World Health Organization

WHO COVID-19 Vaccines Research

Emerging evidence on additional doses of COVID-19 vaccines and their safety

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Executive Summary

Since the start of the pandemic there have been 240 million confirmed COVID-19 cases and almost 5 million deaths. Incident cases have started to decrease globally, while regional heterogeneity remains. Several factors contribute to continued transmission, including unequal vaccine distribution. Many high-income countries with high vaccine coverage plan to or have introduced a booster dose in specific populations such as in the immunosuppressed or elderly. While all agree that the public health community should focus efforts on vaccinating the unvaccinated with a primary series, it is important that decisions to introduce booster doses are based on the best available evidence.

Vaccines thus far have been shown to derive strong and robust protection against severe disease and death. Observational studies may show different results based on methodologic risk of bias, differences in local epidemiology, and varied analytic methods. There is still an opportunity to obtain important additional data on boosters including which vaccine to boost with, appropriate booster dose levels, variant-specific information, the role of vaccination in seropositive populations, durability of the boosting antibody responses, and importantly, remaining questions on safety.

Research to date suggests some vaccines have been shown to be associated with myocarditis in young adult males, though the risk/benefit of COVID-19 vaccination remains favourable. Improving pharmacovigilance systems and systemic collection of real-world safety and effectiveness data is critical to continue updating these assessments, especially as younger populations are included in vaccination schedules and boosters are offered to key populations. Research to understand the pathophysiology of these severe adverse events will also provide support for any risk/benefit assessments.

Overall, international coordination and sharing of data and analyses remains essential. Decisions should be based on data and a transparent scientific process with attention to clear communication.

All information related to these meetings and a summary of the vaccine landscape and associated studies can be found on the WHO website - www.who.int/teams/blueprint/covid-19 and details of this meeting can be found here (https://www.who.int/news-room/events/detail/2021/10/25/default-calendar/who-consultation-on-covid-19-vaccines-research-emerging-evidence-on-safety-and-the-need-for-additional-doses-of-covid-19-vaccines).

Introduction & Global Overview of the Epidemiologic Situation

Since the start of the pandemic there have been 240 million confirmed COVID-19 cases and almost 5 million deaths. Vaccines thus far have been shown to confer strong and robust protection against severe disease and death. Recently the incidence of cases has been decreasing though there is regional heterogeneity. Several factors are driving transmission including evolving variants that are more transmissible such as Delta, unequal vaccine distribution, increasing social mixing and mobility, and misinformation or conflicting messaging.

In the context of this epidemiological situation, this global consultation sought to address key questions related to the safety and need for additional doses of COVID-19 vaccines. Regarding safety, myocarditis and pericarditis have emerged as rare adverse events after vaccination with mRNA vaccines, especially after the second dose in younger males. Some evidence from North America and Nordic countries suggests there is greater risk with Moderna vaccine than Pfizer vaccine and some countries have acted based on these data (e.g., Sweden, Norway, Finland, Ontario Canada), though limited data are publicly available. If post-vaccination myocarditis proves to be immune-mediated, this suggests the importance of determining whether or not the higher immune responses in boosted individuals could be associated with additional immune-mediated adverse events.

The WHO has raised ethical objections to boosting strategies that further concentrate available doses of vaccine in high- and middle-income countries (HMICs) which reduces the chance that people at high risk in low-income countries (LICs) can access vaccines. This has been discussed during previous consultations[1] and a recent Lancet paper summarized the literature indicating no need for widespread boosting in the general population[2]. However, some countries have taken regulatory action and made recommendations regarding boosters in specific populations.

The strategic advisory group of experts on immunization (SAGE) has produced documents to help countries form vaccination policies. 6 products have WHO emergency use listing authorization (EULA) with SAGE recommendations – Pfizer, AstraZeneca, Janssen, Moderna, Sinopharm, and Sinovac. SAGE recognizes that vaccine equity is a major challenge of our time. Less than 3% of people in LICs having received at least one dose of any COVID-19 vaccine while at least 50 countries have started administering boosters/additional doses and 6 plan to start. On any given day, the number of booster doses that are administered is at least three times higher than the number of primary doses administered in LICs. Any need for boosters or additional doses should be based on a decline in the performance of the primary series against severe disease/hospitalization over time, new variants that greatly reduce protection by the original vaccine, or inadequate protection with the primary series for high-risk groups and this decision may be different for each vaccine, epidemiological setting, and risk group.

[1] https://www.who.int/news-room/events/detail/2021/08/13/default-calendar/who-consultation-on-covid-19-vaccines-research-13-august-2021
[2] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02046-8/fulltext

Session 1. What do we know and what additional evidence is needed to inform decisions on safety in naïve and previously vaccinated populations?

Myocarditis is inflammation of the heart muscle and is mostly found in younger men. Myocarditis has diverse causes including infection, drug, autoimmune/inflammatory disease, and hormonal. Before COVID-19, myocarditis made up about 0.04% of hospital admissions in the UK. Overall data suggests the incidence of myocarditis due to COVID-19 is higher than the incidence of myocarditis associated with vaccination.

Multiple surveillance systems globally support the finding of an increased risk of myocarditis and myopericarditis following mRNA COVID-19 vaccination with an increased risk in adolescent and young males within a few days of the second dose. Most cases are clinically mild. The Vaccine Adverse Event Reporting System (VAERs), a passive surveillance monitoring system of the CDC and FDA, identified 877 myocarditis cases in person ≤29 years of age. 829 were hospitalized of which 607 have since been discharged and have recovered. The Vaccine Safety Datalink (VSD) system, which uses electronic health records, also observed an increased risk of myocarditis in adolescent and young adults. Head-to-head comparisons indicated a two-fold greater risk of myocarditis in those who received the Moderna vaccine compared to Pfizer, in both males and females. The FDA Biologics and Effectiveness Safety (BEST) System, an active surveillance system combining four medical claims databases across the US, showed increasing incidence of myocarditis/pericarditis within the first 7 days of either mRNA vaccine in 18–25-year-olds after the second dose. Incidence rates varied across the four databases with wide confidence intervals given the rarity of the outcome. There was no significant difference when comparing Moderna and Pfizer in this younger age group. Other data, not discussed at the meeting, from Ontario and from Nordic countries, also suggest a possible greater incidence of myocarditis after Moderna vs. Pfizer vaccines.

VAERS was also used to monitor safety of the Janssen COVID-19 vaccine, with reports of cerebral venous sinus thrombosis, thrombosis with thrombocytopenia syndrome, Guillain-Barre Syndrome and myocarditis/pericarditis. 92 cases of myocarditis were identified, and continued evaluation is ongoing. The FDA BEST system has not identified any safety signals for adverse events of special interest for the Janssen COVID-19 vaccine.

The mechanisms of myocarditis due to COVID-19 vaccination remains unclear for both mRNA and adenoviral vectored vaccines. Understanding the mechanism could inform predictions about the safety of booster doses. Differences among countries and systems may be contributing to differences in observed patterns of safety among vaccines. Differences in dose schedules could also play a role. All speakers agree that public health messaging is critical to accurately convey what is known and unknown about the risk.

Regulators and public health authorities have learned that that near-real time surveillance is possible with data collection using modern tools such as phone applications and large healthcare databases. These tools can support rapid analyses with large sample sizes. Most

countries have a mix of passive and active surveillance using these tools. Regulators agreed on the importance of transparency and clear communication regarding potential risks of vaccination, which has not led to a reduction in acceptance of immunization. Additional country-specific data is needed to inform regulatory decisions on boosters.

From a research perspective, experts agreed that post-marketing surveillance for rare events was critical. However, in many countries, including LICs, monitoring systems are not sensitive enough to detect these important outcomes. In general, a link between surveillance systems and clinical networks is needed to evaluate specific adverse events such as myocarditis. Follow-up data on these events are also needed to better understand the long-term implications and risk-benefit implications. Understanding the mechanisms of these rare events is also needed to make informed recommendations on booster doses. Studies could evaluate lower dose levels of mRNA vaccines in naïve populations, at risk for myocarditis and the impact on efficacy and safety. Similarly, adjusted (i.e., reduced) dosing for boosters or optimal timing of booster dosing should be assessed. Clinical trials are often conducted in HMICs and more studies are needed in LICs to understand the impact and safety of these vaccines where seroprevalence is over 50%. Supply constraints continue to be in an issue in LICs.

Session 2. Updated evidence and considerations regarding the administration of additional doses

Emerging evidence was presented from Israel, the US, Brazil, and Chile. In Israel, despite high vaccination coverage in June 2021, COVID-19 cases increased due to the Delta variant. A 3rd dose vaccination campaign started in late July. The elderly were the first group offered a booster and younger age groups later became eligible. Starting 12 days after the 3rd dose there was about a 10-fold reduction against confirmed infection with a booster compared to the second dose in those aged 60 and older, with a similar trend across all age groups. Multiple analytic methods consistently confirmed the same pattern though with varying degrees of magnitude. Conservative analytical methods show a reduced risk by 3-6-fold, depending on age group, with other analytical methods suggesting as much as a 18-22 fold reduction in severe disease with boosting. After the booster dose campaign, there was a decrease in the number of daily cases in those <60 years of age and new cases decreased broadly after boosters were provided to all age groups. Passive safety monitoring showed booster doses had a safety profile similar to other doses across all adverse event categories (systemic, local, neurologic, and allergic). 43 serious adverse events were reported, including 17 cases of myocarditis/perimyocarditis, which appears to be less frequent than after the second dose.

In New York State, three statewide databases were used to examine trends in COVID-19 cases and hospitalizations, focusing on different products and timing since vaccination. Vaccine efficacy (VE) against COVID-19 decreased between May and July for all three vaccines (Pfizer, Moderna, Janssen), though decreases in VE leveled off with the saturation of the Delta variant in July 2021. VE for those receiving vaccine in January declined in the same pattern as those vaccinated in April, which is inconsistent with waning immunity. A similar pattern was observed across all age groups, though in the 65+ age the decline was less precipitous. VE

against hospitalizations was persistently strong in the younger age groups with VE >90% for mRNA vaccines and >86% for Janssen. For the older age group, VE against hospitalization declined about 5-7% and the greatest decline was for those vaccinated in January and February, but VE remained >86% for Pfizer, >93% for Moderna, and between 81%-90% for Janssen. Investigators suggests that declines in VE against COVID-19 cases may be a result of the Delta variant and change in behavior instead of time since vaccination.

In Brazil, vaccination started in January 2021 for AstraZeneca and Sinovac vaccines, and in May and June Pfizer and Janssen vaccines were added. VE against severe disease for those fully immunized with AstraZeneca ranged between 67% and 90% depending on age group, with a reduced VE in those 80+ years of age. VE against severe disease for those fully immunized with Sinovac ranged between 30% and 71% depending on age group, with a greatly reduced VE in those 80+ years of age. This prompted a recommendation for a booster dose in the elderly. Another study showed Sinovac and AstraZeneca VE against hospitalization was <60% for the elderly. In the younger age groups, both Janssen and Pfizer were highly protective.

In Chile, Sinovac, Pfizer, AstraZeneca, Cansino, and mix and match boosting with Sinovac as the primary series are available. VE against SARS-CoV-2 infection was between 50% and 80% for the primary series, the greatest VE was with the Pfizer vaccine. Third dose VE against infection ranged between 71% and 93%, the greatest VE came from Sinovac prime with Pfizer boost. VE against symptomatic COVID-19 was between 52% and 84% for the primary series, with the greatest VE from Pfizer vaccine. Third dose VE against COVID-19 ranged between 73% and 95%, the greatest coming from Sinovac prime with Pfizer boost. VE against COVID-19 hospitalization was between 83% and 99% for the primary series, the greatest was AstraZeneca prime with Pfizer boost. Third dose VE against COVID-19 ranged between 81% and 97%, the greatest being Sinovac prime with AstraZeneca boost. VE against ICU admissions was similar to hospital admissions. Heterologous and homologous booster doses significantly increased the effectiveness of primary immunization among those vaccinated with inactivated vaccines.

The COVID-NMA (https://covid-nma.com) international research initiative supported by WHO and Cochrane provides a live mapping of COVID-19 trials and observational studies. Overall mRNA vaccines against the Delta variant show high protection (80-90%). VE for non-replicating viral vector vaccines against severe disease caused by the Delta variant ranged from 32% to 95%. Only one study is available with results for booster dose of mRNA vaccine against severe delta (VE: 94%). In addition to VE, the quality of evidence is determined by assessing the risk of bias of each study. The seven bias domains include: confounding, selection of participants, classification of interventions, departures from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Confounding occurs when there is a common cause of both vaccination and the outcome of interest. Many confounders can be accounted for during the analysis, such as age and calendar time, while others are difficult to address due to lack of data, such as COVID-19 symptoms at the time of planned vaccination. There are risks of bias in all studies and most large studies have accounted for these well.

Studies are ongoing in Germany, the Netherlands, the UK, and the US to examine the humoral and cell-mediated short- and long-term immunogenicity of homologous and heterologous prime/boost schedules with mRNA and adenoviral vaccines. Results suggest an increase of vaccine response over time across variants even with any boosting regimen, though heterologous boosts most often have a strong short-term effect. Boosting with an mRNA vaccine was often the most immunogenic. One study found priming with adenoviral vaccine was better for cellular immunity compared to priming with mRNA vaccines.

Experts agreed that authorized vaccines are highly effective against severe disease and death, which is the most important outcome that could inform the need for a booster. There may be some waning in the elderly, as observed in Israel and Brazil. Most data discussed during this meeting was in countries with successful rollout of vaccination, yet 82 countries have limited vaccine coverage and are unlikely to meet the WHO target of 40% vaccinated by December. Additional research is needed in these settings.

There was discussion regarding the interpretation of results in Israel and New York state, with Israel showing waning immunity even against severe disease leading to policymakers to recommend mass booster vaccination, and with New York State studies observing consistent protection with slight decreases in apparent VE attributed to changing behavior and evolving variants. Some reasons for differences in study results include definitions of the outcomes, the analytic method and comparison group (unvaccinated vs. two doses), and unmeasured confounding such as non-pharmaceutical interventions. In the US increases in severe disease in the vaccinated population was not observed, but this trend was seen in Israel before the third dose was offered. It was noted that a reduction in vaccine efficacy from 95% to 85% corresponds to a 3-fold increase in cases, which could have different implications depending on exposure rates and incidence of disease.

Experts emphasized that in the discussion of boosters, the focus on the unvaccinated population can get lost. The speed that we immunize unvaccinated groups will determine the arc of the pandemic while boosters will have a more incremental impact. We want to make sure we don't do more harm than good with our focus and resources. Notably, long-term impact of booster doses, including on viral transmission, is unclear.

Synthesis of the Evidence and Next Steps

There are situations where additional doses of a COVID-19 vaccine in previously vaccinated individuals would likely be beneficial. This includes circumstances where the primary vaccination never induced enough immunity to be protective as in immunocompromised populations or in those receiving vaccine with low or unproven efficacy, among individuals at risk of severe disease and high risk of exposure to the virus, if vaccine induced immunity wanes to the point where previous vaccination no longer protects, and if new variants arise that escape vaccine induced immunity. Boosting should be considered in a benefit-risk framework, where risks of "boosting" may include immediate safety concerns for vaccinees, unknown long-term consequences of boosting, and adverse public health outcomes. Therefore, benefits of boosting should be clear in order to make a favourable benefit-risk assessment.

Regarding safety, myocarditis is associated with COVID-19 disease and COVID-19 vaccination is associated with myocarditis. Myocarditis after vaccine is less common and typically less severe than with COVD-19. It is unclear whether there are differences in risk of myocarditis in those receiving Pfizer compared to Moderna vaccines, though some data suggests an increased risk for Moderna. Nonetheless, all vaccines are safe, and their risks do not outweigh the benefit. Developers presented booster safety and immunogenicity data, showing an increased immune response after boosting. While clinical trial data generally support safety, not all vaccines have controlled or systematic analyses of post-authorization safety data. Systematic data of VE over time is also not available. Boosters may provide an opportunity for dose-sparing.

Pathogenesis of vaccine adverse events is unclear – some could be due to adaptive immune responses or innate responses, which influences the benefit-risk assessment of boosters. Notably, myocarditis in Israel does not appear to be increased after the third dose of Pfizer vaccine. Experts agreed on the importance of being able to link safety surveillance to clinical networks with longer term follow-up data. Benefit-risk analyses could consider age and other risk factors, both for COVID-19 and for vaccine-associated events. Current data do not suggest that additional doses carry greater risks that the primary vaccination series.

Decision-making about boosting should be based on important and valid study outcomes of long-term vaccine protection. Most would agree that primary protection against severe disease is the most important and long COVID occurs most frequently in those with severe disease. Mild disease is tolerated for many other illnesses and may even confer long term protection advantages. Most transmission is driven by the unvaccinated and long-term protection against transmission may be impossible using the currently deployed vaccines. Impact of vaccine on transmission is often difficult to assess in clinical trials and we don't have direct evidence regarding impact on transmission for most vaccines used today. Preventing infection would protect again all disease types, but most vaccines are not successful in completely preventing infection and this can be difficult to assess in clinical trials. Regarding loss of antibodies, even if antibody responses were unambiguously predictive of short-term protection, long-term VE is unlikely to be well-predicted by circulating antibody level because vaccines also induce strong memory and cell-mediated responses. Protection against severe disease is through to be mostly mediated by cellular immune responses, not circulating antibodies.

Observational studies of vaccine effectiveness may be biased due to unmeasured confounding, misclassification of "unvaccinated" individuals, misclassification of previous infections, and the effect of prioritization for early vaccination. Test-negative case control studies usually do not adequately control for health-seeking behaviours. Studies of severe disease endpoints are closely aligned with the goals of vaccination and are most accurately assessed in observational studies and thus provide the most reliable assessments of possible waning protection. These studies do not suggest substantial waning of vaccine-induced protection.

Regulators evaluate boosters based on perceived need for in specific subgroups – including age, comorbidities, and level of exposure. Data are different for each vaccine. To evaluate efficacy, immune responses after boosting are bridged to responses shortly after the primary vaccination series that were shown to be protective in clinical trials. This provides a basis for believing that VE post-boost will be similar to that after the primary series. If immune responses post-boost are higher than after the primary series, this suggests a good response but does not provide assurance that protection will be higher. Reports from Israel, Chile, and Pfizer suggest high relative protection after boosts and heterologous boosters may have some advantages. Duration of any additional protection observed after boosters is not yet established.

A decision to implement boosting should be based on careful consideration of the need for them. Strong endorsement of boosters could reduce confidence in the primary series, making it more difficult to vaccinate the susceptible population that is driving the pandemic. Vaccinating the unvaccinated is critical to reducing transmission and the evolution of new variants. Each dose of vaccine will save more lives if provided to the unvaccinated as opposed to a booster in the general population.

In conclusion, we need to focus efforts on vaccinating more people in all countries, regardless of wealth. Authorized vaccines are highly effective, and the available evidence does not support the need for widespread deployment of boosters. There is an opportunity to obtain additional data on the type and dose of vaccine to use as a booster. Important research gaps include systematic collection of real-world safety and VE data on more vaccines, investigation of dose-sparing, timing of boosting, and better understanding of how variants affect VE. Overall international coordination and sharing of data/analyses remains essential. Decisions should be based on data and a transparent scientific process with attention to clear communication.

WHO R&D Blueprint Secretariat

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Appendix I: Agenda

Time	Topic	Speakers
13:00 - 13:10	Global overview of the epidemiologic situation	Maria van Kerkhove
13:10 - 13:20	Objectives of the meeting	Philip Krause
13:20 - 13:30	Current recommendations from SAGE regarding COVID-19 vaccines	Hanna Nohynek
Session 1. What do we know and what additional evidence is needed to inform decisions on safety in naïve and previously vaccinated populations?		
13:30 - 13:40	COVID-19 Myocarditis	Dan Sado
13:40 - 14:10	Experience with COVID-19 vaccines and myocarditis in selected countries	Tom Shimabukuro – VSD (USA) Hui-Lee Wong - FDA (USA) – mRNA vaccines Narayan Nair – FDA (USA) – Non replicating viral vector
14:10 - 14:30	What conclusions can be drawn from the totality of the evidence?	Panel Discussion moderated by **Terry Nolan** Participants from above talks
14:30 - 15:00	Evidence of vaccine safety, developer's perspective	CanSinoBIO - Xuefeng Yu Janssen - Macaya Douoguih Medigen - Allen Lien Moderna - Randy Hyer Sinopharm - Li Meng Sinovac - Liming Wang (All developers with vaccines deployed were invited)
15:00 - 15:45	Lessons learned from monitoring vaccine safety	Panel Discussion moderated by **Rogerio Gaspar** Speakers invited from regulatory authorities Gustavo Santos & Brenda Valente, ANVISA (Brazil)

		Marco Cavaleri, EMA (Europe) Seth Seaneke, Ghana FDA Michael Rosu-Myles & Dean Smith, Health Canada Marie-Christine Bielsky MHRA (UK) Svein Rune Andersen, Norwegian Medicines Agency Flora Matlala, SAHPRA (South Africa) Peter Marks, US FDA (USA)
15:45 - 16:05	What additional research and strategies are needed?	Panel Discussion moderated by **Helen Rees** Rita Helfand Mary Ramsay Susan Ellenberg Hanna Nohynek Benjamin Ong
16:05 – 16:10	**BREAK**	
Session 2. Updated evidence and considerations regarding the administration of additional doses		
16:10 – 16:30	Emerging data from Israel	Sharon Alroy-Preis Ron Milo
16:30 - 16:40	COVID-19 vaccine effectiveness by product and timing in New York state	Eli Rosenberg
16:40 - 17:10	Emerging data from Brazil	Daniel Villela Manoel Barral Netto Rosana Leite de Melo
17:10 – 17:20	Emerging data from Chile	Rafael Araos
17:20 - 17:35	Observational evidence on vaccine effectiveness against the delta variant – latest results and risk of bias considerations	Julian Higgins
17:35 – 18:05	Emerging data on homologous and heterologous boosting	Reinhold Förster Rory de Vries Matthew Snape Robert Atmar
18:05 - 18:50	Booster Doses: Overview of evidence and remaining gaps	Panel Discussion moderated by **Liz Miller** Peter Figueroa

		Narendra Arora Ricardo Ruttimann Lelièvre Jean-Daniel Sharon Alroy-Preis Ron Milo Manoel Barral Netto Rosana Leite de Melo Rafael Araos Eli Rosenberg Dan Barouch
18:50 - 19:10	Synthesis of the Evidence and Next Steps	Philip Krause
19:10	**END OF MEETING**	