Coadministration of seasonal inactivated influenza and COVID-19 vaccines

Interim guidance

21 October 2021

World Health Organization

Background

This interim guidance has been developed on the basis of the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its meeting on 7 October 2021 *(1)*.

Declarations of interests were collected from all external contributors, assessed for any conflicts of interest and appropriate measures taken. Summaries of the reported interests can be found on the SAGE meeting website and SAGE Working Group website.

The guidance is based on the evidence outlined in this document which was presented to SAGE on 7 October 2021.

All referenced documents are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

Methods

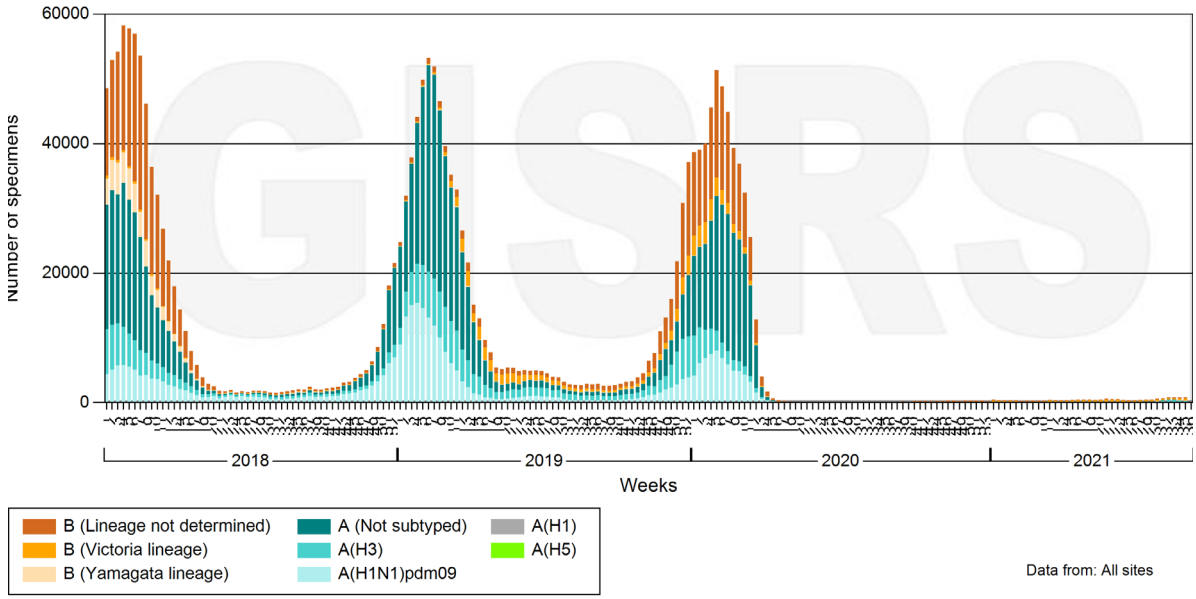
SAGE applies the principles of evidence-based medicine and has set in place a thorough methodological process for issuing and updating recommendations. A detailed description of the methodological processes can be found in the SAGE guidance for the development of evidence-based vaccine-related recommendations *(2)*. An ongoing, WHO and Cochrane supported, living systematic review of evidence on COVID-19 vaccines is used to identify relevant randomized controlled trials. The living mapping and evidence synthesis can be found on the COVID-NMA website: https://covid-nma.com/.

Current situation

Since the outbreak of COVID-19 was declared a public health emergency of international concern in January 2020, the virus has spread throughout the world, with an enormous impact on the health and well-being of individuals and populations, and with major disruptions to various sectors of society and economies. To curb COVID-19 transmission, countries have implemented large scale public health and social measures, such as physical distancing and wearing of facemasks.

As shown in Figure 1, global influenza virus detection, based on virological surveillance data from the Global Influenza Surveillance and Response System (GISRS), has decreased drastically during the COVID-19 pandemic, probably as a result of the measures put in place to prevent and limit the spread of COVID-19. This decrease is not an artifact due to weakened or absent surveillance systems, as influenza surveillance has been maintained or rapidly re-established in the course of the COVID-19 pandemic.

Figure 1. Global circulation of influenza viruses, 2018-2021 (number of specimens positive for influenza by subtype).



Source of data: FluNet (www.who.int/tools/flunet), GISRS

The 2021-22 influenza season in the northern hemisphere is approaching, and the potential co-circulation of COVID-19 and influenza could place additional stress on health systems, particularly as public health and social measures are lifted. Further, it remains unclear how the potentially decreased population immunity, resulting from lack of influenza virus exposure in 2020 and 2021, will affect the incidence of influenza in this and coming seasons.

Considerations on coadministration

Vaccination programmes against COVID-19 and seasonal influenza are currently being implemented in parallel in many countries. Administration of both vaccines during the same visit would have several benefits. On an individual level, it would reduce the number of health care visits needed and provide timely protection against both diseases; these individual benefits may encourage a greater uptake of the two vaccines. On a programme and health systems level, coadministration could facilitate implementation of both vaccine programmes and decrease the overall burden on health services.

Until recently, no evidence was available on coadministration of WHO emergency use listed (EUL) COVID-19 vaccines with other vaccines; WHO thus initially recommended an interval of 14 days between administration of COVID-19 vaccines and any other vaccine.

Limited evidence now suggests that coadministration of COVID-19 vaccines with inactivated vaccines is acceptable in terms of immunogenicity and reactogenicity. Nevertheless, concerns have been raised, in particular around the potential for increased reactogenicity of COVID-19 and influenza vaccines if given at a single visit, as some COVID-19 vaccine products have already shown a high reactogenicity when given alone.

Data have now emerged on coadministration of influenza and COVID-19 vaccines. In light of these data, SAGE revisited the issue of coadministration during its plenary meeting in October 2021 *(1)*.

Evidence

Two publications that address coadministration of two EUL COVID-19 vaccines *(3)* and one, to date, non-EUL COVID-19 vaccine *(4)* with certain seasonal influenza vaccines are currently available as pre-prints. These publications have not yet undergone peer-review; therefore, no external, independent assessment of potential weaknesses in assumptions, methods, and conclusions has occurred. Given the paucity of available evidence and the public health concern for the potential re-emergence of influenza in the upcoming months, SAGE deemed it important to consider all available data, including evidence for COVID-19 vaccines that have not (yet) obtained EUL.

The ComFluCOV study assessed vaccine safety and immunogenicity of concomitant administration of either AstraZeneca ChAdOx1-S [recombinant] or Pfizer/BioNTech BNT162b2 COVID-19 vaccine with seasonal influenza vaccines *(3)*.

This phase 4, multicentre randomized controlled trial enrolled 679 volunteers aged 18 years or over from England and Wales who had already received one dose of ChAdOx1-S [recombinant] or BNT162b2 vaccine. In total, 340 participants were randomised to concomitant administration of influenza and COVID-19 vaccine and 339 were randomised to placebo and COVID-19 vaccine

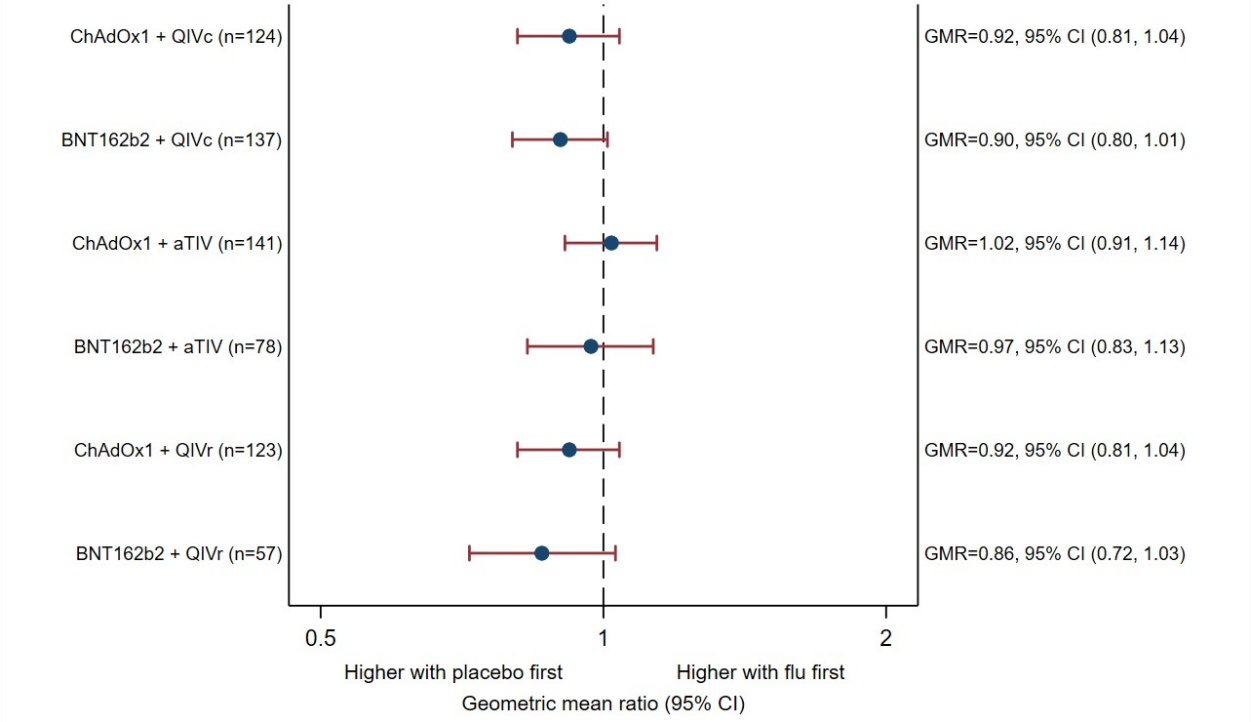
administration. Influenza vaccine was administered with the second dose of the COVID-19 vaccine. Participants aged 65 years or over received an adjuvanted trivalent influenza vaccine (aTIV) while those under 65 years received either a cell-based quadrivalent influenza vaccine (QIVc) or a recombinant quadrivalent influenza vaccine (QIVr).

Overall, for 651/679 (96%) participants, one or more systemic solicited reaction could be determined. 254 of 330 (77.0%) participants in the group randomized to concomitant COVID-19 and influenza vaccines had one or more solicited systemic reactions in the seven days following vaccination compared with 239 of 321 (74.5%) in the group randomized to COVID-19 vaccine alone. In all groups most reactions were mild or moderate.

The primary endpoint was one or more participant-reported solicited systemic reaction in the seven days after first trial vaccination(s), with a difference of <25% considered to be non-inferior. Concomitant administration of the two vaccines was found to be non-inferior to the administration of the COVID-19 vaccine alone in four cohorts: ChAdOx1/QIVc, BNT162b2/QIVc, BNT162b2/aTIV, and ChAdOx1/QIVr; in the other two cohorts, ChAdOx1/aTIV and BNT162b2/QIVr, the upper limit of the 95% confidence interval (CI) very slightly exceeded the 25% non-inferiority margin (ChAdOx1/aTIV: 10.3% (-5.44%, 26.0%) and BNT162b2/QIVr: 6·75% (-11.8%, 25.3%)).

Anti-S IgG geometric mean titres (GMTs), measured 21 days after receipt of either ChAdOx1 or BNT162b2, were similar in those who received concomitant vaccination or COVID-19 vaccine alone in all cohorts (Figure 2).

Figure 2. Anti-S IgG GMT ratios between participants given COVID-19 vaccine with or without influenza vaccine.



First visit (day 0): Placebo first=COVID-19 vaccine alone; Flu first=concomitant COVID-19 and influenza vaccines. GMR=geometric mean ratio. CI=confidence interval. Individuals were later provided with COVID-19 or placebo, respectively, during a second visit on day 21-28.

Reproduced from Lazarus et al. (3): Humoral responses (haemagglutinin antibody inhibition) to all influenza vaccines were similar between groups within each cohort, except for the BNT162b2/QIVr cohort where GMTs were significantly higher for three strains when given with the COVID-19 vaccine.

This trial showed that concomitant administration of influenza and COVID-19 vaccines was acceptable in terms of reactogenicity and tolerability. There was no evidence of negative immune interference for either COVID-19 or influenza vaccine.

As part of the Novavax NVX-CoV2373 COVID-19 vaccine phase 3 trial, a sub-study assessed the safety, immunogenicity and efficacy of NVX-CoV2373 vaccine coadministered with seasonal influenza vaccines *(4)*. Participants were randomized in a 1:1 ratio to receive NVX-CoV2373 ($n = 217$) or placebo (n = 214). Those in the coadministration group received an age-appropriate, licensed influenza vaccine (QIVc for those aged 18–64 years and aTIV for those aged 65 years or over) with dose 1 of NVX-CoV2373. Reactogenicity was evaluated in an electronic diary for 7 days post-vaccination, and participants were monitored for unsolicited adverse events (AEs), medically attended AEs (MAAEs), and serious AEs (SAEs).

Reactogenicity events were more common in the coadministration group and included tenderness (70.1% vs 57.6%) or pain (39.7% vs 29.3%) at the injection site, fatigue (27.7% vs 19.4%), and muscle pain (28.3% vs 21.4%). Rates of unsolicited AEs, MAAEs, and SAEs were low and similar between the two groups.

Coadministration resulted in no change to influenza vaccine immune response, but antibody responses to the NVX-CoV2373 vaccine were reduced.

Vaccine efficacy against symptomatic COVID-19 (confirmed by polymerase chain reaction) in the sub-study was 87.5% (95% CI: –0.2%, 98.4%) while efficacy in the main study was 89.8% (95% CI: 79.7%, 95.5%).

Yet to be published preliminary results from a clinical trial (no pre-print available) (5) on the safety and immunogenicity of coadministration of a high-dose QIV with a third dose of the Moderna mRNA-1273 COVID-19 vaccine to adults aged 65 and above appear reassuring, pending peer-review and publication in a medical journal.

SAGE considered the limitations of the above mentioned trials. These include, among other, pending peer-review, limited number of COVID-19 and influenza vaccines assessed, limited sample size, trials sites limited to certain geographies and relative ethnic homogeneity of participants.

In conclusion, limited safety and immunogenicity data suggest that coadministration of the second dose (of a 2-dose homologous COVID-19 vaccine schedule) of ChAdOx1-S/nCoV-19 [recombinant] or BNT162b2COVID-19 vaccine with inactivated influenza vaccine (cell-based QIV, recombinant QIV or adjuvanted TIV (for people aged 65 years and over)) is acceptable (publication forthcoming). As of 15 October 2021, no data are available on coadministration with any other WHO EUL COVID-19 vaccine. In addition, a study of coadministration of the NVX-CoV2373 COVID-19 vaccine and seasonal inactivated influenza vaccines demonstrated the safety and immunogenicity of the seasonal influenza vaccines, and the safety and efficacy of the NVX-CoV2373 vaccine; however a reduction in antibody responses to dose 1 of the NVX-CoV2373 vaccine was noted *(4)* .

Recommendations

It is important to implement a robust influenza vaccination programme, in addition to the ongoing implementation of COVID-19 vaccination. Influenza vaccines can be given at separate time intervals to COVID-19 vaccines. However, to allow for more programmatic ease and higher uptake of both vaccines, countries can consider administering COVID-19 vaccines and influenza vaccines during the same visit. Only limited evidence on COVID-19 vaccine coadministration with influenza vaccine exist, but available evidence does not show increased adverse events. Therefore, WHO considers that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial. While there is no theoretical concern, WHO recommends using the contralateral limb for injection, when the two vaccines are administered during the same visit, to minimize any perceived risk. Continued pharmacovigilance monitoring of coadministration of the two vaccines is recommended.

Recommendations on addressing current knowledge gaps through further research

WHO recommends the following post-authorization monitoring activities and research.

Research on coadministration of live-attenuated influenza vaccines and COVID-19 vaccines would be beneficial, as well as the generation of data on safety, immunogenicity and efficacy/effectiveness of influenza vaccines given concomitantly with the first, second and, where applicable, third dose of COVID-19 vaccine.

References

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

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