Statement for healthcare professionals: How COVID-19 vaccines are regulated for safety and effectiveness (Revised 17 May 2022)

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, and hospitalisation caused by infectious diseases, and are contributing to controlling the spread of the disease, thus their impact on infection and serious illness is significant. Both vaccinated and unvaccinated people also 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 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 in many, but not all, children and young adults are less clinically affected by COVID-19 infection and therefore some may see limited value in vaccinating this population. Clear and consistent communication of evidence and uncertainties is therefore essential to support people in making the critical 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 has contributed to fewer people getting sick and being hospitalised, ultimately alleviating the burden of COVID-19 on healthcare systems. It has also helped allow the move back 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 to regulators as part of 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 have collaborated extensively with other global regulatory counterparts in premarket and safety reviews.

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 to 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 authorisation. Typically, regulators will require that participants in clinical trials have been followed for generally at least 2 months after receiving their final vaccine dose for decisions made under emergency or provisional or conditional approval processes, with longer follow up required before full market authorisation is granted. One year or longer safety data are now available for many of the most widely used vaccines. While rare adverse events might not be recognised until after wide population use, based on both the current experience with COVID-19 vaccines and previous experience with other vaccines, most adverse events occur days to a few weeks of vaccination and will be identified in clinical trials. There will also be longer term (for example 1 to 2 years) follow up of those who participated in the clinical trials of each vaccine, which is standard practice in clinical trials, as well as population wide observational safety studies. Safety data from these longer-term trials and population studies are being carefully reviewed by regulators as part of post approval monitoring of safety. International regulators collaborate on the review of safety allowing an increase in the size of the populations for which safety data can be assessed.

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. Since the population-wide roll out of COVID-19 vaccines

commenced in December 2020, a significant number of effectiveness studies have been published in refereed international medical journals. The population wide effectiveness data have been in line with the findings of the clinical trial results and shown high effectiveness against infection and even higher effectiveness against serious illness, hospitalisation or death from COVID-19 infection. Progressive waning of the effectiveness of one or two doses, particularly against mild infection and against the SARS-CoV-2 Omicron variant has emphasised the importance of a third booster vaccination.

For COVID-19 vaccines, it is becoming increasingly difficult to conduct placebo-controlled disease endpoint efficacy trials in some countries, as few individuals are willing and available to participate. Appropriately designed immuno-bridging studies are an acceptable alternative approach for authorising vaccines including for variants, boosters and paediatric populations. Neutralising antibody titres may be a suitable primary endpoint to predict vaccine effectiveness. The applicant for regulatory approval must also have justified the choice of appropriate vaccine comparators, statistical criteria and population comparator groups (for example, matched by age, gender, prior vaccination/infection status). Efficacy data should also include characterisation of comparative immunogenicity profiles, including cell-mediated immunity and characterisation of comparative in vitro neutralisation against Variants of Concern.

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 have implemented enhanced passive surveillance systems. These include systems to rapidly compare numbers of suspected adverse events reported with vaccines to the number of events expected to occur by chance, and includes access to near real-time data on vaccine usage in different settings. Several regulators have also implemented traceability systems for different vaccine brands and batches;
- Taking rapid action to mitigate risks, also considering the information about emerging safety issues that is 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 associated with their vaccines, including post authorisation safety studies that will continue to evaluate the safety and benefit-risk of their vaccine.

There has been a significant commitment by healthcare professionals and hospitals to report any adverse events they see in their patients, and it is important that this continues. Reporting of 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 adverse events reported for vaccines, regulators have developed lists of “Adverse Events of Special Interest”. These lists include some events that have been associated with other vaccines or could be theoretically linked to the COVID-19 vaccines. They may be included on these lists because they are serious events that are important to monitor closely, even though there may be no evidence that a particular adverse event is 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, thoroughly reviewed and investigated by regulators.

The widespread use of COVID-19 vaccines, including in the elderly and in patients with underlying health conditions, means that there have been deaths and serious illnesses that are purely coincidental and unrelated to vaccinations. The job of each regulator, often supported by independent committees of relevant medical experts together with vaccine manufacturers, is to review the cases and determine if there are potential safety signals with the vaccines. There is a special focus on monitoring safety in some groups of people that may not have been included in clinical trials or included as a small number, 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, can take decisive action if a safety issue is identified. These actions can 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. 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.

Commonly reported adverse events

The most commonly reported adverse 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 associated with specific vaccines

mRNA vaccines

The most significant adverse events of special interest reported for these vaccines, which include the Pfizer and Moderna vaccines are myocarditis, pericarditis and anaphylaxis.

Myocarditis is inflammation of the heart muscle while pericarditis is an inflammation of the membrane around the heart. They can occur as very rare adverse events after vaccination with mRNA vaccines. Cases typically occur within 10 days, with symptom onset often within 5 days of vaccination. Pericarditis symptoms may occur later, typically 2 to 3 weeks after vaccination. Myocarditis and pericarditis are often mild, and symptoms usually resolve after a short time with standard treatment and rest. Some cases are more serious and need to be treated in hospital, but very few cases require intensive care.

Myocarditis has most often been reported after the second dose in 12 to 17 year old boys and men under 30. Several countries have observed higher reporting rates of myocarditis with those vaccinated with the Moderna COVID-19 vaccine than the Pfizer vaccine, but the reported difference in rates has differed between studies and countries may be influenced by a variety of factors. The benefit-risk of both of the vaccines remains positive. Pericarditis following a mRNA vaccine tends to occur at an older median age than myocarditis, but it is nonetheless more common in people under 50 years of age than in older people.

Myocarditis and pericarditis can occur after a booster dose, but this is so far reported to be more rare than after the primary doses. There is no indication that these events are more serious than after earlier doses.

Anaphylaxis has been reported with mRNA vaccines (and other COVID-19 vaccines). Anaphylaxis reports remain very rare (in the order of 1 case per 100,000 people vaccinated). 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. 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 any vaccine should not be given to those people who have experienced anaphylaxis after the first dose of a COVID-19 vaccine.

Adenovirus vector vaccines

These include the AstraZeneca, Janssen, Gamaleya and CanSino Biologics COVID-19 vaccines. The most significant adverse events of special interest reported for these vaccines are Thrombosis with Thrombocytopenia Syndrome (TTS), Immune Thrombocytopenic purpura (ITP) and Guillain-Barre Syndrome (GBS).

TTS is a very rare, but serious clotting syndrome involving thromboembolic events (blood clots) with thrombocytopenia (low blood platelet count). TTS symptoms usually start between 4 to 30 days after vaccination. It occurs in about 2 out of every 100,000 people after a first dose. The risk of TTS after a second vaccine dose of the AstraZeneca vaccine appears to be much lower and is under 0.5 of every 100,000 people after a second dose. Younger women, and people under 60 years seem to be slightly more likely to have serious outcomes from TTS as they more often experience clots in unusual locations, such as the brain or abdomen. Thromboembolic events with thrombocytopenia have also been reported in the United States for the Janssen vaccine, at a rate of about 2 to 3 per million doses administered.

Immune thrombocytopenia (ITP) and Guillain-Barre Syndrome (GBS) have been reported in about one in every 100,000 people following the AstraZeneca and Janssen vaccines. ITP is a rare immune reaction that occurs when platelets are mistakenly destroyed by the immune system. In suspected ITP following vaccination with the AstraZeneca vaccine, patients had an extremely low platelet count, and signs of thrombocytopenia which may include unusual bruising, a nosebleed and/or blood blisters in the mouth. About 5% of people with ITP develop severe bleeding. In a very small number of people, it can be fatal.

GBS is a rare but sometimes serious (and rarely fatal) immune disorder affecting the nerves and can result in pain, numbness, muscle weakness and difficulty walking. GBS can occur when the immune system is activated and has been associated with infections, including SARS-CoV-2, and vaccines. GBS typically occurs days or weeks after an infection or vaccination. However, sometimes a trigger for GBS cannot be identified.

Several other COVID-19 vaccines have also been authorised in some other countries. Less information is available internationally about adverse events for other manufactured vaccines. Regulators monitor and carefully review if there is a causal relationship between any of the vaccines associated with adverse events, and, if appropriate, information will be included in Product Information / Product Label of vaccines of concern.

Health care professionals are encouraged to check the approved Product label/ product information or Fact Sheets for the vaccine in their country for safety information specific to the vaccines they are administering. In addition, where a new safety issue is identified regulators communicate this to health care professionals and consumers through alerts on their websites and through social media.

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 therefore 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 to 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 internationally, 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 have been shown to be highly protective from COVID-19 disease.
- **The massive financial investment** by governments, industry and philanthropic organisations in vaccine development and the redirection of much of the global research and commercial infrastructure for the development and manufacture of vaccines has taken place. Governments also enabled companies to take the commercial risk of manufacturing some vaccine stocks ahead of regulatory approvals.
- **Real world safety experience.** As of March 2022, about 11 billion doses of COVID-19 vaccines have been administered globally, and so there is an immense global data base on the safety of these vaccines. The benefit-risk ratio remains overwhelmingly positive.

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-CoV-2 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: A number of "real world" vaccine effectiveness studies have provided information on the duration of protection from different COVID-19 vaccines. Two doses of the major mRNA and adenovirus vaccines provided strong (over 75 %) protection from serious illness,

hospitalisation and death from the alpha, delta and original (wild type) SARS-COV-2 variants for 6 months. However, with emergence of the Omicron variant in late November 2021, evidence suggests that a third (booster vaccination) is required to restore and maintain protection against serious illness or death. Early results indicate that protection against serious illness or death is maintained for many months or longer after a third vaccination, and at present, there is not a widespread view that a fourth vaccination (second booster) is required to maintain immunity, except for in people who are immunocompromised. While those who become infected with SARS-CoV-2 following primary vaccination typically experience milder illness, protection against the level of severity of infection does seem to decrease over time without a booster vaccination.

Q: Should the same type of vaccine be used for a booster as the original vaccine?

A: Several studies have now been published examining the use of the same vaccine as a booster (third dose) after the first two doses (homologous boosting) and the use of a different vaccine as a third dose (heterologous boosting). While virtually all combinations of booster and initial course vaccines provided significant increase in immune response, most studies have shown that the greatest increase in immune response resulted when a booster of an mRNA vaccine was used following a primary course of either an mRNA vaccine or an adenovirus vector vaccine.

Q: Are vaccines effective against COVID-19 variants?

A: Mutations in key viral proteins can result in the emergence of virus variants emerge. The SARS-CoV-2-coronavirus is prone to mutations that create variants, some of which have become established in many parts of the world. The scientific community and regulators are actively monitoring protection by vaccines against infection and disease with new variants. For example, decreases in the level and duration of protection against the Omicron variant following a two-vaccine course led to many countries adopting a third dose booster program, three or more months following the second vaccination.

A number of vaccine developers are currently developing vaccines against the range of variants, while others are attempting to develop multivalent or pan-specific vaccines, which may protect against future 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. However, evidence to date suggests that for people who are not immunocompromised, three doses of the current vaccines provided robust protection against serious illness, hospitalisation or death from the Omicron variant.

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 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 a specific serious adverse event may be linked to a particular COVID-19 vaccine, then regulators will take action by 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: Should children be vaccinated? Are COVID-19 vaccines safe in children?

A: In many children aged under 12 years, SARS-CoV-2 infection is often asymptomatic or causes a brief illness with mild symptoms. Children at increased risk of severe outcomes from COVID-19 include those with obesity, chronic pulmonary disease, congenital heart disease and neurological disease, as well as those with neurodevelopmental disorders or epilepsy. The sheer number of COVID-19 infections during the Omicron wave, including in children has meant that most countries have experienced numbers of hospitalisation of children (and sadly some deaths) following COVID-19 infection.

Vaccination is also protective against paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (also known as MIS-C), a potentially life-threatening syndrome that occurs in approximately 1 in 3,000 children after infection. In addition to a reduction in illness, vaccination can also reduce the need for isolation in

children (and therefore the disruption to education and social activities) and potentially a reduction in parental absenteeism from employment.

Experience to date with the mRNA vaccines approved for paediatric use is that they are well-tolerated vaccines; where side effects occur, they are generally mild with pain, swelling, and redness at the vaccination site being the most commonly reported side effect. In addition, while myocarditis and pericarditis cases have very rarely been found in under 12's following vaccination, the rates seem much lower than in older teenagers and adults.

Q: Are COVID-19 vaccines safe in pregnancy?

A: Although pregnant women were not deliberately included in the clinical trials of the COVID-19 vaccines, since the roll out of the vaccines in December 2020 there has been significant experience (particularly with the mRNA vaccines) on COVID-19 vaccination and pregnancy outcomes. A series of studies in a number of countries, both those published in the medical literature and surveillance following use of COVID-19 vaccines carried out by public health bodies and regulators, examining many tens of thousands of pregnancies did not find a higher risk of severe side effects, complications, miscarriages or premature births following vaccination.

At the same time, several studies have shown that COVID-19 infection can have very serious impacts on pregnancy outcomes in certain women, and that the benefits of receiving mRNA outweigh risks for pregnant women and their unborn children. In addition, recent data shows that maternal COVID-19 vaccination is linked to a lower risk of still births, and that perinatal mortality was more than fourfold higher for women giving birth within 28 days of infection.

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 or a conditional 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 or myocarditis/pericarditis with mRNA vaccines picked up during clinical trials?

A: Both of these types of adverse events are very rare with one to a few cases per hundred thousand vaccinated individuals. 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. As with most medicines and vaccines, very rare side effects such as TTS are not identified until there have been a large number of the population vaccinated. This shows the importance of continual safety monitoring during the use of these vaccines in real world setting, to allow very rare events to be detected and investigated further.

About ICMRA

ICMRA brings together the heads of 39 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; India Ministry of Health and Family Welfare (MoHFW); 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); Egyptian Drug Authority (EDA); Ghana FDA; Icelandic Medicines Agency (IMA), 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) and The State Expert Centre of the Ministry of Health of the Ukraine.

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.
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