EVIDENCE-TO-DECISION TABLE FOR FRACTIONAL DOSE YELLOW FEVER VACCINATION

Yellow fever vaccine: WHO position on the use of fractional doses, June 2017

Question: In immunocompetent individuals, should an IM/SC fractional dose (1/2 or 1/5 th 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 YF outbreak
Intervention: Dose-sparing strategies through fractional dose of YF vaccine.
Comparison(s): Continued use of full dose/ no vaccination.
Outcome: Individual short-term protection, containing of ongoing outbreak.

Background:
Ongoing YF 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. Dose-sparing strategies through fractional dosing of YF vaccine (fYF) may be promising in the context of the current outbreak. These dose-sparing strategies were 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* ☐	Outbreaks of YF remain of great concern to WHO.	New WHO strategy *Eliminating Yellow fever Epidemics (EYE)* http://www.who.int/csr/disease/yellowfev/eye-strategy/en/
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	2-5 fold increased in the number of doses to be obtained by using fractional dose.	
	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. The first programmatic experience with fYF vaccination suggested no signals of increased risk of serious adverse events following immunization. There was also no safety issue identified based on the administration of ~50 doses from a 10-dose vial with multiple punctures of the rubber seal and consecutive contamination of the vial.	Vial sizes greater than 10 0.5mL standard doses are not recommended for fractional dosing.

	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	Given the known protective effect of the vaccine and the benefits of preventing illness and outbreaks the intervention should be favoured	
	What is the overall quality of this evidence for the critical outcomes?	*No included studies* ☐ *Very Low* ☐ *Low* ☒ *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 a separate table was not 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* ☒ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☐ *No known undersirable 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* ☐ *Yes* ☐ *Probably 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* ☐	Resources may be higher for implementation of immunization campaigns and ensuring adequate social mobilization.	This was not prohibitive during the 2016 campaign with fYF vaccination in Kinshasa, DRC.
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	No available evidence, but expected to be equivalent or better to cost-effectiveness of a standard dose of YF vaccine as cost of fractioned vaccine lower for same number to vaccinate	Further data are needed on the duration of protection for the fractional dose, which may impact cost-effectiveness.
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ *Varies* ☐	Urban YF can affect 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.	Intervention was acceptable to stakeholders during the 2016 campaign with fYF vaccination in Kinshasa, DRC.
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Intervention is likely to be acceptable to the target population.	Intervention was acceptable to target population during the 2016 campaign with fYF vaccination in Kinshasa, DRC.
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Yes* ☐ *Probably Yes* ☒ *Varies* ☐	There may be programmatic Challenges (e.g. syringe availability) to implement the use of a fractional dose, but nevertheless the intervention is likely to be feasible.	Intervention was feasible during the 2016 campaign with fYF vaccination in Kinshasa, DRC.

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)	A fractional YF vaccine dose can be used as part of an emergency response to an outbreak situation and a shortage of vaccine that exceeds the capacity of the global stockpile. This is not intended to serve as a longer-term strategy or to replace established routine immunization practices. Administration of fYF vaccine constitutes an off-label use of the vaccine. In general, the same indication and contraindications apply as for the standard full dose. Preference should be given to YF vaccine products for which immunogenicity and safety data on a fractional dose administered subcutaneously or intramuscularly are available. As soon as the YF vaccine supply situation can meet the immediate need, the use of fYF vaccination should be replaced by standard full dose YF vaccination. Based on the available clinical data, the minimal dose administered should preferentially contain 3000 IU/dose, but no less than 1000 IU/dose, and the minimum volume of the dose should be not less than 0.1 ml because of practical difficulties actually delivering dose volumes smaller than this Until data relevant to specific subgroups becomes available, children aged <2 years, pregnant women, and individuals known to be HIV-infected should preferentially be vaccinated using a standard dose. While available clinical trial data and the experience with fYF in Kinshasa do not suggest a need for revaccination after receipt of fYF, monitoring of immunogenicity, duration of immunity, and vaccine failures is needed to validate this assumption. Until long-term protection is better documented, fYF vaccination does not meet YF vaccination requirements under the International Health Regulations (IHR), and proof of vaccination for international travel currently requires re-vaccination with a standard full dose.

Implementation considerations	- The vaccine should be reconstituted according to the manufacturer's specifications, and under no circumstances should the vaccine be diluted. - The fYF dose should be administered subcutaneously or intramuscularly using the appropriate auto-disabled syringes (i.e., 0.25 mL or 0.1 mL) depending on the volume to be administered. - Reconstituted YF vaccine is highly 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 ulti-dose vials containing more than 10 standard 0.5 mL doses should not be used for fractional dose administration to mit the increased risk of contamination through large numbers of punctures of the vial septum To ensure acceptance of fYF by the political, medical, and general communities, an appropriate communications plan should be in place.
Monitoring and evaluation	Safety and effectiveness assessments should be put in place when fYF vaccination is used, to include evaluation of potential programmatic errors related to fYF as well YF vaccine-associated neurologic and viscerotropic disease. Vaccination with a fractional dose should be recorded using individual vaccination records and nominal registries for purpose of safety and effectiveness monitoring.
Research priorities	Taking a short-term and pragmatic approach, non-inferiority immunogenicity studies of all 4 WHO prequalified YF vaccines are needed, as are non-inferiority immunogenicity studies in special populations with consideration of ethnicity, age, and prior flavivirus exposure. Of particular importance, given the consequences for international travel involving IHR requirements, is the confirmation of long-term protection with fractional dosing, including the potential need for revaccination.