Draft recommendations on YF vaccine fractional dose and key research needs

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Development of a YF vaccine fractional dose policy

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Meeting of the Emergency Committee under the International Health Regulations (2005) concerning Yellow Fever

WHO statement
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"Recognizing the limited international supply of YF vaccines, the committee also advised the immediate application of the policy of 1 lifetime dose of YF vaccine and the rapid evaluation of YF vaccine dose-sparing strategies by the WHO SAGE."

WHO Secretariat paper, "vetted" by SAGE"

Experience from campaign in Kinshasa/DRC

Comprehensive discussion at WHO SAGE

Research agenda to make policy more robust

WHO policy of fractional dose use of YF vaccine in emergency situations

Recommendation: indication for use of fraction dose

- YF fractional dose vaccination should be considered in response to an emergency situation in which current vaccine supply is insufficient.
  - Fractional dose vaccination should not be used for routine immunization or pre-emptive campaigns.
  - As soon as the vaccine supply situation normalizes, the - ***off-label*** - fractional dose use should be replaced by full dose vaccination.
  - Need for revaccination to be determined, and therefore does currently not count for YF certificate.

Recommendation: vaccine handling

- Under no circumstances should YF vaccine be reconstituted in different volume or type of diluent as recommended by the manufacturer, and no attempts should be undertaken to otherwise dilute the vaccine.
- When YF vaccine is administered in fractional dose, preference should be given to the administration of the vaccine according to standard route, i.e. SC or IM.

Recommendations: dose reduction*

- The minimal dose administered should preferentially contain 3000 IU/dose, but no less than 1000 IU/dose and the minimum volume of administration should be not less than 0.1 ml.

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

*(*With these considerations it might be more appropriate to speak of **fractional volume**)*

Recommendation: exclusions*

- In the absence of data on the use of fractional dose in young children, children below the age of 2 years should preferentially be offered a full dose of vaccine (i.e. 3000 IU or higher) during emergency campaigns.
- The same applies to pregnant women and HIV-infected subjects.

*(*Recommendation may change depending on outcomes of special studies under discussion)*

Recommendation: programmatic aspects

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

Recommendation: M&E

- Every effort must be made to monitor safety and YF vaccine AEFI's.
- Vaccination with fractional dose should be recorded using personalized registries for purpose of safety and effectiveness monitoring. Such information could be useful in assessing eventual re-vaccination needs with full dose, for which currently there is no recommendation.

Key research needs to broaden and simplify WHO's recommendation (1)

Question	Proposed study
Can all WHO-prequalified YF vaccines be administered SC using fractional dose approach?	Immunological non-inferiority trial in adults comparing fractional dose to standard dose of all four WHO-prequalified vaccines.
Is fractional dose vaccination sufficiently immunogenic in infants?	Immunological non-inferiority trial comparing fractionate dose to standard dose in children down to 9 -12 months of age.
Is the long-term immunity affected by the reduced dose?	Long-term immunological assessments of fractional dose recipients (option to enroll previous cohort)
Is there increased incidence of severe AEFI following vaccination with a fractional dose compared to a standard dose?	Close monitoring during the vaccination campaign up to 1 month post vaccination.

Key research needs to broaden and simplify WHO's recommendation (2)

Question	Proposed study
Is fractional dose vaccination sufficiently immunogenic in individuals with HIV infection (CD4 counts >200 cells/ml)?	Immunological non-inferiority trial comparing full dose to fractionate dose in immunocompromised HIV infected subjects.
Is immune response to YF fractional dose comparable across different genetic backgrounds?	Proposed study should include as first priority populations from Sub-Saharan Africa.