 1/5 th fractional dose SC, depending on potency of the batch. In such a context, use of Stamaril ® (Sanofi) via ID administration (0.1.ml) is, while off-label, also acceptable, depending on the preferences of the country. Generally use of fractionate doses should not go below the aforementioned minimal dose range (see recommendation 3).

7. **Reconstituted YF vaccine is heat labile and must be kept at 2-8°C at all times and discarded after 6 hours in accordance with WHO's open vial policy**.

8. No multi-dose vials containing more than 10 full doses should be used for fractional dose administration to reduce risk of contamination through multiple puncture of the septum.

9. All other precautions and recommendations for YF vaccination prevail as detailed in the WHO VPP.

10. Every effort must be made to monitor safety and YF vaccine AEFI's.

11. Vaccination with fractional dose should be recorded using personalized registries for purpose of safety and effectiveness monitoring. Such information could be useful in assessing eventual re-vaccination needs with full dose, for which currently there is no recommendation.

14.   Research needs

The data appear sufficiently strong for emergency policy-decision making for the vaccines from 2 manufacturers (Sanofi Pasteur & Bio-Manguinhos) in relation to fractional dose administration of YF vaccine by ID and IM/SC route, respectively. However, to support a broader recommendation on fractional dose use of YF vaccine can be made, additional data should be generated and ideally all 4 WHO prequalified YF vaccine should be studied. Furthermore, since the data on fractional doses were generated in adult study populations, there is an urgent need to compile clinical trial data in children and infants. The specific research needs include:

- Immunological non-inferiority trials should be conducted comparing the full dose vs. a fractional dose of ½ (0.25ml) and 1/5 th of the volume (0.1ml) using the same route of administration for all prequalified vaccines;
- Vaccine should include lots ex-factory and end of shelf-live, with recently measured potency expressed in IU.
- Studies should be conducted in healthy adults in *flavivirus*-naïve subjects, and with representative background of *flavivirus* pre-existing immunity, which should be duly characterized (dengue, YF, Zika, WNV in priority).
- An age de-escalation study should be conducted in children down to 9 months in order to assess immunogenicity.
- All studies should report baseline immune status, measure YF functional antibodies at 28 days and 12 months after vaccination using validated PRNT; viraemia (adults only), and safety and reactogenicity using standard procedures;
- Measures should be put in place for long-term follow up with of vaccinated subjects, and booster vaccination should be offered in case that titres fall below the protective threshold.

15.   Annexes

Annex 1: Search strategies for the use of yellow fever vaccine for IM/SC delivery

Search engine: PubMed

Search term: "yellow fever vaccine" and ("fractional dose*" or "dose-sparing" or "dose sparing" or "subdose*")

Language: no limitation
Period: no limitation

Result: only 1 study (= study#4 was identified)

The other 2 studies (study#1 and #3 were identified by the references of study#4)

Search strategies for the use of yellow fever vaccine for intradermal delivery

Search engine: PubMed

Search term: "yellow fever vaccine" and "intradermal"

Language: no limitation

Period: no limitation

Result: Of 5 articles identified, 2 articles were dose-sparing related studies. 1 study is study#2 of our review. I excluded another study identified from our review because of (i) sample number was only 7, and (ii) target population was only egg allergy.

Annex 2: GRADE tables

GRADE table 1 on the use of a fractional dose 17DD YF vaccine (1/5th of full dose) via regular route of administration

Population : Immunocompetent individuals
Intervention : Fractional dose 17DD YF vaccine with 1/5th of 0.5ml (full dose) SC/IM within a YF vaccination campaign
Comparision: Full dose of 17DD YF vaccine
Outcome : Cases of YF in outbreak settings

In immunocompetent individuals, does a fractional dose (1/5th of full dose (0.5ml)) administered via regular route of administration prevent YF disease?			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/RCT 2/Observational	4
	Factors decreasing confidence	Limitation in study design	Serious[xxiii]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[xxiv]	-1
		Imprecision	Not serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
Final numerical rating of quality of evidence				**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome**
	Conclusion			**In outbreak setting, using a fractional dose of 17DD YF vaccine via regular route of administration in vaccination campaign may be warranted to mitigate the risk of YF disease individuals and discontinue further spread of the virus despite limited confidence in the quality of the evidence.**

References

1. Martins RM, Maia MDLS, Farias RHG, Camacho LAB, Freire MS, Galler R, et al. A double blind, randomized clinical trial of immunogenicity and safety on a dose-response study 17DD yellow fever vaccine. Human Vaccines & Immunotherapeutics 2013; 9: 879–88.
2. Campi-azevedo AC, Estevam PDA, Coelho-dos-reis JG, Peruhype-magalhães V, Villela-rezende G, Quaresma PF, et al. Subdoses of 17DD yellow fever vaccine elicit equivalent virological / immunological kinetics timeline. BMC Infect Dis 2014; 14: 391.
3. Lopes O de S, Guimaráes SDA, de Carvalho R. Studies on yellow fever vaccine. III-Dose respons in volunteers. J Biol Stand 1988; 16: 77-82.

[xxiii] No allocation concealment reported.
[xxiv] Administered to healthy male volunteers only; Immunogenicity data only; Study results stem from one WHO prequalified YF vaccine and might not be extrapolated to the other WHO prequalified vaccines; Potency of the vaccine may vary by batch and time of administration.

GRADE table 2 on the use of a fractional dose 17D YF vaccine (1/5th of full dose) administered intradermally

Population : Immunocompetent individuals
Intervention : Fractional dose 17DD YF vaccine with 1/5th of 0.5mL (full dose) SC/IM within a YF vaccination campaign
Comparision: Full dose of 17DD YF vaccine
Outcome : Cases of YF in outbreak settings

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/RCT	4
	Factors decreasing confidence	Limitation in study design	Serious[xxv]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[xxvi]	-1
		Imprecision	Not serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome**
	Conclusion			**In outbreak setting, using a fractional dose of 17D YF vaccine ID in vaccination campaign may be warranted to mitigate the risk of YF disease individuals and discontinue further spread of the virus despite limited confidence in the quality of the evidence.**

References

1. Roukens A. Intradermally Administered Yellow Fever Vaccine at Reduced Dose Induces a Protective Immune Response: A Randomized Controlled Non-Inferiority Trial. Volume 3, Issue 4, Plos One 2008

[xxv] No blinding of participants.
[xxvi] Study results stem from one WHO prequalified YF vaccine and might not be extrapolated to the other WHO prequalified vaccines; Potency of the vaccine may vary by batch and time of administration.

Annex 3: Risk of bias assessment using Cochrane Collaboration's tool

Campi-Azevedo AC et al. 2014

Methods	Randomized controlled trial
Participants	900 healthy male volunteers (mean age 19.4 years) from military units in Rio de Janeiro, Brazil
Interventions	Full dose of yellow fever vaccine and five lower alternative formulations (Bio Manguinhos)
Outcomes	Neutralizing antibody titers, viremia, cytokins and chemokins.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk / Unclear risk / Unclear risk / Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk / Unclear risk / Unclear risk / Unclear risk	Not reported.
Blinding of participants and personnel (performance bias)	Unclear risk / Unclear risk / Unclear risk / Unclear risk	Not reported.
Blinding of outcome assessment (detection bias)	Unclear risk / Unclear risk / Unclear risk / Unclear risk	Not reported

Incomplete outcome data (attrition bias)	Unclear risk ▼	
	Unclear risk ▼	Not reported.
	Unclear risk ▼	
	Unclear risk ▼	

Selective reporting (reporting bias)	Unclear risk ▼	
	Unclear risk ▼	Not reported.
	Unclear risk ▼	
	Unclear risk ▼	

Other bias	Unclear risk ▼	
	Unclear risk ▼	
	Unclear risk ▼	
	Unclear risk ▼	

Lopes O et al. 1988

Methods	Observational study
Participants	300 healthy male volunteers from military units in Rio de Janeiro, Brazil. Age range: 18-47 years (Mean 21.7 years).
Interventions	Yellow fever vaccine administered by different dilutions (Undiluted; 1:10; 1:60; 1:100, 1:1000)
Outcomes	Immunogenicity; Adverse events following immunization.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk ▼	
	High risk ▼	Participants were allocated to each vaccine group
	High risk ▼	in the order they reported for occulation.
	High risk ▼	
Allocation concealment (selection bias)	High risk ▼	No reported allocation concealment.

High risk	▼
High risk	▼
High risk	▼

Blinding of participants and personnel (performance bias)

High risk	▼	
High risk	▼	No reported blinding of participants.
High risk	▼	
High risk	▼	

Blinding of outcome assessment (detection bias)

High risk	▼	
High risk	▼	Self-reporting of adverse reactions following
High risk	▼	immunization to unit dispensary.
High risk	▼	

Incomplete outcome data (attrition bias)

Low risk	▼	
Low risk	▼	3.6% did not provide a serum sample after
Low risk	▼	immunization. 10% had yellow fever antibodies
Low risk	▼	before vaccination and were therefore excluded.

Selective reporting (reporting bias)

Unclear risk	▼	
Unclear risk	▼	Unclear whether any outcomes were measured but
Unclear risk	▼	not reported based on the results.
Unclear risk	▼	

Other bias

Unclear risk	▼	
Unclear risk	▼	No other sources of bias identified.
Unclear risk	▼	
Unclear risk	▼	

Martins RM et al. 2013

Methods	Randomized controlled trial
Participants	900 healthy male volunteers (mean age 19.4 years) from military units in Rio de Janeiro, Brazil
Interventions	Full dose of yellow fever vaccine and five lower alternative formulations

(Bio Manguinhos)

Outcomes Seroconversion, and neutralizing antibodies geometric mean titer; Adverse events following immunization

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk Unclear risk Unclear risk Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk Unclear risk Unclear risk Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk Unclear risk Unclear risk Unclear risk	Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Unclear risk Unclear risk Unclear risk Unclear risk	Self-reporting of adverse reactions following immunization
Incomplete outcome data (attrition bias)	Unclear risk Unclear risk Unclear risk Unclear risk	First and last blood sample obtained from all volunteers, 2nd blood sample obtained from 85.6% of volunteers.
Selective reporting (reporting bias)	Unclear risk Unclear risk	Unclear whether any outcomes were measured but not reported based on the results

| | Unclear risk | ▼ |
| | Unclear risk | ▼ |

Other bias	Unclear risk	▼	
	Unclear risk	▼	No other sources of bias identified.
	Unclear risk	▼	
	Unclear risk	▼	

Roukens AH et al. 2008

Methods	Randomized controlled non-inferiority trial
Participants	Healthy volunteers (18 years and older) 155 primary vaccinees and 20 revaccinees
Interventions	Intradermal 0.1ml yellow fever vaccine; 0.5ml yellow fever vaccine subcutaneously (Sanofi)
Outcomes	Immunogenicity; Adverse events following immunization.
Notes	

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk ▼ Unclear risk ▼ Unclear risk ▼ Unclear risk ▼	Randomization by the investigator using permuted-block randomization.
Allocation concealment (selection bias)	Unclear risk ▼ Unclear risk ▼ Unclear risk ▼ Unclear risk ▼	Treatment allocation was concealed in sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk ▼ High risk ▼ High risk ▼	Participants could identify to which group they were allocated to by location of vaccination and type of syringe used.

High risk ▾

Blinding of outcome assessment (detection bias)

Unclear risk ▾

Unclear risk ▾

Self-reported adverse reactions following immunization documented by participants during 3 weeks after immunization who were blind to treatment allocation.

Unclear risk ▾

Unclear risk ▾

Incomplete outcome data (attrition bias)

Low risk ▾

Low risk ▾

Participants completed outcomes assessment.

Low risk ▾

Low risk ▾

Selective reporting (reporting bias)

Unclear risk ▾

Unclear risk ▾

Unclear whether any outcomes were measured but not reported based on the results.

Unclear risk ▾

Unclear risk ▾

Other bias

Unclear risk ▾

Unclear risk ▾

No other sources of bias identified.

Unclear risk ▾

Unclear risk ▾

Question: In immunocompetent individuals, should a fractional dose (1/2 or 1/5th of full dose (0.5ml)) of YF vaccine be administered in case of YF vaccine supply shortages?

Population: Immunocompetent individuals in the context of the current yellow fever outbreak

Intervention: Dose-sparing strategies through fractional dosing of YF vaccine.

Comparison(s): Continued use of full dose/ no vaccination.

Outcome: Individual short-term protection, containing of ongoing outbreak.

Background:

Ongoing Yellow fever outbreaks are sharply increasing the demand for YF vaccine, are exhausting the global stockpile and are putting at risk the immunization of endemic populations and travellers to those areas for which YF vaccine is mandatory. Dose-sparing strategies through fractional dosing of YF vaccine may be promising in the context of the current outbreak. These dose-sparing strategies are assessed by the Strategic Advisory Group of Experts (SAGE) on Immunization.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The current outbreak remains of great concern to WHO.	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Number of dose to be obtained by fractional dose-use is double/ five-fold.	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☐	*Varies* ☒	Reactogenicity of a fractional dose is comparable to administration of a full dose. No risk of serious adverse events following immunization have been assessed. Nevertheless, there may be programmatic safety considerations arising from the use of the fractional dose through multiple punctures of the rubber seal and consecutive contamination of the vial.	

32

	Balance between benefits and harms	*Favours intervention* [X] *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	Balancing the benefits and harms of the intervention and the risk of yellow fever disease within the context of the current outbreak, the intervention should be favoured.	
	What is the overall quality of this evidence for the critical outcomes?	*No included studies* ☐ *Very low* ☐ *Low* [X] *Moderate* ☐ *High* ☐	Quality of the available evidence on the use of the fractional dose is low due to study limitations and indirectness in terms of the target population of the trials (for further information, see the GRADE tables. Although no different table was done for the use of ½ dose of YF vaccine, this quality of the evidence is as for the 1/5 fractional dose SC, hence represents a possibility to use).	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* [X] *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☐ *No known undesirable outcomes* ☐	No evidence available but the importance of the desirable and undesirable outcomes may vary within the target population.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* [X] *Yes* ☐ *Varies* ☐	It is assumed that the values and preferences of the target population are in favour of the fractional dose to avoid the risk of acquiring the natural disease despite the potential harms associated with the fractional dose use.	

RESOURCE USE	Are the resources required small?	*No*	*Uncertain* ☒	*Yes* ☐	*Varies*		No evidence available but resources may be relatively considerable for implementation of immunization campaigns and ensuring adequate social mobilization.
	Cost-effectiveness	*No* ☐	*Uncertain* ☒	*Yes* ☐	*Varies* ☐		No available evidence, but likely less of a priority in the context of the current public health threat.
EQUITY	What would be the impact on health inequities?	*Increased* ☐	*Uncertain* ☐	*Reduced* ☒	Varies ☐		YF affects poor populations in densely-populated urban slums. Implementation of a fractional dose may reduce health inequities.
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Unclear* ☐	Intervention is likely to be acceptable to the stakeholders.
	Which option is acceptable to target group?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Unclear* ☐	Intervention is likely to be acceptable to the target population.
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	There may be programmatic challenges to implement the use of a fractional dose, but nevertheless the intervention is likely to be feasible.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☒	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

Recommendation (text)	1. The use of YF fractional dose vaccination should be considered in response to an emergency situation in which current vaccine supply is insufficient. Fractional dose vaccination should be used for vaccination campaigns in response to an outbreak or in settings where the extension of the outbreak is imminent and should not be used for routine immunization. As soon as the vaccine supply situation normalizes, fractional dose should be replaced by full dose vaccination. Fractional dose vaccination is an off-label use of the product.
	2. Under no circumstances should YF vaccine be reconstituted in different volume of diluent as recommended by the manufacturer, and no efforts should be undertaken to otherwise dilute the vaccine.
	3. When YF vaccine is administered in fractional dose, preference should be given to the administration of the vaccine according to standard route, i.e. SC or IM. The minimal dose administered **should preferentially contain 3000 IU/dose, but no less than 1000 IU/dose and the minimum volume of administration should be not less than 0.1 ml**.
	4. **The dose fractioning (e.g., ½ or 1/5th) should be done considering the potency of the vaccine batch, the shortage of supply and availability of suitable injection devices**.
	5. In the absence of data on the use of fractional dose in young children, children below the age of 2 years should preferentially be offered a full dose of vaccine (i.e. 3000 IU or higher) during emergency campaigns.
	6. Different expansion scenarios for YF vaccine fractional dose administration should be considered in view of the anticipated risk of the spread of the disease, and shortage in vaccine supply. Actual potencies of available vaccines need to be considered to meet potency levels as discussed before:
	    a. 1/2 dose of Biomanguinhos vaccine administered SC.
	    b. Should the shortage of vaccine exceed the use of ½ dose, use of a 1/5th dose of Biomanguinhos vaccine administered SC could be considered.
	    c. If the shortage even exceeds this fractional dose supply, all WHO prequalified vaccines could be administered as ½ or 1/5 th fractional dose SC, depending on potency of the batch. In such a context, use of Stamaril ® (Sanofi) via ID administration (0.1.ml) is, while off-label, also acceptable, depending on the preferences of the country. Generally use of fractionate doses should not go below the aforementioned minimal dose range (see recommendation 3).
	7. **Reconstituted YF vaccine is heat labile and must be kept at 2-8°C at all times and discarded after 6 hours in accordance with WHO's open vial policy**.
	8. No multi-dose vials containing more than 10 full doses should be used for fractional dose administration to reduce risk of contamination through multiple puncture of the septum.

Implementation considerations	- No multi-dose vials containing more than 10 full doses should be used for fractional dose administration to reduce risk of contamination through multiple puncture of the septum. - During the vaccination session every effort must be made to keep reconstituted vaccine cold. - Appropriate syringes (0.1 ml AD syringes) must be used for vaccine administration. Adequate communication and training of Health Care Workers is required.
Monitoring and evaluation	When administering vaccination as a fractional dose within a campaign, individual vaccination records need to be established to allow for assessment of duration of protection, effectiveness, tracking of break-through cases and fractional dose vaccine safety (in particular rare serious adverse events following immunization, such as neurotropic and viscerotropic disease) according to age and pending on how close to expiry date the vials are.
Research priorities	The specific research needs include: - Immunological non-inferiority trials should be conducted comparing the full dose vs. a fractional dose of ½ (0.25ml) and 1/5 [th] of the volume (0.1ml) using the same route of administration for all prequalified vaccines; - Vaccine should include lots ex-factory and end of shelf-live, with recently measured potency expressed in IU. - Studies should be conducted in healthy adults in *flavivirus*-naïve subjects, and with representative background of *flavivirus* pre-existing immunity, which should be duly characterized (dengue, YF, Zika, WNV in priority). - An age de-escalation study should be conducted in children down to 9 months in order to assess immunogenicity. - All studies should report baseline immune status, measure YF functional antibodies D 28 and after 12 months using validated PRNT; viraemia (adults only), and safety and reactogenicity using standard procedures; - Measures should be put in place for long term follow up with of vaccinated subjects, and booster vaccination should be offered in case that titres fall below the protective threshold.

Annex 5: Programme experience in the routine immunization programme with delivering vaccines ID

Beyond administration of BCG, there is limited programme experience in the routine immunization programme with delivering vaccines ID, and particularly in a mass campaign setting. ID inoculation is a difficult field technique and under a mass campaign setting, would be particularly stressful for health workers to exercise confidently and with precision. Experience in Nigeria with BCG administration during child health days has reportedly been unsuccessful, leading to frustrated health workers and dissatisfaction or departure by clients due to long waiting times. Furthermore, incorrect administration may lead to unpleasant local reactions, as described in the injection safety section. As a consequence, ID delivery of YF is the least preferable from a programmatic perspective.

In early 2016, India began administering inactivated polio vaccine (IPV) fractional dose via ID delivery in 8 states, using BCG syringes, indicating that in higher performing programmes with skilled heath workers, combined with adequate training, this approach is feasible in a routine setting. However, it is important to note that India has already implemented ID vaccination beyond BCG, administering rabies vaccination using insulin syringes. Monitoring of programme challenges and success are ongoing.

To understand the feasibility of ID vaccination for the administration of fractional dose (1/5th of full dose) inactivated polio vaccine, the WHO's Global Polio Eradication Initiative (GPEI) and PATH have clinically evaluated ID delivery technologies (PharmaJet Tropis disposable-syringe jet injector[27], West Pharmaceutical Services' ID Adapters[28]). In early 2017, these injectors for ID administration will become available for mass administration of IPV. However, the regulatory agency in the countries of manufacturing might require an application for license of these injectors with a specific vaccine, in this case YF vaccine. Lead production times are expected to be around 10 months.

---

[27] Resik S, Tejeda A, Mach O, Sein C, Molodecky N, Jarrahian C, et al. Needle-free jet injector intradermal delivery of fractional dose inactivated poliovirus vaccine: Association between injection quality and immunogenicity. Vaccine. 2015;33:5873-7.

[28] Tsals I, Jarrahian C, Snyder FE, Saganic L, Saxon E, Zehrung D, et al. Clinical performance and safety of adapters for intradermal delivery with conventional and autodisable syringes. Vaccine. 2015;33:4705-11.

16.   References

1. Monath TP, Gershamn M, Staples UE, and Barrett ADT. Yellow Fever Vaccine. In: Plotkin SA, Orenstein WA, and Offit P. Vaccines 6th ed. China. Saunders Elsevier; 2013.
2. Hickling J, Jones KR, Friede M, Zehrung D, Chen D, Kristensen D. Intradermal delivery of vaccines: potential benefits and current challenges. *Bull World Health Organ* 2011; 89:221-226.
3. Hickling J and Jones R. Intradermal delivery of vaccines: A review of the literature and the potential for development for use in low- and middle- income countries. Program for Appropriate Technology in Health and World Health Organization. 2009. Available from: http://www.path.org/publications/files/TS_opt_idd_review.pdf
4. Hickling J, Jones R. Yellow fever vaccination: the potential of dose-sparing to increase vaccine supply and availability. Seattle, WA: PATH, 2013:118 http://www.path.org/publications/files/TS_vtg_yf_rpt.pdf
5. Lopes O de S, Guimaráes SDA, de Carvalho R. Studies on yellow fever vaccine. III-Dose respons in volunteers. *J Biol Stand* 1988; 16: 77-82.
6. Roukens AH, Vossen AC, Bredenbeek PJ, Dissel JT, and Visse LG. Intradermally administered yellow fever vaccine at reduced dose induces a protective immune response: a randomized controlled non-inferiority trial. *PLoS One* 2008; 3.
7. Martins RM, Maia MDLS, Farias RHG, Camacho LAB, Freire MS, Galler R, et al. A double blind, randomized clinical trial of immunogenicity and safety on a dose-response study 17DD yellow fever vaccine. *Human Vaccines & Immunotherapeutics* 2013; 9: 879–88.
8. Campi-azevedo AC, Estevam PDA, Coelho-dos-reis JG, Peruhype-magalhães V, Villela-rezende G, Quaresma PF, et al. Subdoses of 17DD yellow fever vaccine elicit equivalent virological / immunological kinetics timeline. *BMC Infect Dis* 2014; 14: 391.