World Health Organization

Interim statement on dose-sparing strategies for COVID-19 vaccines (fractionated vaccine doses)

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WHO, with support of the Strategic Advisory Group of Experts (SAGE) on Immunization and its COVID-19 Vaccines Working Group, is reviewing the role of fractionating doses as a dose-sparing strategy in light of global vaccine supply constraints. SAGE is continuously reviewing the literature and has reached out to vaccine manufacturers and the research community for available information.

Evidence for fractionated doses

All current COVID-19 vaccines have undergone dose-finding studies in their clinical development. The potential for dose-reduction may depend on the individual vaccine and its platform technology (e.g., mRNA, vectored or inactivated virus). Safety, immunogenicity and programmatic feasibility of fractionating doses has been shown and implemented for various, hitherto well characterized vaccines (e.g., polio, rabies, and yellow fever vaccines) (1, 2). Intradermal administration may enable reduction of dose volume, but intradermal application may also change the immunogenicity, safety and increase the reactogenicity profile of the vaccines. Scaling up intradermal administration at a global level would also have major programmatic challenges that would require substantial investments in training and logistics to address.

Reducing the amount of vaccine given (e.g., 1/2, 1/3 or 1/5) could theoretically be considered with various options: fractionated doses for the priming schedule, or fractionated doses for any booster doses should booster doses prove to be needed in the future.

However, policy recommendations for reducing doses should only be made after an extensive

evidence review in terms of immunogenicity and safety. Emergency use listing for all COVID-19 vaccines for which SAGE has issued policy recommendations has been based on the evidence derived from Phase 3 trials using the full dose. Additional clinical studies would therefore be needed to inform policy.

Vaccines for which limited evidence exists for fractionating doses

For the Phase 3 trial of the ChAdOx-1 S (recombinant) vaccine one study arm received half of the currently recommended dose. An initial half dose showed a lower immune response than a full dose while a half dose followed by full dose gave similar post-second dose immune responses as two full doses. However, immune responses were lower with two half doses, and also lower with a full dose followed by a half dose, than after two full doses. Without a correlate of protection, the clinical significance of these findings remain uncertain.

A Phase 2 trial for the mRNA-1273 vaccine compared 50 versus 100 µg: seroconversion rates were lower after the first vaccination with the 50 versus first dose 100 µg, but similarly high after two vaccinations for both doses; GMT titres were generally higher for the 100 µg versus 50 µg *(4).* The mRNA-1273 vaccine is currently undergoing studies using a half dose for booster doses and data are awaited.

SAGE is not aware of studies using reduced doses for either of the inactivated whole virus vaccines Sinovac-CoronaVac and COVID-19 vaccine BIBP, the BNT162b2 vaccine, nor the Ad26.COV2.S vaccine.

Points for consideration

To inform a possible dose reduction recommendation several questions need to be addressed: Do fractional doses result in non-inferior neutralising antibody levels, cell-mediated immunity, cross-protection against variants and duration of immune response? If fractional doses were to be used, what is the vaccine effectiveness against various clinical endpoints (deaths, severe disease, mild to moderate or, asymptomatic infections) and against different variants of concern? Are fractional doses non-inferior in certain subpopulations, in particular in persons with immune suppression, comorbidities or those with immunosenescence related to older age? How does the safety profile of fractionated doses compare to full dose schedules? There are also several programmatic considerations as currently licensed vaccine formulations may not be suitable for fractional dose administration because of the way they are currently presented or need to be administered. This may relate to small dose volumes, or for certain multi-dose vaccines, difficulties in adjusting the diluent volume, and other programmatic issues which may limit feasibility.

Research

SAGE encourages further research such as prospective randomised trials to assess the safety

and immunologic non-inferiority of fractional versus full doses given for the priming schedule, and in particular as a single booster vaccination in primed and unprimed subjects. In addition, vaccine effectiveness and safety studies should be instituted as part of the follow-up.

Conclusion

While SAGE acknowledges the potential public health benefits of dose-sparing strategies to increase vaccine supply and accelerate population-level vaccination coverage, and possibly also a reduction in reactogenicity, SAGE considers there is currently insufficient evidence to recommend the use of fractional doses. Any use of a fractional dose at this point in time constitutes an off-label use of the vaccine. SAGE encourages research in the area, with a particular emphasis on research into using fractionated doses as potential boosters and fractional doses in children and adolescents. Programmatic and operational considerations should be considered from the start.

References:

1. Yellow fever vaccine: WHO position on the use of fractional doses – June 2017. Weekly epidemiological record.25:345-56.
2. Rabies Vaccine WHO Position Paper. Weekly Epidemiological Record. 2018;16:201-20.