Statement for healthcare professionals: How COVID-19 vaccines are regulated for safety and effectiveness

(Revised 11 June 2021)

Joint Statement from the International Coalition of Medicines Regulatory Authorities and World Health Organization

Healthcare professionals and public health authorities have a central role in discussing vaccination against COVID-19 with their patients. Vaccines play a critical role in preventing deaths, hospitalisation caused by infectious diseases. Emerging data on effectiveness indicates that licenced COVID-19vaccines are contributing to controlling the spread of the disease. Until widespread vaccination has been achieved, both vaccinated and unvaccinated people need to be aware of the additional protective behaviours required to control the pandemic locally.

The global impact of the COVID-19 pandemic has resulted in an unprecedented level of public interest in vaccines. This includes a focus on the development of vaccines and their regulatory review and safety monitoring. Much of this coverage has taken place through mass and social media. Reports of adverse events (side effects) have led some people to express concerns about getting vaccinated, delay getting vaccinated or even be strongly opposed to vaccination. There are also differences in individual confidence in national safety monitoring systems. Another challenge in communicating the importance of COVID-19 vaccination is that younger adults are typically less clinically affected by COVID-19 infection and so may see limited value in getting vaccinated, including until further data confirms that vaccines prevent transmission and that vaccines are effective against variants. Clear and consistent communication is therefore essential to support people in making the choice to be vaccinated.

We appreciate that you, your colleagues and your patients may have a number of questions around the development, regulatory review and ongoing safety monitoring of COVID-19 vaccines.

Purpose

This joint International Coalition of Medicines Regulatory Authorities (ICMRA)* and World Health Organization (WHO) statement aims to help healthcare professionals answer questions about the role of regulators in the oversight of COVID-19 vaccines. It explains how vaccines undergo robust scientific evaluation to determine their safety, efficacy and quality and how safety is closely and continually monitored after approval.

Vaccination has been shown to contribute to reducing deaths and severe illness from COVID-19, and to reduce the transmission of COVID-19. Vaccinating as many people as possible and reducing the spread of disease is important. Vaccination of a significant proportion of the population also protects vulnerable people, including those who cannot receive vaccines, or the small proportion of people who might remain at risk of infection after vaccination. Failure to vaccinate widely also enables continued circulation of the virus and the generation of variants, including some that may pose a greater risk. Widespread vaccination will help prevent people from having to go to hospital and contribute to fewer people getting sick, ultimately alleviating the burden of COVID-19 on healthcare systems. It will also help allow a return to normal societal functioning and the re-opening of economies.

Vaccines and the regulatory process

How do regulatory authorities evaluate COVID-19 vaccines?

Regulators rigorously evaluate scientific and clinical evidence provided by vaccine manufacturers. Vaccine manufactures are legally obliged to follow defined standards in the data they provide, and their clinical research and manufacturing operations are subject to regulatory oversight. Either full or summary data from clinical trials is made available following vaccine evaluation. Each vaccine is thoroughly assessed for safety, efficacy and quality to determine whether it can be approved for use. Regulators use available scientific evidence from preclinical laboratory research, human clinical trials, and manufacturing information to assess benefits and risks of candidate vaccines.

Regulators may seek additional expert advice from independent scientific advisory committees to help inform their decision on whether to approve a vaccine. These committees are made up of experts in science, medicine (including infectious diseases) and public health, and often include consumer and healthcare professional representatives.

Public health agencies have a different role than regulatory authorities. They develop and deliver vaccination programmes, often working with their expert immunisation technical advisory committees. This includes prioritising and designating populations for vaccination with specific vaccines, issuing additional recommendations and providing information more broadly about vaccines and immunization. They also collaborate with regulators to monitor the safety of vaccines after they are approved for use.

Globally, the public can have confidence in the rigour of the process used to scientifically evaluate the safety, efficacy and quality of vaccines before they are approved for use in the wider population.

Safety evidence prior to potential regulatory authorisation:

Safety evidence is an essential part of each regulatory submission for a COVID-19 vaccine. It is gathered during all phases of the vaccine development process. Robust assessment of safety is carried out in the clinical trials and submitted to regulators for review as part of the approval process.

All adverse events need to be examined and reported in the regulatory submission by the companies for a marketing licence. Typically, regulators will require that participants in clinical trials have been followed for at least 1-2 months after receiving their final vaccine dose. Generally, based on previous experience with vaccines, most adverse events occur within such timeframes, though rare adverse events might not be recognised until after wide population use. There will also be longer-term (for example for 6-12 months or more) follow-up of those who participated in the earlier phases of the clinical trials of each vaccine. Many trial participants will also be followed for at least one year to assess the duration of protection and longer-term safety of individual vaccines, and safety data from these longer-term trials will be carefully reviewed by regulators as part of post-approval monitoring of safety.

Efficacy:

Apart from information on the types of immune responses induced by the vaccine, companies must submit data from well-designed clinical trials to regulators to demonstrate that the vaccine prevents COVID-19. The data showed there were sufficient numbers of people included in the clinical trials receiving the vaccine so that the efficacy of the vaccine can be accurately measured (generally at least 10,000 and usually 15,000 or more people who receive the vaccine, in addition to those in the control arm). Populations in clinical trials should include a range of age groups and people with co-morbidities. Given the disproportionate impact of COVID-19 on older people, COVID-19 vaccine clinical trials have included significant numbers of older participants.

Vaccine clinical trials for a new candidate vaccine showed that vaccines very significantly reduced COVID-19 in people who were vaccinated, compared to a control group of people who did not receive the vaccine, through a reduction in numbers of laboratory confirmed SARS-CoV-2 infections.

Quality:

Any COVID-19 vaccine that receives regulatory authorisation must be manufactured according to internationally accepted stringent regulatory standards of good manufacturing practices (GMP). Regulators review data to confirm that the manufacturing process at each production site is well-controlled and consistent. This will include data on the composition and purity of the vaccine and its potency, as well as data on every step of manufacturing and on the controls used to ensure that each batch of vaccine is consistently of a high quality. Data on vaccine stability must also be provided before a vaccine can be approved. After approval, batches may also undergo evaluation by individual national regulatory authorities to ensure they meet national requirements, before they can be supplied.

Monitoring safety and effectiveness after vaccine approval:

After a vaccine is approved for use, regulators conduct robust effectiveness monitoring as well as monitoring of safety and risk minimisation activities (pharmacovigilance). They need to continuously monitor vaccine safety to ensure that the benefits of the vaccine continue to outweigh the risks. Regulators do this by:

- Reviewing and analysing adverse events reported by healthcare professionals and consumers and requiring industry vaccine companies (sometimes called “sponsors”) to report to regulators on adverse events received both within the regulator’s home country and globally;

- Many regulators will implement enhanced passive surveillance systems. These include systems to rapidly compare numbers of suspected side effects reported with vaccines to the numbers of events expected to occur by chance, and include access to near real-time data on vaccine usage in different settings. Several regulators also implemented traceability systems for different vaccine brands and batches;

- Taking rapid action to mitigate risks, also considering the information about emerging safety issues shared among regulators and researchers through international collaboration;

- Reviewing medical literature and other sources of new safety information;

- Requiring vaccine manufacturers to continue safety surveillance from the ongoing clinical trials of their products; and

- Many regulators also require vaccine manufacturers to have risk management plans describing how they will monitor and minimise risks, including further epidemiological studies, associated with their vaccines.

It is very important that healthcare professionals not only diligently report any adverse events they see in their patients, but also encourage people who are vaccinated to immediately report adverse events to their healthcare professionals or to the medicines regulator in countries where direct reports from members of the public are accepted by the regulator. Reporting all relevant events helps regulators assess the possible role of the vaccine in causing the adverse event and assists in identifying safety issues relating to newly introduced vaccines.

As part of the safety monitoring and review of all suspected side effects reporting for vaccines, regulators have developed lists of “Adverse Events of Special Interest”. These lists include some events that have been associated with other vaccines (for example anaphylaxis). Others are included on these lists because they are serious events that are important to monitor extremely closely, even though there is no evidence that they are causally associated with specific vaccines. Having information on the background rates of these events that would be expected in people who have not received a vaccine will help ensure that any increased reporting of these events can be quickly detected and thoroughly investigated by regulators.

The widespread use of COVID-19 vaccines, including in the elderly and in patients with underlying health conditions, will unfortunately mean that there will be deaths and serious illnesses that are purely coincidental and unrelated to vaccinations. The job of each regulator, together with the relevant medical experts and vaccine manufacturers, is to determine causality. There will be a special focus on monitoring safety in some groups of people, such as pregnant women, persons with severe pre-existing illness, older people, children, and in people also receiving vaccines for prevention of other diseases.

Regulators, often in collaboration with public health authorities, are able to take decisive action if a safety issue is identified. These actions might include: issuing safety communications for patients, healthcare professionals and the community; updating the product information or consumer information for the vaccine; preventing the release of a particular batch of vaccine; and, taking other regulatory actions such as restriction of vaccine authorisation to a particular subgroup of the community or revocation of authorisation.

Commonly-reported adverse events

The most commonly-reported events with COVID-19 vaccines are expected vaccine side effects, such as headache, fatigue, muscle and joint pain, fever and chills and pain at the site of injection. The occurrence of these adverse events is consistent with what is already known about the vaccines from clinical trials.

Adverse events of special interest

Regulators approve and maintain an approval of a vaccine only if they determine that the known and potential benefits of the vaccine outweigh its known and potential risks.

Anaphylaxis is a very rare side effect that may occur with any vaccine. There have been some other reported adverse events which include facial weakness, seizures, loss of sense of taste or small and cardiac events, but none are confirmed to be causally related to the vaccines.

mRNA vaccines

The major adverse event of special interest reported for these vaccines, which include the Pfizer and Moderna vaccines is anaphylaxis. Regulators carefully review the reports of possible anaphylaxis to determine whether they are consistent with true anaphylaxis and whether they may have been caused by the vaccine. Anaphylaxis reports remains very rare (in the order of 10 cases per million vaccinated).

Guidance on the management of possible anaphylaxis is included in the Product Information/Label for these vaccines. Routine vaccination procedures include keeping people under observation for at least 15 minutes after vaccination and having appropriate medical treatment on hand so that anaphylaxis can be rapidly managed. These vaccines should not be given to people with a known history of a severe allergic reaction to any of the vaccine components. A second dose of mRNA vaccine should not be given to those who have experienced anaphylaxis to the first dose.

There have been some other reported adverse events which include unusual bleeding, facial weakness, seizures, loss of sense of taste or smell and cardiac events. Regulators monitor and carefully review if there is a causal relationship between the vaccines with those adverse events,

and, if appropriate, they will be included in Product Information / Product Label of vaccines of concern. Overall, the current evidence does not suggest a causal relation

Adenovirus vector vaccines

These include the AstraZeneca, Janssen, Gamaleya and CanSino Biologics vaccines. Internationally, the AstraZeneca and Janssen COVID-19 vaccines have been associated with a very rare and unusual clotting syndrome involving thromboembolic events (blood clots) with thrombocytopenia (low blood platelet count). This condition has been termed Thrombosis with Thrombocytopenia Syndrome (TTS). Medicines regulators are meeting regularly to share information about cases to better characterise this risk and understand this syndrome. Less information is available internationally about adverse events following the Gamaleya and CanSino Biologics vaccines.

The overall number of reports received of blood clots in the veins or arteries (including venous thrombosis or venous thromboembolism) occurring without thrombocytopenia is no higher than the expected background population rate for the more common type of blood clots in most countries.

The spontaneous reporting rates of thromboembolic events with thrombocytopenia vary by country and the precise incidences are difficult to estimate, but for the AstraZeneca vaccine, based on substantial use in Europe and the UK, the frequency of such events is very rare. Available estimates are of the order of 10-15 per million people vaccinated (note that for some countries this statistic is based on the numbers of reports of suspected cases of TTS rather than numbers of confirmed cases). Thromboembolic events with thrombocytopenia have also been reported in the United States for the Janssen vaccine, at a rate of about 2-3 per million doses administered. National regulators are continuing to monitor the issue closely and to publish up to date information on the numbers of cases reported and the latest estimates of the incidence.

The cases of thromboembolic events with thrombocytopenia after vaccination were mainly reported for younger rather than older individuals. This, together with the risk of serious illness or death associated with COVID-19 being much higher in middle-aged and older people, has led public health authorities in some countries to recommend that vaccination with the Astra Zeneca vaccine not be initiated in younger individuals.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and thrombocytopenia as well as coagulopathies after vaccination as TTS requires specific management. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms such as a severe or persistent headache, blurred vision, shortness of breath, chest pain, leg swelling, persistent abdominal pain or unusual skin bruising and/or petechiae (tiny purple, red, or brown spots on the skin) mostly occurring within around 4-20 days after vaccination, although some cases have been reported later than 20 days post vaccination. This information is in the Product Information / Product Label of the vaccines as approved by regulators.

Questions and Answers on COVID-19 vaccines

Q: How have the vaccines been developed so quickly? Does this mean that their safety and efficacy has been compromised?

A: The speed of development of COVID-19 vaccines has been unprecedented for several reasons, but the safety and efficacy requirements for vaccines have not been compromised, Vaccine development was facilitated by:

- **New technologies adapted from the development of other vaccines** – mRNA vaccines were developed for COVID-19 very rapidly after the sequence of the COVID-19 virus was determined, but the underlying technology had been under development since much longer and production could be scaled up very quickly. The adenovirus technology used for adenovirus vector vaccines was first tested with SARS, MERS and Ebola virus over the last 20 years, and so was able to be adapted quickly to COVID-19, which has several similarities to these viruses.

- **Clinical trial successes** - it has been possible to rapidly recruit large numbers of volunteers into clinical trials and, with unfortunately high rates of infection in several countries, to complete trials with 10,000-50,000 people in a short period of time. Under normal circumstances, it may take many months or even a few years to carry out trials of this size to determine whether a vaccine is effective.

- **Very close collaboration** - between regulators, industry and clinical researchers enabled clear indications of regulatory requirements and early access to results.

- **Intensive and insightful research** - researchers predicted that the "spike protein" on the virus would be a good target for vaccine development, and almost all vaccines have been designed to induce a response to this protein. So far, the spike protein has produced a strong immune response in those vaccinated, and for those vaccines that have reported clinical results are highly protective from COVID-19 disease.

- **The massive financial investment** by governments, industry and philanthropic organisations in vaccine development and the re-direction of much of the global research and commercial infrastructure for the development and manufacture of vaccines. Governments also enabled companies to take the commercial risk of manufacturing some vaccine stocks ahead of regulatory approvals.

Q: Will mRNA vaccines affect the DNA of vaccine recipients?

A: No. The mRNA in the vaccine has not been shown to incorporate itself into the genes of vaccine recipients and breaks down in the weeks after vaccination. mRNA vaccines contain genetic instructions for our cells, which only read them and provide copies of the SARS-CoV2 spike protein. This enables the body's natural immune systems to cause a response in vaccine recipients if they are later exposed to the virus.

Q: How long will COVID-19 vaccination provide protection for immunised people?

A: We do not yet know how long protection from any of these vaccines lasts. We will get better insights over the next 12 months.

- The duration of protection provided by vaccines can vary. For example, the seasonal influenza vaccine is given annually, because the influenza virus mutates, and protection wanes over a number of months. Other vaccines, such as those for rubella or measles provide multi-year or even life-long protection from disease. Mutations in key viral proteins can mean that virus variants emerge. The SARS-CoV-2-coronavirus is prone to mutations that creates variants, some of which have become established in a number of regions of the world. The scientific community and regulators are very actively monitoring whether the current vaccines can continue protecting people from infection with new variants.

- A number of vaccine developers are currently developing vaccines against the range of variants, and it is likely that booster shots with these vaccines will increase protection against known variants. Regulators have agreed that review of data on vaccines against variants will be facilitated based on assessment of immune response to the variant, in the same way that new seasonal influenza vaccines are evaluated each year.

Q: Why are there so many vaccine candidates?

A: As the global seriousness of the pandemic became rapidly apparent, development of effective vaccines for COVID-19 became the top priority of many pharmaceutical companies and medical research institutes. There was also unprecedented government and private sector investment in vaccine development. There is now a wide range of technologies for developing new vaccines - and many of the organisations developing COVID-19 vaccines have particular experience in one or more of these technologies. This has ensured that there would still be vaccines available if some were not approved for reasons of efficacy, safety or manufacturing challenges.

Q: What if many people start getting a reaction from a particular COVID-19 vaccine?

A: Short-term reactions, such as soreness at the injection site, fatigue or headache are common following any vaccination with COVID-19 vaccines. These reactions usually pass in a day or two. If new evidence becomes available that suggests that a specific serious adverse event may be linked to a particular COVID-19 vaccine then regulators will take action, working collaboratively on a global basis and liaise with public health authorities. The type of actions that can be taken depend on the nature of the adverse event, and could range from issuing safety warnings for patients, healthcare professionals and the community; updating the product information or consumer information for the vaccine to show contraindications for the use in particular patients (e.g. those with certain co-morbidities); to closely monitoring adverse events in certain groups of patients; preventing the release of a particular batch of vaccine through to temporary suspension of the use of the vaccine until more is known.

Q: How are regulators speeding up the time it takes to authorise a COVID-19 vaccine?

A: Many regulators globally have implemented faster access pathways for COVID-19 vaccines, without compromising on strict standards of safety, quality and efficacy.

- Some countries have Emergency Use Authorisation pathways which assess the available data at the time of authorisation. Exercising these provisions is a matter for those countries, taking into account the benefits versus risks in the context of the prevailing domestic pandemic situation. Different countries may coin this pathway or authorisation routes differently but essentially they follow the same principles.

- Other countries have implemented accelerated/priority, conditional or provisional approval schemes.

- Under normal circumstances, regulatory assessment begins once all information to support registration is available. For COVID-19 vaccines, many regulators have agreed to accept data on a rolling basis to enable early evaluation of data as it becomes available. Regulators will only be in a position to make a provisional approval decision for a vaccine once there is sufficient data to support adequately the safety, quality and effectiveness of the vaccine for its intended use. If a decision is made to grant provisional or conditional approval, it will be based on the requirement for the sponsor to submit more comprehensive, longer term clinical data, stability data and other information with agreed timelines.

Q: Did our country approve this COVID-19 vaccine, or are we relying on another country's approval?

A: Most countries are carrying out independent regulatory evaluations on the submitted data for each vaccine. However, to ensure a more efficient use of resources and expertise, regulators in different countries are communicating closely on safety, efficacy and quality data and discussing technical issues as they may arise. In many cases principles of WHO Good Reliance Practices and collaborative mechanisms leverage the output of other regulators.

Q: Why weren't very rare blood clots with low platelets with the AstraZeneca or Janssen vaccines picked up during clinical trials?

A: Thromboembolic events with concurrent thrombocytopenia are very rare – with estimates based on the number of spontaneous reports suggesting an overall incidence on the order of 10-15 cases per million doses. The clinical trials of these vaccines included large numbers of people, often with 10,000 to 20,000 individuals in the active vaccine arms, but even in trials of this size it was statistically unlikely that such very rare events would be detected. This shows the importance of continual safety monitoring during the use of these vaccines, to allow very rare events to be detected and investigated further.

About ICMRA

ICMRA brings together the heads of 30 medicines regulatory authorities* from every region in the world, with the WHO as an observer. Medicines regulators recognise their role in facilitating access to safe and effective high-quality medicinal products essential to human health and well-being. This includes ensuring that benefits of vaccines outweigh their risks.

ICMRA is an international executive-level coalition of key regulators from every region in the world. It provides a global strategic focus for medicines regulators and gives strategic leadership on shared regulatory issues and challenges. Priorities include coordinated response to crisis situations.

Members of ICMRA include: Therapeutic Goods Administration (TGA), Australia; National Health Surveillance (ANVISA), Brazil; Health Products and Food Branch, Health Canada (HPFB-HC), Canada; China National Medical Products Administration (NMPA), China; European Medicines Agency (EMA) and European Commission - Directorate General for Health and Food Safety (DG - SANTE), European Union; French National Agency for Medicines and Health Products Safety (ANSM), France; Paul-Ehrlich-Institute (PEI), Germany; Health Product Regulatory Authority (HPRA), Ireland; Italian Medicines Agency (AIFA), Italy; Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA), Japan; Ministry of Food and Drug Safety (MFDS), Korea; Federal Commission for the Protection against Sanitary Risks (COFEPRIS), Mexico; Medicines Evaluation Board (MEB), Netherlands; Medsafe, Clinical Leadership, Protection & Regulation, Ministry of Health, New Zealand; National Agency for Food Drug Administration and Control (NAFDAC), Nigeria; Health Sciences Authority (HSA) Singapore; South African Health Products Regulatory Authority (SAHPRA), South Africa; Medical Products Agency, Sweden; Swissmedic, Switzerland; Medicines and Healthcare Products Regulatory Agency (MHRA), United Kingdom; Food and Drug Administration (FDA), United States.

Associate members include: Argentina national Administration of Drugs, Foods and Medical Devices (ANMAT); Austrian Medicines and Medical Devices Agency (AGES), Colombia National Food and Drug Surveillance Institute (INVIMA); Cuba Center for State Control of Medicines, Equipment and Medical Devices (CECMED); Danish Medicines Agency (DKMA); Israel Ministry of Health (MOH); Poland Office of Registration of Medicinal Products and Biocidal Products (URPLWMiPB); Portugal National Authority of Medicines and Health Products (INFARMED); Russia Federal Service for Surveillance in Healthcare (Roszdravnadzor); Saudi Food and Drug Authority (SFDA); Spanish Agency of Medicines and Medical Devices (AEMPS).

The World Health Organization is an **Observer** to ICMRA.

For updates on ICMRA, including its role in the COVID-19 response, visit http://www.icmra.info

About the World Health Organization

The World Health Organization provides global leadership in public health within the United Nations system. Founded in 1948, WHO works with 194 Member States, across six regions and from 149 offices, to promote health, keep the world safe and serve the vulnerable. Our goal for 2019-2023 is to ensure that a billion more people have universal health coverage, to protect a billion more people from health emergencies, and provide a further billion people with better health and wellbeing.

For updates on COVID-19 and public health advice to protect yourself from coronavirus, visit www.who.int and follow WHO on Twitter, Facebook, Instagram, LinkedIn, TikTok, Pinterest, Snapchat, YouTube, Twitch