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Review

Review

Fractional-dose yellow fever vaccination: an expert review

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Abstract

Rationale for review: The global yellow fever vaccine supply is insufficient to provide full-dose vaccination to millions threatened by outbreaks. Given the excess of live-attenuated 17D yellow fever virus in the current single dose vials, dose sparing would increase available vaccine doses manifold. Fractional-dose yellow fever vaccination is now accepted as an emergency solution, as short-term protection has been confirmed in an outbreak situation in the Democratic Republic of Congo, but broader application of this dose-sparing strategy is still not recommended. In this review, important knowledge gaps that hamper this application such as long-term protection after fractional-dose vaccination, safety, comparability across different genetic backgrounds and different World Health Organization-licensed yellow fever vaccines and immunogenicity in infants are addressed.

Main findings: Recently, published results on long-term protection after fractional-dose vaccination in healthy young volunteers indicate that if a person mounts a protective response shortly after vaccination, the protective response will persist for 10 years and possibly longer. It also appears that fractional-dose vaccination does not elicit more serious adverse events than standard dose vaccination. Short-term immunogenicity studies are currently underway in specific populations (infants, human immunodeficiency virus (HIV)-infected persons and healthy adults living in Uganda and Kenya), of which the results will become available in 2021–22.

Conclusions: Available results on long-lasting immunogenicity of fractional-dose yellow fever vaccination are encouraging, although confirmation is required in larger populations including young children living in yellow fever endemic areas.

Key words: Yellow fever, fractional-dose vaccination, immunogenicity, safety, knowledge gaps, pratical implications

Introduction

Following the large urban outbreaks in Angola and the Democratic Republic of Congo, a revised strategy to Eliminate Yellow Fever Epidemics (EYE) was launched by the World Health Organization (WHO) in 2017. The objective is to eliminate yellow fever epidemics globally by 2026 by protecting at-risk populations in endemic areas, preventing international spread of the disease through travel and rapidly containing outbreaks.[1]

Since there is no treatment available for the disease, sustained vector control is extremely difficult, and the non-human primate reservoir cannot be targeted to eliminate yellow fever transmission; the most important means to contain yellow fever is by vaccination of at-risk populations. A single vaccine dose is sufficient to induce long-lasting, potentially lifelong protection.[2] Since the 1950's, preventive mass vaccination programs have been introduced with great success in outbreak prevention. But, due to waning population immunity and complacency, outbreaks have re-emerged.

The increasing incidence of yellow fever over the past two decades has sparked several new initiatives and important collaborations, which boosted preventive mass vaccination campaigns and emergency outbreak response activities. In 2001, a global stockpile of 6 million yellow vaccine doses was set up for emergency outbreak response. In 2015, a large outbreak in Angola led to depletion of the emergency stockpiles, and with a large non-immune population at risk, the WHO

recommended fractional-dose vaccination in the neighbouring country the Democratic Republic of Congo, where almost 8 million individuals were vaccinated with a fractional vaccine dose.[3] Since the outbreak in Africa, Brazil is dealing with a large and ongoing sylvatic yellow fever outbreak. In response to the gradual geographical expansion that was threatening large urban centres, Brazil has also resorted to fractional-dose vaccination strategy. To date, no vaccine failure after fractional-dose vaccination have been reported. Nevertheless, this approach has also raised questions, which will be discussed in this review, together with new research questions that could lead to optimization of the dose-sparing use of yellow fever vaccine.

Rationale behind fractional-dose vaccination

The yellow fever epidemic in Angola and Congo in 2015–16 and shortage of yellow fever vaccine for emergency vaccination of the population at risk prompted the WHO to the emergency solution of vaccinating with a one-fifth dose to increase the number of vaccine doses by 5-fold.[3] This fractional dose should contain at least 1000 IU.

The WHO recommendation for dose sparing was based on two clinical studies. The first, a Dutch study, is a non-inferiority, randomized controlled study that showed that the 0.1-ml fractional dose administered intradermally was non-inferior to the standard dose 0.5 ml administered subcutaneously.[4] Seroprotection was measured by 80% plaque reduction neutralization in the least diluted serum, from 2 weeks until 1 year after vaccination. The fractional dose (0.1 ml) contained 3200-IU live attenuated 17D yellow fever virus. Our initial hypothesis was that the intradermally administered yellow fever vaccine would be more immunogenic compared with the subcutaneous route because of direct targeting of antigen-presenting cells in the papillary dermis. In fact, despite the lower vaccine dose, the percentage of participants vaccinated intradermally in which viraemia was demonstrated by reverse transcriptase polymerase chain reaction (RT-PCR) was as high as in the standard full dose group (in both groups viraemia was detected in 50% of the participants). This can be explained by the fact that following injection—regardless of the route—live vaccines will rapidly disseminate throughout the body to reach their target cells as in a natural infection.[5]

In hindsight, a third study group should have been included in which the fractional dose of 0.1 ml would have been administered subcutaneously to investigate whether intradermal vaccination of a fractional dose is superior to subcutaneous vaccination.

The second clinical study, a Brazilian study, upon which the WHO based its recommendation was also a randomized controlled non-inferiority study, but with a rational dose-finding design with de-escalating doses of the yellow fever vaccine. The reference dose was 27 476 IU, with de-escalation to a minimum of 31 IU per vaccine dose).[6] The different vaccine doses were all administered subcutaneously in a volume of 0.5 ml. In this study, 587 IU was the lowest vaccine dose, which was non-inferior to the reference dose, but surprisingly the two lowest doses, of 158 IU and 31 IU, still induced seroconversion in 88.5% and 67% of the participants, respectively. More importantly, of those in the lowest dose groups who did seroconvert in the first month after fractional-dose vaccination, 98% still had protective neutralizing antibodies titers 10 months later. Also in this study, the occurrence of viraemia after vaccination did not appear to be related to the vaccine dose administered, although there was a slight reduced and delayed viraemia peak after 587 IU. The limitation being that only 10% of participants had a detectable viraemia by RT-PCR.

Another important limitation was that both studies were performed in healthy young adult volunteers who represent travellers and not the diverse population living in yellow fever endemic areas.

Therefore, the results of the observational study performed by Ahuka-Mundeke and colleagues, measuring the response of fractional dose yellow fever vaccination in a cohort in Kinshasa taking part in the emergency vaccination program, were much awaited for.[7] Persons at risk received a fractional dose of 0.1 ml, all from six different vaccine batches with a minimum batch potency of 2700 IU per dose. In this campaign, 10-dose vials were used, meaning that up to 50 vaccine doses were retrieved from one vial. Children under the age of two and pregnant women received a standard dose vaccine. In persons who were seronegative before vaccination ($n = 493$), 98% underwent seroconversion 1 month after fractional-dose vaccination, regardless of age or gender. Nevertheless, the geometrical mean titers (GMT) were lower in the 2- to 5-year-olds and showed a peak in the 13- to 50-year age group.

This study also shows that justifiable concerns with the cold chain and the multiple use of vials can be resolved in emergency vaccination campaigns.

Safety of fractional-dose vaccination

Safety of the fractional-dose vaccination was measured in the studies by Roukens *et al.* and Martins *et al*. In the latter, pain at the injection site was the only reaction more often reported in the highest vaccine dose group than in the lower dose groups (21% vs 10%). There was no difference in headache, fever, fatigue or arthralgia. Roukens *et al.* reported slightly more myalgia in the standard dose group. Local injection site reactions could not be compared due to the different routes of vaccine administration. So, if there are any, the standard vaccine dose leads to more mild adverse events than the fractional dose.

Recently, a study was published in which an attempt was made to monitor pharmacovigilance of the fractional-dose vaccination in Congo in 2016.[8] More than 4000 persons reported over 5000 adverse events, mostly fever and pain at the injection site. Five adverse events were serious events requiring hospitalization, but all occurred on the same day of vaccination, so before the onset of viraemia could be expected. It is difficult to draw conclusions from this study, as there was no control group that received the standard-dose vaccine, no denominator, and participants were actively recruited in churches and universities, resulting in a skewed study population. Nonetheless, it appears that not many serious adverse events occurred in this selected population.

Long-term protection after fractional-dose vaccination

The WHO is restrictive in recommending dose sparing as a long-term solution for vaccine shortage.[9] It states very clearly

that the use of fractional-dose yellow vaccine is only a dose-sparing option in outbreak situations, and that International Health Regulations requirements are not met after fractional-dose vaccination until long-term protection is better documented.

Expecting this uncertainty on long-term protection, the investigators of the two studies on which the WHO based its original recommendation for fractional-dose vaccination[4,6] performed an observational follow-up study of the same participants to investigate the long-term protection after fractional-dose vaccination.

In the Brazilian study,[10] the time since vaccination was 8 years, and 48% (381 of 786) of all participants who seroconverted to any of the vaccine doses (from 31 IU to 27 500 IU) in the initial study were eligible for re-testing. In all vaccine groups, 80–96% of participants still had protective neutralizing antibodies after 8 years, with a GMT that was 2.5-fold lower than the GMT at 10 months after vaccination. Surprisingly, the lowest vaccine dose group (dose of 31 IU, $n = 23$) showed the highest seroprotection rate of 96% after 8 years. This implicates that despite the very low vaccine dose, if one manages to mount a protective response in the month after vaccination (when vaccinated with a vaccine dose of 158 IU or more), this response will remain robust for many years. Of the persons vaccinated with 158 IU or more who did seroconvert after 1 month, 97–100% still had protective antibody titers after 10 months, and in the 31 IU group with seroprotection after 1 month, 89% were still protected after 10 months.

The Dutch study had a similar design and included 49% of the initial participants.[11] Ten years after primary vaccination with a fractional dose of 0.1 ml, the response was still comparable (seroprotection rate in 98%, $n = 40$) to the standard 0.5-ml dose (seroprotection rate in 97%, $n = 35$). Although statistically non-inferiority was not met because of the smaller number of participants, these results, together with the results of the Brazilian study, are very encouraging.

In our opinion, these results on long-term protection after fractional-dose vaccination show that if a person mounts a protective response shortly after vaccination, when the initial vaccine dose is above a minimum concentration, the response will remain sufficient throughout 10 years and probably longer. We should mention that these studies were limited to healthy participants who have not lived under circumstances that could potentially have suppressed their immunity, such as malnutrition or chronic parasitic infections. Therefore, we hope that it is possible to further monitor the cohort described by Ahuka-Mundeke *et al*., and investigate their long-term response to fractional-dose vaccination.

Dose-sparing vaccination for different purposes

With the expected growth of the global demand for yellow fever vaccine from ~102 million doses in 2016 to ~140 million doses in 2021, any major disruption by one manufacturer would have an impact on the implementation of campaigns. In fact, depending on the estimates, base-case supplies available to Africa between 2017 and 2021 could be 14% short of demand. With the results of the coming studies on fractional-dose yellow fever vaccination, we expect that a wider implementation of fractional dosing could be a catalyst for the EYE initiative.[12]

For now, dose sparing is recommended in emergency outbreak situations, but with the limitation that the International Certificate of Vaccination or Prophylaxis should not be issued when a partial dose is administered.[13]

The WHO recommends standard dose vaccination for routine mass vaccination programs and international travellers visiting yellow fever endemic areas, as long as enough yellow fever vaccine is available. We propose that if these routine immunization programs are hampered or if travellers cannot be protected against yellow fever because of vaccine shortage, use of fractional-dose vaccination should be encouraged.[14,15]

Last year, a shortage of ~40% of the normal supply of yellow fever vaccine caused a problem for Canadian travellers.[16] The Canadian Advisory Committee on Tropical Medicine and Travel recommended the use of fractional-dose vaccine as interim measure, with protection deemed adequate for 1-year post-vaccination. To meet the WHO recommendations, they recorded the fractional-dose vaccine administration on a waiver in order to avoid problems for travellers at border entry points.

The final small group of persons that benefit from fractional-dose vaccination is individuals with a possible but possible chicken egg allergy. In our Travel Clinic, we administer a fractional test dose of 0.1 ml intradermally to these persons and withhold further vaccination (the additional 0.4 ml) if they develop any immediate-type allergic reaction. When neutralizing antibodies are measured after at least 3 weeks, they all have a sufficient protective response to the fractional dose,[17] with a mean concentration of 5.3 IU/ml [99% confidence interval: 2.0–8.6 IU/ml], including children. Most of these individuals received vaccines from different batches, of which the potency of the fractional dose was not determined.

Remaining knowledge gaps

In 2016, the WHO formulated six short-term research priorities for dose sparing of yellow fever vaccine, which should be addressed before the WHO can permit broadening of its recommendations on fractional dose beyond the use for emergency campaigns.[18]

1. Can all WHO pre-qualified yellow fever vaccines be administered subcutaneously using the dose-sparing approach?
2. Is fractional-dose yellow fever vaccination sufficiently immunogenic in infants?
3. Is long-term immunity affected by the reduced dose?
4. Is the immune response to fractional-dose yellow fever vaccine comparable across different genetic backgrounds?
5. Is fractional-dose vaccination sufficiently immunogenic in human immunodeficiency virus (HIV)-infected individuals with CD4 counts > 200 cells/ml?
6. Is there increased incidence of severe adverse events following vaccination with a fractional dose vs standard dose?

In this review, we have addressed knowledge gaps 3 and 4. Importantly, the results of the fractional-dose emergency vaccination campaign in Kinshasa also suggest that a different genetic background does not influence the short-term immune

response after fractional-dose vaccination.[7] The effect on the long-term immunity remains to be determined.

Whether all WHO-pre-qualified yellow fever vaccines can be used for fractional-dose vaccination (knowledge gap 1) will be investigated in a large randomized, non-inferiority study performed in Uganda and Kenya (registered in Clinicaltrials.gov NCT02991495). In this trial, the immunogenicity and safety of the yellow fever vaccines produced by Bio-Manguinhos, Sanofi Pasteur, Institut Pasteur and Chumakov institute will be compared after subcutaneous administration of fractional dose (0.1 ml) or standard dose (0.5 ml) vaccine in 1630 participants, consisting of 960 adults (18–60 years), 420 children (9 to 59 months) and 250 HIV-infected persons with CD4 counts >200 cells/ml. Children and HIV-infected persons will only be vaccinated with the Chumakov vaccine. Pregnant women are excluded. The follow-up period will be 1 year after vaccination and the estimated study completion date is 31 December 2020.

Another study (registered in Clinicaltrials.gov NCT03725618) will investigate two different fractional doses (0.1 ml, 0.25 ml) compared with standard dose (0.5 ml) yellow fever vaccine 17DD in children (9–23 months) in Uganda (knowledge gap 2). The immunogenicity will be assessed at 4 weeks and 1 year after vaccination. A total of 1788 participants will be included and the estimated study completion is September 2020. The exclusion criteria mentioned in the trial registration are described in detail, except for the last criterion being 'any chronic or other condition that, in the opinion of the study staff, represents a health risk to the participant or interferes with the evaluation of the response to the vaccine'. If a child is not eligible based on this last criterion, it is essential that the reason why is carefully recorded to avoid discussion on representativeness of the study population after study completion.

Immunogenicity after fractional-dose vaccination in young children is indeed a very relevant question as the study in Kinshasa showed that the 2- to 5-year-old children had a 3-fold lower GMT than the adolescents and adults.[7]

Until now, no evidence has been reported that severe adverse events, such as yellow fever vaccine-associated visceral and neurological disease (YEL-AVD and YEL-AND), occur more frequently after fractional-dose vaccination compared with standard dose vaccination, but these events are rare and require monitoring in very large populations (knowledge gap 6). The published studies on dose sparing did not reveal more non-severe adverse events in the fractional dose groups.[4,6] Hypothetically, if severe adverse events are related to longer and higher viraemia, a fractional dose is not likely to lead to more severe events than the standard dose.

Besides these knowledge gaps that focus largely on practical application and efficacy of fractional-dose yellow fever vaccination, we believe that also more biological knowledge gaps need to be considered. This knowledge will help us to predict whether in certain circumstances fractional-dose vaccination is not favourable over standard dose vaccination.

Important questions to be answered in addition to the WHO-formulated research priorities are as follows:

1. Is replication of the live-attenuated YF vaccine virus required in order to induce a robust and long-lasting seroprotective response? In other words, is the antibody-response elicited by the live attenuated yellow fever vaccine virus more robust than the response elicited by an inactivated yellow fever virus?

The intuitive answer to this question is yes, but it has not yet been demonstrated. In one study published in 2011, the inactivated yellow fever virus (XRX-001 purified whole-virus derived from 17D, inactivated by β-propiolactone) adsorbed to aluminum hydroxide adjuvant induced seroconversion after 1 month in 100% of healthy subjects ($n = 22$, 18–49 years) receiving 4.8-µg antigen per intramuscular injection in two injections 21 days apart.[19] In the 10-fold lower dose group, participants received 0.48 µg per injection, which corresponds to 7.3 $\log_{10}$ virus equivalents per 0.5-ml dose. Seventy-five percent of these participants ($n = 24$) seroconverted after 1 month but had a 4-fold lower GMT than the high-dose group. A control group with the equivalent dose live attenuated vaccine virus was not included.

The question remains whether this response lasts longer than the follow-up period of 42 days in the study. Although the authors write that the duration of the neutralizing antibody response to XRX-001 will be determined after the 12-month follow-up period in an ongoing study, to our knowledge, these results have not been published.

In conclusion, replication of the vaccine virus is not necessary to induce a short-term protective immune response in healthy persons, but is possibly necessary for long-term protection.

2. What is the lowest dose of live-attenuated yellow fever virus that can induce a robust seroprotective response, and could the route of administration influence this threshold?

Martins and colleagues have de-escalated the dose of live attenuated yellow fever 17DD vaccine to 31 IU, almost 900-fold lower than the reference dose in their study, and 30-fold lower that the minimal dose of 1000 IU per vaccine dose recommended by the WHO.[3] They found that 31 IU administered subcutaneously still induced seroconversion in 67% of the participants, and in those who seroconverted this response was long-lasting. Whether the responders and non-responders in this lowest-dose group were different was not reported but is very interesting, in terms of predicting the development of neutralizing antibodies in individuals.

If the intradermal route of vaccination would be a more immunogenic route than the subcutaneous or intramuscular routes, this should be investigated in a dose-de-escalating study comparing very low doses administered intradermally and subcutaneously.

Conclusion

Based on the available data, fractional-dose yellow fever vaccination is becoming more accepted as a dose-sparing measure in times of vaccine shortage, as long as the minimum potency requirement is met. The latest evidence of long-term protection is encouraging and shows that the short-term seroresponse is

probably predictive of the long-term seroresponse, although the study population in which long-term protection is measured is small and not always representative to the populations living in yellow fever endemic areas. Several questions on practical issues to implement dose-sparing vaccination world-wide remain to be answered but are addressed in a study currently recruiting participants in Uganda and Kenya, of which the results are expected in 2021–22. These results are essential in providing evidence for a broader support of the implementation of fractional-dose vaccination, in order for the EYE strategy to be successful. Data on long-term protection after fractional-dose vaccination in populations living in endemic areas will evidently take more time, as these populations have been vaccinated in 2016.

Author contributions

A.R. and L.V. contributed to writing of the manuscript.

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