

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

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1. Preamble

This document represents the World Health Organization (WHO) Secretariat position on the use of yellow fever (YF) vaccine in the context of supply shortages in response to the current outbreak in Africa in 2016. The development of this paper was led by the WHO Initiative for Vaccine Research with contributions to specific sections from the WHO Departments of Pandemic and Epidemic Diseases, Essential Medicines, and Immunization Vaccines and Biologicals. The evidence and the proposed recommendations, reflected in this document, has been discussed with YF experts and reviewed by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization. SAGE and the YF experts provided input to this paper. The recommendations were vetted by SAGE, but they don't represent a formal SAGE recommendation. The paper will be updated as additional data become available. A full review on the use of fractional dose YF vaccine 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. The campaigns currently planned have led to a shortage of the vaccine, a situation which could deteriorate further should expansion of outbreaks necessitate additional immunization campaigns on a large scale. An assessment of existing opportunities to increase the availability of vaccine in response to ongoing outbreaks is therefore urgently required. This paper reviews the evidence on dose-sparing strategies through fractional dosing of YF vaccine as an immediate and short-term option to meet the needs of large-scale campaigns, and proposes recommendations for fractional dose vaccination in case of imminent need in the context of outbreak response. The paper is intended to support efforts to introduce YF vaccine fractional dose use in situations where supply capacity is threatened or inadequate, e.g. following the spread of YF into densely populated areas. This is not proposed as a longer-term strategy or to replace established routine immunization practices.

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, deathⁱ. 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 32 Yellow Fever endemic African countries, analysis suggests an annual burden of 84 000 – 170 000 severe cases and 29 000 – 60 000 deaths due to YF in the year 2013.ⁱⁱ 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

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

ⁱⁱ http://www.who.int/csr/disease/yellowfev/YellowFeverBurdenEstimation_Summary2013.pdf, accessed July 2016

two immunization strategies: (1) delivery of YF vaccine in endemic settings via routine childhood immunization programmes, and (2) mass vaccination campaigns to catch-up on immunization in unvaccinated cohorts not eligible for routine immunization, or in response to an outbreak of the disease.

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

By definition, YF outbreaks may constitute one or more cases. Currently, YF outbreaks are ongoing in Africa (Angola, Democratic Republic of the Congo (DRC) and Uganda) as well as in South America (Brazil, Colombia, and Peru). As of 7 June 2016, 2945 suspected cases and 329 deaths were reported from Angola, of which 819 cases and 108 deaths were laboratory confirmed. In DRC, 57 cases were confirmed as of 7 June, of which 51 were imported from Angola, 6 were autochthonous (2 Kinshasa, 1 Kwango, 1 Congo Central; and 2 from the Northern provinces which were not related to this outbreak). In Uganda, as of 7 June, a 61 suspected cases and 7 confirmed cases were reported. The most recent situation report is available on the WHO website.ⁱⁱⁱ Imported cases among unvaccinated individuals have been reported from China (11 cases), Morocco (1 suspected case) and Kenya (2 cases).

4. International Health Regulations (IHR 2005)

YF is the only disease specified in the International Health Regulations (IHR) 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 traveller is not in possession of a YF vaccination certificate. WHO publishes an annually updated list of countries with risk of YF transmission and countries requiring YF vaccination^{iv}. However, in practice, the vaccination requirements are unevenly applied; for example many international workers in Angola were not vaccinated at the start of the current outbreaks. To interrupt the international spread, it is urgent and essential that the provisions in the IHR be rigorously enforced by requiring travellers to present YF vaccination certificates when entering the countries where this is mandatory. 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 stipulate that the YF vaccine used must be approved by WHO. Annex 7 was amended in 2014^v to indicate that a single dose of the vaccine is enough to confer immunity for life, removing the need for booster vaccination after 10 years, and that the vaccination certificate remains valid throughout the life of the person vaccinated. This amendment entered into force on 11 July 2016, and all countries are required to abide by the new requirement^{vi}.

ⁱⁱⁱ WHO Yellow Fever situation report. <http://www.who.int/emergencies/yellow-fever/situation-reports/26-may-2016/en/>, accessed June 2016

^{iv} <http://www.who.int/ith/2016-ith-annex1.pdf?ua=1>, accessed June 2016

^v World Health Assembly Resolution WHA 67.13

^{vi} <http://www.who.int/ith/annex7-ihp.pdf?ua=1>, accessed June 2016

Under the auspices of the IHR, an Emergency Committee concerning YF was convened by the WHO Director-General on 19 May 2016. The Director-General accepted the Committee's assessment that the current YF situation is serious and of great concern and requires intensified control measures, and urged Member States to enforce the YF vaccination requirement for travellers to and from Angola and the DRC in accordance with the IHR, as set out in Annex 7^{vii}.

Recognizing that the supply of YF vaccines is limited, the Committee advised the immediate application of the policy of 1 lifetime dose of YF vaccine^v and the rapid evaluation of YF vaccine dose-sparing strategies by the WHO SAGE. This information paper is prepared to brief SAGE in case of an emergency in which SAGE will be asked to provide their advice 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 for YF vaccination as required by 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, particularly among poorer sections of the population without access to a proper water supply and basic health services, and an increase in international travel, both have the potential to contribute to increased densities of *Aedes aegypti*, the vector of YF virus.

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^{viii}, 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 low resource settings, country commitment, intersectoral collaboration and capacity building for entomological surveillance, as well as sustained effective YF control and a rapid outbreak response, are critical factors for strengthening vector control.

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

^{vii} <http://www.who.int/mediacentre/news/statements/2016/ec-yellow-fever/en/>, accessed May 2016

^{viii} http://www.who.int/neglected_diseases/vector_ecology/VCAG/en/, accessed July 2016

6. Yellow fever vaccine characteristics

YF vaccines are recommended to be given as a single dose (0.5 ml) administered by subcutaneous (SC) or intramuscular (IM) inoculation. The evidence in this briefing note is mostly derived from data on vaccination by the SC route. Healthy individuals almost always 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 be life-long. Limited data suggest that seroconversion is somewhat lower in children <2 years of age, but the clinical relevance of this is uncertain.^{ix} No evidence on potential differences in immunogenicity and efficacy between SC and IM administration could be identified.

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^x the immunizing dose recommended for use should not be less than 3.0 log₁₀, 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. Of these sub-strains, 17D-204 is used by Sanofi and by Institut Pasteur, Dakar, (at different passage levels), 17D-213 is used by Federal State Unitary Enterprise of Chumakov Institute, and 17DD is used by Bio-Manguinhos, Brazil.^x Therefore, any extrapolation of clinical trial data between different products, in particular of different sub-strains, should be done with caution.

7. Fractional-dose yellow fever vaccine immunogenicity when administered by subcutaneous, intramuscular or intradermal injection

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. The authors concluded that this approach could be implemented in the short to medium term, provided that clinical evidence for non-inferiority, safety, and dose levels has been generated. It could also be useful in public health emergencies if an acute shortage of YF vaccine occurs. (2) A systematic review by WHO of recent evidence on fractional dose administration of YF vaccine via the usual routes (SC or IM) and by ID injection. Since the review by 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.

^{ix} 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

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

While the study by Lopes et al dates from 1988, there are two recent vaccine trials which examined 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 titres (GMT). Fractional dose via IM/SC and by ID delivery showed similar immunogenicity as the full dose. Table 1 summarizes the findings in these studies.

Table 1: Studies assessing immunogenicity of fractional dose YF vaccine administered by SC/IM or ID inoculation.*

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 and complied with WHO minimum 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
Fractional dose	1/5 th of 1000 PFU	1/5 th of full dose (which was 3.5 x 10 ⁶ 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 seropositive 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 (primovaccines), 20 revaccines	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 full doses of 17DD YF vaccine.
Follow up period	28 days	1 year	10 months	1 year
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. Primovaccines: Blood samples were collected before vaccination, 4 wks and 8 wks after vaccination. Revaccines: Blood samples were collected before vaccination, 5 d 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 was 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 1000 PFU.	From 2 wks to 1 yr after vaccination, the maximum serum dilution (1:16) at which 80% of virus plaques were neutralized did not differ between those given a reduced ID or standard SC 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 titres of anti-YF PRNT. Analysis of serum biomarkers in association to PRNT and viraemia, support 10-fold lower subdose (3013 IU) of 17DD YF vaccine.
Vaccine Safety	No description	Redness, swelling and itching were reported more by ID group. 3 SC participants rated events as severe.	No serious adverse events were reported from any groups.	No description
Other findings		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.

Intradermal administration of a fractional dose

Roukens et al demonstrated that ID injection of 17D-204 YF vaccine with 1/5th of 0.5ml (full dose) was equally immunogenic compared to the SC delivery of a full dose (6). In 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 (i.e. neutralizing antibody titres) 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).

Fractional dose using the normal route of SC administration

Lopes O et al showed that seroconversion occurred following administration of 17DD YF vaccine in 100% of the participants in 28 days with 1/5th to 1/2 of the WHO standard 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 et al showed that even a 46x dilution resulted in equivalent humoral response as that induced by the full dose. Seroconversion occurred in 97% of the participants at 30 days with 1/46th of the full dose, and neutralizing antibody titres reached equivalent levels to those induced by the full dose. Campi-Azevedo et al carried out further investigation into viraemia and chemokine and cytokine responses. The viraemia pattern was equivalent to that with the full dose down to a dilution of 1/9 (3013 IU), whereas with the 1/46 dilution (587 IU) there was 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 those following the full dose (8).

It should be noted that the Martins/Campi-Azevedo studies used vaccine of high potency of above 10 000 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 on the minimum potency specifications for YF vaccines, 2007) ranging from 1995 log₁₀ IU to 2 511 886 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 potency for fractional vaccine doses. Below this value (about 3000–600 IU), protection, but possibly less than life-long protection, needs to be assumed. Dose fractioning below a potency of about 1000 IU/dose is not advisable, in order to leave a safety margin to 600 IU below which the humoral immune response was inferior to that with 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 vaccines 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 vaccination 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, principally in persons with known egg sensitivity^{xi}. 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 per 2 million people vaccinated in preventive campaigns).

Serious adverse events related to vaccination include YF vaccine-associated viscerotropic disease, neurological diseases, and severe hypersensitivity 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,xii,xiii}

The available data on adverse reactions after fractional doses of YF vaccine are limited to the studies described above and the number of persons vaccinated is too low to appropriately assess the rate of rare but serious adverse events (SAE). A recent study^{xiv} to compare the immunogenicity and safety of 5 alternative formulations of YF vaccine with lower concentrations of virus 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, experienced more frequently with the full dose vaccine.

^{xi} Vaccines, SIXTH EDITION, STANLEY A. PLOTKIN

^{xii} Detection and investigation of serious adverse events following yellow fever vaccination. Guidance from an informal consultation of experts. 18–19 November 2008. Geneva, Switzerland

^{xiii} Risk of yellow fever vaccine-associated viscerotropic disease among the elderly: a systematic review. Rafferty et al Vaccine 2013, 31(49):5789-805

^{xiv} 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^{xv}, in 155 primovaccinated 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 vaccinees. 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^{xvi}. This is primarily based on the observation that vaccine virus viraemia does not correlate with infectious dose^{xvii}. A common explanation is that high virus replication compensates for a small inoculum. However, Campi-Azevedo et al showed that intensity of viraemia stays the same with all fractional dose steps down to 3000 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 SAEs has not been described and there are no data to indicate an increase of severe side effects (viscerotropic complications) when using a fractional dose. However, active surveillance to report and respond to AEFIs is recommended during the introduction of YF vaccines in fractional doses.

9. Considerations related to regulatory approval

Exploring alternative potential strategies on dose optimization of YF vaccine to increase supply or surge capacity is of critical importance for deployment of the vaccine in outbreak control. The recommendations on fractional dose administration of YF vaccine discussed in this paper constitute an off-label use of the vaccine. Vaccine administration via the ID route is also an off-label use of the vaccine. 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 that variability of the manufacturing process results in different vaccine titres, extrapolation to all YF vaccines requires careful consideration. Product-specific data are needed to support regulatory approval and subsequent prequalification of the new dose. Dose reduction initiatives must be accompanied by relevant stability data and clinical data.

xv 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

xvi 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

xvii 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 increase 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 a manufacturer needs to change the target potency during manufacturing, then it would be necessary to demonstrate to the NRA and later prequalified, that there is no impact of this change on the quality and efficacy of the vaccine, as well as no impact on its shelf-life.

Regarding the rubber seal (septum) of multidose 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. Appropriate monitoring of any programmatic issues in practice should be included in campaigns as a precautionary measure. Currently, trials on fractional dose use with IPV are ongoing in India; these may provide lessons on practical aspects of fractional dose use with 10-dose vials.

10. Programmatic considerations

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

The four WHO prequalified YF vaccines are currently available in multidose vials containing 2, 5, 10, and 20 doses 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). The vaccine vials carry a vaccine vial monitor type 14 (VVM 14), which indicates that the lyophilized vaccine can withstand cumulative exposure to 37 °C for up to 14 days without loss of potency. Due to the limited heat stability of YF vaccine after reconstitution, opened multidose vials of YF vaccine must be kept at 2–8 °C, and must be discarded at the end of the immunization session, or within six hours of opening, whichever comes first.

Table 2: WHO prequalified YF vaccines and their characteristics^{xviii}

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
Institut 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.

According to current practice, deployment of YF vaccine 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. As YF vaccine is a live attenuated viral vaccine, a risk-benefit assessment should be undertaken for all pregnant and lactating women^{xix}. 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 for routinely used vaccine in the country, using traditional injection equipment. 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. Injection of a smaller volume of vaccine leads to difficulties such as oozing/loss of volume at injection site, limited availability of appropriately graduated auto-disable syringes, etc.

It is not advised to achieve dose sparing by diluting the vaccine with a larger volume than recommended by the manufacturer while maintaining a 0.5ml inoculum, due to programmatic and safety concerns.

If fractional dosing of YF is to be adopted, it is recommended that the dose should be administered using the same technique to which vaccinators are accustomed in their daily practice. Most of the injections

^{xviii} Adapted from https://extranet.who.int/gavi/PQ_Web/, accessed June 2016

^{xix} 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)

provided through the immunization programmes are administered by IM or SC injection. For more information on experience in routine immunization programmes with delivering vaccines by the ID route see Annex 5. For Stamaril[®] (Sanofi), a programme may opt to administer the vaccine via the ID route, which is off-label, if the personnel are experienced in the administering via this route; otherwise, this vaccine should be administered by the SC route.

Wastage

Since opened vials of YF vaccine should usually be 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 first, fractional dose administration could theoretically increase wastage. Data from YF mass vaccination campaigns indicate a 5% wastage rate (similar to measles and rubella vaccine campaigns that have similar handling characteristics) for 10-dose or 20-dose vials. This rate is significantly smaller than the indicative wastage rates for routine immunization. As 2-dose and 50-dose vials are not generally available and 5-dose vials are reserved for routine immunization, typically 10-dose vials are considered for use in vaccination campaigns.

Consequently, it could be expected that the administration of YF vaccination through wide age range campaigns could result in an effective use of the multidose vials, even the larger presentations, if the following factors 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, e.g. 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 numbers 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 injection devices

Implementation of fractional-dose use of vaccines would entail a major increase in the use of injection devices with a smaller volume than those used with the full dose. Dose fractioning strategies must therefore be based on sufficient availability of suitable injection devices.

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

Vaccine management and handling

Currently, the vial presentations of WHO prequalified YF vaccines are 2, 5, 10 and 20 doses. If used in a 1/2 dose approach, this represents 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 current information on the stopper, 10-dose vials are the best-available choice for mass campaigns (rapid consumption).

Several countries' experiences with implementation of wide age-range supplementary immunization activities demonstrate that administration of YF vaccination using multidose vials – even of larger presentation – could be effective provided the factors concerning wastage 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 large multidose vials are used. This is also borne out by estimations for measles and rubella supplemental immunization activities (SIAs), using a lyophilised vaccine with similar handling characteristics post-reconstitution to those of YF vaccine.

The question of whether multiple piercings of the rubber seal (septum) affects the integrity of the seal may need to be considered. As YF vaccine contains no preservative there is a potential increased risk of 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 reduce the risk of contamination.^{xx}

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 partial efficacy, which could jeopardize the credibility of the entire immunization programme.

Increased pain and swelling due to ID administration is a real risk, which 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 on what to expect are key to community acceptance. The communication strategy should therefore 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 and more generally trained on aspects related to YF mass vaccination campaigns^{xxi}. Depending on the administration technique chosen (ID or SC), appropriate training materials or guidance will need to be developed, which should also include all relevant aspects on safety and vaccine management, specifically adapted for the vaccine/manufacturer

^{xx} 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.

^{xxi} http://apps.who.int/iris/bitstream/10665/156053/1/WHO_HSE_PED_CED_2015.1_eng.pdf?ua=1&ua=1, accessed June 2016

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 types of 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 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 should be adequately planned and budgeted.

11. Surveillance and monitoring

Surveillance

When administering vaccination using 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 SAEs following immunization, such as neurotropic and viscerotropic disease) according to age and closeness to the vial expiry date.

A YF Laboratory Network (YFLN) has been developed in the African Region based on the framework of the 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 in order 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 diagnosis of a suspected case is confirmed by positive genome detection (PCR) or the detection of YF specific IgM that is negative for other flaviviruses (e.g. dengue, West Nile, or Zika viruses) by plaque reduction neutralization test (PRNT). Of note, YF specific IgM antibodies that are formed in response to infection with YF virus or to 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, USA, which routinely provides the network with essential reagents to

conduct YF IgM testing using a protocol developed by CDC and rolled out throughout the global laboratory network (LabNet). CDC also has a role in upgrading the expertise of individual laboratories and conducts referral testing, as well as quality assurance. A Regional Reference Laboratory (RRL) for the African Region has been established at the Institut Pasteur, Dakar, Senegal which provides 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 follows that of both GMRLN and GPLN (Global Polio LabNet).

As part of its guidance to the YFLN, WHO has published a laboratory manual for YF diagnosis^{xxii}. During the last 15 years, WHO has organized several laboratory-training workshops to strengthen skills of the YF laboratory staff. In addition, annual YFLN meetings are conducted jointly with polio and measles networks to share and benefit from their experience and highlight the integrated LabNet approach that WHO is striving for.

Currently, efforts are underway to strengthen laboratory capacity for YF testing in countries not previously dealing with YF transmission, and establishment of additional RRLs is being considered to relieve the workload of the Institut Pasteur in Dakar.

The integrated approach for YF with polio and measles diagnosis is also reflected in the integrated approach for YF surveillance.

Monitoring

A new WHO guideline *Planning and Implementing High Quality Supplementary Immunization Activities for Measles-Rubella and other Injectable Vaccines* has recently been developed.^{xxiii} The principles of campaign planning, implementation and monitoring recommended for measles-rubella vaccine can also be applied to mass YF vaccination campaigns. The 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 health record is essential for the valid verification of immunization coverage during post-campaigns surveys, and for determining 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 revaccination with the full dose. Although the use of 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

^{xxii} http://apps.who.int/immunization_monitoring/Manual_YF.pdf?ua=1, accessed June 2016

^{xxiii} <http://www.who.int/immunization/diseases/measles/SIA-Field-Guide-revised.pdf?ua=1>, accessed June 2016

WHO.^{xxiv} Training and supervision will need to constantly reinforce this issue because in many countries cards are not marked during measles or measles/rubella SIAs or polio national immunization days.

It is also important to note that a recorded receipt of a fractional dose does not constitute a YF vaccination certificate as stipulated in the 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 uncertain and unconventional situations, but ethical principles need to be adhered to even in these situations.

In the face of shortages, a usual strategy is prioritization among different population groups. Another is to use a dose-sparing approach in order to cover as much of the population as possible. Both options could also be combined. The best of these options should be chosen based on a rigorous public health and ethical analysis.

A number of ethical issues arise when choosing a dose-sparing approach:

Risk-benefit considerations

First, the risk of harm to populations and individuals needs to be analysed (the ‘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 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 entails 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 so that the final ethics review can be expedited.

Distributive justice and 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 population groups. Special measures should be taken to facilitate the access of vulnerable groups, such as children and pregnant women.

^{xxiv} 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 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 strategy 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 must be disseminated widely in an accessible format, and that it is ensured that members of the public know 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. Fractional dose YF vaccination, an off-label use of the product, 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 a different volume of diluent than that recommended by the manufacturer, and no other method of diluting the vaccine should be used.
3. When fractional dose YF vaccine is used, 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 the inoculum should be not less than 0.1 ml.
4. The dose fractioning (e.g. 1/2 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 YF vaccination in young children, children aged less than 2 years should preferentially be offered a full dose of vaccine (i.e. at least 3000 IU) during emergency campaigns.
6. Different expansion scenarios for YF vaccine fractional dose administration should be considered in view of the potential risk of further spread of the disease, and shortage of vaccine supply. Actual potencies of available vaccines need to be considered to meet the necessary potency levels:
 - a. 1/2 dose of Bio-Manguinhos vaccine administered SC.
 - b. Should the shortage of vaccine limit the use of a 1/2 dose, use of a 1/5th dose of Bio-Manguinhos vaccine administered SC could be considered.
 - c. If the shortage limits fractional dose supplies, all WHO prequalified vaccines could be administered as 1/2 or 1/5th fractional dose SC, depending on potency of the batch. In this context, use of Stamaril[®] (Sanofi) via ID administration (0.1.ml) is, while off-label, also acceptable, depending on the preferences of the country. As a general rule, fractional doses should not be less than the 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. Multidose vials containing more than 10 full doses should not be used for fractional dose administration in order to avoid increased risk of contamination due to multiple punctures of the septum.

9. Every effort should be made to monitor safety and YF vaccine AEFIs.

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

11. All other precautions and recommendations for YF vaccination remain valid as detailed in the WHO yellow fever vaccine position paper (2013).

14. Research needs

The currently available data appear sufficiently strong for emergency policy decision-making on use of the YF vaccines from two manufacturers (Sanofi Pasteur and Bio-Manguinhos) with fractional dose administration by ID and IM/SC injection, respectively. However, to support a broader recommendation on fractional dose use of YF vaccine, additional data are needed and ideally all 4 WHO prequalified YF vaccines 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 the following:-

- Immunological non-inferiority trials should be conducted to compare the full dose vs. a fractional dose of $\frac{1}{2}$ (0.25ml) and $\frac{1}{5}^{\text{th}}$ 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-life, 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 of vaccinated subjects, and booster vaccination should be offered in case titres may 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 this review. Another study identified from the review was excluded because (i) sample number was only 7, and (ii) target population was only persons with 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

Comparison: 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 ^{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 17DD YF vaccine via regular route of administration in vaccination campaign may be warranted to mitigate the risk of YF disease 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, Guimarães SDA, de Carvalho R. Studies on yellow fever vaccine. III-Dose respons in volunteers. *J Biol Stand* 1988; 16: 77-82.

^{xxv} No allocation concealment reported.

^{xxvi} 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

Comparison: Full dose of 17DD YF vaccine

Outcome : Cases of YF in outbreak settings

In immunocompetent individuals, does a fractional dose (1/5 th of full dose (0.5ml)) administered intradermally prevent YF disease?				
		Rating	Adjustment to rating	
Quality Assessment	No. of studies/starting rating		1/RCT	4
	Factors decreasing confidence	Limitation in study design	Serious ^{xxvii}	-1
		Inconsistency	None serious	0
		Indirectness	Serious ^{xxviii}	-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 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

^{xxvii} No blinding of participants.

^{xxviii} 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 titres, viraemia, cytokines and chemokines.
Notes	

Risk of bias table

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

Incomplete outcome data (attrition bias)

Unclear risk	▼
Unclear risk	▼
Unclear risk	▼
Unclear risk	▼

Not reported.

Selective reporting (reporting bias)

Unclear risk	▼
Unclear risk	▼
Unclear risk	▼
Unclear risk	▼

Not reported.

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 at 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	▼
High risk	▼
High risk	▼

Participants were allocated to each vaccine group in the order they reported for inoculation.

Allocation concealment (selection bias)

High risk	▼
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No reported allocation concealment.

	<input type="text" value="High risk"/> <input type="text" value="High risk"/> <input type="text" value="High risk"/>	
Blinding of participants and personnel (performance bias)	<input type="text" value="High risk"/> <input type="text" value="High risk"/> <input type="text" value="High risk"/> <input type="text" value="High risk"/>	No reported blinding of participants.
Blinding of outcome assessment (detection bias)	<input type="text" value="High risk"/> <input type="text" value="High risk"/> <input type="text" value="High risk"/> <input type="text" value="High risk"/>	Self-reporting of adverse reactions following immunization to unit dispensary.
Incomplete outcome data (attrition bias)	<input type="text" value="Low risk"/> <input type="text" value="Low risk"/> <input type="text" value="Low risk"/> <input type="text" value="Low risk"/>	3.6% did not provide a serum sample after immunization. 10% had yellow fever antibodies before vaccination and were therefore excluded.
Selective reporting (reporting bias)	<input type="text" value="Unclear risk"/> <input type="text" value="Unclear risk"/> <input type="text" value="Unclear risk"/> <input type="text" value="Unclear risk"/>	Unclear whether any outcomes were measured but not reported based on the results.
Other bias	<input type="text" value="Unclear risk"/> <input type="text" value="Unclear risk"/> <input type="text" value="Unclear risk"/> <input type="text" value="Unclear risk"/>	No other sources of bias identified.

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 titre; 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 whether any outcomes were measured but

Unclear risk ▼ 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 ▼ Randomization by the investigator using permuted-block randomization.
 Unclear risk ▼
 Unclear risk ▼

Allocation concealment (selection bias)

Unclear risk ▼
 Unclear risk ▼ Treatment allocation was concealed in sealed envelopes.
 Unclear risk ▼
 Unclear risk ▼

Blinding of participants and personnel (performance bias)

High risk ▼ Participants could identify to which group they were allocated to by location of vaccination and
 High risk ▼

High risk
High risk

type of syringe used.

Blinding of outcome assessment (detection bias)

Unclear risk
Unclear risk
Unclear risk
Unclear risk

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

Incomplete outcome data (attrition bias)

Low risk
Low risk
Low risk
Low risk

Participants completed outcomes assessment.

Selective reporting (reporting bias)

Unclear risk
Unclear risk
Unclear risk
Unclear risk

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

Other bias

Unclear risk
Unclear risk
Unclear risk
Unclear risk

No other sources of bias identified.

Annex 4: Evidence-to-recommendation table (draft table, to be completed after more data/recommendations are available)

<p>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?</p> <p>Population: Immunocompetent individuals in the context of the current yellow fever outbreak</p> <p>Intervention: Dose-sparing strategies through fractional dosing of YF vaccine.</p> <p>Comparison(s): Continued use of full dose/ no vaccination.</p> <p>Outcome: Individual short-term protection, containing of ongoing outbreak.</p>							
<p>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 countries 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.</p>							
	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	No <input type="checkbox"/>	Uncertain <input type="checkbox"/>	Yes <input checked="" type="checkbox"/>	Varies by setting <input type="checkbox"/>	The current outbreak remains of great concern to WHO.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	No <input type="checkbox"/>	Uncertain <input type="checkbox"/>	Yes <input checked="" type="checkbox"/>	Varies <input type="checkbox"/>	Number of doses to be obtained by fractional dose use is double/ five-fold.	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	No <input type="checkbox"/>	Uncertain <input type="checkbox"/>	Yes <input type="checkbox"/>	Varies <input checked="" type="checkbox"/>	Reactogenicity of a fractional dose is comparable to that of a full dose. No risk of serious adverse events following immunization has 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.	

	Balance between benefits and harms	<i>Favours intervention</i> <input checked="" type="checkbox"/> <i>Favours comparison</i> <input type="checkbox"/> <i>Favours both</i> <input type="checkbox"/> <i>Favours neither</i> <input type="checkbox"/> <i>Unclear</i> <input type="checkbox"/>	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?	<i>No included studies</i> <input type="checkbox"/> <i>Very low</i> <input type="checkbox"/> <i>Low</i> <input checked="" type="checkbox"/> <i>Moderate</i> <input type="checkbox"/> <i>High</i> <input type="checkbox"/>	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, the quality of this 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?	<i>Important uncertainty or variability</i> <input checked="" type="checkbox"/> <i>Possibly important uncertainty or variability</i> <input type="checkbox"/> <i>Probably no important uncertainty or variability</i> <input type="checkbox"/> <i>No important uncertainty or variability</i> <input type="checkbox"/> <i>No known undesirable outcomes</i> <input type="checkbox"/>	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?	<i>No</i> <input type="checkbox"/> <i>Probably No</i> <input type="checkbox"/> <i>Uncertain</i> <input type="checkbox"/> <i>Probably Yes</i> <input checked="" type="checkbox"/> <i>Yes</i> <input type="checkbox"/> <i>Varies</i> <input type="checkbox"/>	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 <input type="checkbox"/>	Uncertain <input checked="" type="checkbox"/>	Yes <input type="checkbox"/>	Varies <input type="checkbox"/>	No evidence available but resources may be relatively considerable for implementation of immunization campaigns and ensuring adequate social mobilization.			
	Cost-effectiveness	No <input type="checkbox"/>	Uncertain <input checked="" type="checkbox"/>	Yes <input type="checkbox"/>	Varies <input type="checkbox"/>	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 <input type="checkbox"/>	Uncertain <input type="checkbox"/>	Reduced <input checked="" type="checkbox"/>	Varies <input type="checkbox"/>	YF mainly 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 <input checked="" type="checkbox"/>	Comparison <input type="checkbox"/>	Both <input type="checkbox"/>	Neither <input type="checkbox"/>	Unclear <input type="checkbox"/>	Intervention is likely to be acceptable to the stakeholders.		
	Which option is acceptable to target group?	Intervention <input checked="" type="checkbox"/>	Comparison <input type="checkbox"/>	Both <input type="checkbox"/>	Neither <input type="checkbox"/>	Unclear <input type="checkbox"/>	Intervention is likely to be acceptable to the target population.		
FEASIBILITY	Is the intervention feasible to implement?	No <input type="checkbox"/>	Probably No <input type="checkbox"/>	Uncertain <input type="checkbox"/>	Probably Yes <input checked="" type="checkbox"/>	Yes <input type="checkbox"/>	Varies <input type="checkbox"/>	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 <i>clearly outweigh</i> desirable consequences in most settings <input type="checkbox"/>	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings <input type="checkbox"/>	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i> <input type="checkbox"/>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings <input checked="" type="checkbox"/>	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings <input type="checkbox"/>				

<p>Type of recommendation</p>	<p>We recommend the intervention</p> <p style="text-align: center;"><input type="checkbox"/></p>	<p>We suggest considering recommendation of the intervention</p> <ul style="list-style-type: none"> <input type="checkbox"/> Only in the context of rigorous research <input type="checkbox"/> Only with targeted monitoring and evaluation <input checked="" type="checkbox"/> Only in specific contexts or specific (sub)populations 	<p>We recommend the comparison</p> <p style="text-align: center;"><input type="checkbox"/></p>	<p>We recommend against the intervention and the comparison</p> <p style="text-align: center;"><input type="checkbox"/></p>
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<p>Recommendation (text)</p>	<ol style="list-style-type: none"> 1. The use of YF fractional dose vaccination, which is an off-label use of the product, 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 than that recommended by the manufacturer, and no dilution of the vaccine should be done by any other methods. 3. When YF vaccine is administered in fractional doses, 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 the inoculum should be not less than 0.1 ml. 4. The dose fractioning (1/2 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. at least 3000 IU) 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: <ol style="list-style-type: none"> a. 1/2 dose of Bio-Manguinhos vaccine administered SC. b. Should the shortage of vaccine limit the use of 1/2 dose, use of a 1/5th dose of Bio-Manguinhos vaccine administered SC could be considered. c. If the shortage affects fractional dose supply, all WHO prequalified vaccines could be administered as ½ or 1/5th 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. As a general rule, fractional doses should not be less than the recommended minimal dose range. 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 multidose vials containing more than 10 full doses should be used for fractional dose administration in order to reduce risk of contamination through multiple punctures of the rubber seal (septum).
<p>Implementation considerations</p>	<ul style="list-style-type: none"> - 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. <p>Adequate communication and training of Health Care Workers is required.</p>

Monitoring and evaluation	When administering vaccination as a fractional dose during 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 closeness of the vials to expiry date.
Research priorities	<p>The specific research needs include:</p> <ul style="list-style-type: none"> - Immunological non-inferiority trials should be conducted comparing the full dose vs. a fractional dose of ½ (0.25ml) and 1/5th 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 of vaccinated subjects, and booster vaccination should be offered in case titres may fall below the protective threshold.

Annex 5: Programme experience in routine immunization programmes with delivery of vaccines intradermally (ID)

Beyond administration of BCG, there is limited experience in routine immunization programmes with delivery of vaccines by the ID route, and particularly in a mass campaign setting. ID inoculation is a difficult field technique, and in 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. Consequently, ID delivery of YF is the least preferable method 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 health 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) IPV, the WHO Global Polio Eradication Initiative (GPEI) and PATH have clinically evaluated ID delivery technologies (PharmaJet Tropis disposable-syringe jet injector²⁹, West Pharmaceutical Services' ID Adapters³⁰). In early 2017, these injectors for ID administration will become available for mass administration of IPV. However, the regulatory agency in the countries of manufacture 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.

²⁹ Resik S, Tejada 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.

³⁰ 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

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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, Guimarães SDA, de Carvalho R. Studies on yellow fever vaccine. III-Dose response 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.