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

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1. Preamble

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

2. Introduction

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

3. Background

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

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

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

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

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

4. International Health Regulations

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

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

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

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

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

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

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

5. Vector control measures

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

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

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

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

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

6. Yellow fever vaccine characteristics

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

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

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

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

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

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

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

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

The following table summarizes their findings.