The life-long protective immunity of yellow fever vaccination: time to review?

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Yellow fever, a viral infectious disease transmitted by mosquitoes, has re-emerged as a major international public health threat.[1] Yellow fever is endemic in 34 countries in Africa and in 13 countries in central and South America.[2] Yellow fever epidemiology is affected by factors such as urbanisation, population movements, deforestation, and climate change.[3] The risk of yellow fever transmission to large urban endemic areas is thus greater than ever, and the potential spread to non-endemic areas, such as in Asia where *Aedes aegypti*, the vector responsible for most large urban outbreaks, is a threat.[4] Vaccination remains the critical means of prevention and reducing related morbidity and mortality. Yellow fever vaccination is recommended, unless contraindicated, to all individuals aged 9 months and younger living in yellow fever endemic countries and for people travelling to and from areas at risk.[5] To maintain population immunity and avoid outbreaks, a sustained vaccination coverage of at least 80% is needed.[6] In 2013, WHO reviewed vaccination recommendations and concluded that a single dose is sufficient to confer life-long protective immunity against the disease. However, surveillance and clinical studies should continue to identify specific groups, including infants and HIV-infected people, who could benefit from a booster dose.[5] Since, 2013, several studies have focused on the long-term immunogenicity provided by yellow fever vaccines.

In this issue of *The Lancet Global Health*, Jenny Schnyder and colleagues[7] present the results of a systematic review and meta-analysis assessing the long-term immunity (>10 years) provided by a single dose of a licensed yellow fever vaccine in adults and children living in areas both endemic and non-endemic for yellow fever. This review included randomised clinical trials and prospective and retrospective cohort and cross-sectional studies. In total, 39 studies were included in the systematic review and 20 studies, classified as of moderate or good quality, were included in the meta-analysis. The authors state that in non-endemic areas, a single dose in adults resulted in high seroprotection rates over time (pooled seroprotection rate 94% [95% CI 86–99]), thus providing life-long protection for travellers. In endemic areas, adult vaccination resulted in somewhat lower seroprotection rates (76% [65–85]). However, the studies from endemic areas were all conducted in Brazil and generally used a higher threshold for the definition of seroprotection, which could explain the differences. No studies conducted in sub-Saharan Africa were included in the meta-analysis. Lower seroprotection rates were found in children (47% [35–60]) and in people living with HIV (61% [38–82]), indicating a potential need for booster vaccination in these groups.

The results of the review reconfirm the long-term immune protection of a single dose of yellow fever vaccine in adults, in particular those from non-endemic areas. The small number of studies in children show significantly lower seroprotection rates, a finding that has previously been discussed and led some countries to recommend the administration of a booster dose. Given the substantial implications for vaccine programmes and for supply, the decision on the need for a paediatric booster dose should be made on more robust data. Indeed, more data are expected from ongoing paediatric immunogenicity studies. The lower seroprotection rates in people living with HIV also need attention. Additionally, surveillance should continue to ascertain the long-term immunity in endemic areas, particularly in sub-Saharan Africa. To date, there is no indication of waning protection in populations vaccinated in early childhood.

Also of interest is the long-term protection conferred by fractional doses of yellow fever vaccine. In 2016, large outbreaks of yellow fever in Angola and the Democratic Republic of Congo resulted in a dramatic supply shortage of the vaccine, which led WHO to issue an interim recommendation to use fractional yellow fever vaccination in the context of major supply shortages.[8] Fractional doses were also used in Brazil, in response to the 2017–18 outbreaks. It is possible that the immune protection conferred by fractional doses remains sufficient for 10 years or longer.[9] The use of fractional doses in emergency situations that require a vaccine supply beyond the existing stockpile remains an important measure. It is therefore important to

ascertain the longer-term protection of the yellow fever vaccine to clarify whether potential follow-up campaigns to sustain population immunity are needed.

An important limitation in the interpretation of immune results was the use of a variety of assays in the included studies, without the use of an international reference preparation, and differing cutoffs for the definition of seroprotection. The use of standardised assays and cutoff definitions would allow to better combine and interpret the results shown by the different studies, without a need for stratification, and would result in more robust estimates. Furthermore, protection might be sustained despite waning antibody titres.

Lastly, the single most important measure to control yellow fever is to increase vaccination coverage.

We declare no competing interests. The views expressed in this article do not necessarily represent those of WHO.

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