BMJ

ADB

Webinar meeting report May 2021

COVID-19 vaccine safety - From bench to bedside

Introduction

Within a year of the start of the pandemic, a number of COVID-19 vaccines were approved and administered to populations around the world.

There is significant global interest in ensuring they are safe and effective and healthcare professionals need credible information to build trust with their patients and answer their questions.

A webinar, organised by BMJ and the Asian Development Bank explored COVID-19 vaccine safety in clinical trials, post-authorization safety methods, and risk communication.

Clinical trials and vaccine safety

Developing a vaccine or treatment during a pandemic is never ideal and presents many challenges, Dr Stephen Prior, microbiologist and president of Therax, Inc., USA told the webinar. "It has been described as building the plane as we fly."

The good news is that the current COVID-19 vaccines could adapt existing technologies and platforms and build on work previously carried out for SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) as well as earlier research on other human coronaviruses. Dr Prior said the other positive has been the "unprecedented level of cooperation and collaboration." This has occurred at a national and international level, between manufacturers and regulators, and even between different vaccine developers.

However, one of the key reasons that vaccine development occurred in such an unprecedented timeframe was that governments or organisations adopted cost risk. Companies could gamble on starting large-scale testing and manufacturing of vaccine candidates that might not work out. "This meant that vaccines could be developed and even if they failed the full costs of development would be covered," Dr Prior told the webinar.

Traditional vaccine development can take 15 years or longer. It's a sequential process from design and laboratory work through to large scale production and distribution, Dr Prior explained. Phase I, II and III clinical trials can take five to seven years and regulatory review by bodies such as the Food and Drug Administration or the European Medicines Agency can take one to two years. For SARS-CoV-2 vaccine development this process has been condensed to 10 months to 1.5 years. This was achieved by parallel versus batch processes. For example phase 1 and phase II trials overlapped and manufacturers could scale up production before a vaccine received approval. The use of emergency use authorizations instead of full product licenses that permitted widespread use of the vaccine while additional data was collected also speeded up the process. The first application for full licensure by the US FDA was announced by Pfizer as recently as May 7. "All of the things that are normally done to ensure the safety of a vaccine were done for these SARS-CoV-2 vaccines but they were done in a compressed timescale," Dr Prior emphasised.

All vaccines for use in humans are subject to review by regulatory authorities. Safety reviews include vaccine manufacturing standards – including purity, potency and stability of the vaccine. Clinical studies involving thousands of volunteer participants are conducted to assess both safety and efficacy of the vaccine. Volunteers are monitored and followed up for vaccine related issues which can be as simple as soreness at the injection site through mild, moderate or severe side effects.

During all phases of clinical trials, safety is an important focus area. Trials focus on adverse events; life threatening adverse events or life-threatening suspected adverse

> **"There is a fallacy that because one event is followed by another then it must be caused by it. We must be cautious not to presume causality because of a temporal relationship."**
>
> Dr Daniel Salmon, director of the Institute for Vaccine Safety at John Hopkins Bloomberg School of Public Health, USA

> **"All of the things that are normally done to ensure the safety of a vaccine were done for these SARS-CoV-2 vaccines but they were done in a compressed timescale,"**
>
> Dr Stephen Prior, microbiologist and president of Therax, Inc., USA

reactions; serious adverse events or serious suspected adverse reaction; suspected adverse reaction; unexpected adverse events or unexpected suspected adverse reaction.

Dr Prior told the webinar that COVID-19 vaccine trials included more people who were older, obese or had a coexisting condition than is usually the case in vaccine trials as it was recognised early on that these were important risk factors that needed to be looked at. A monitoring scheme that includes safety stopping rules ensures a trial is paused if there are adverse reactions. For example, single cases of a possible vaccine-linked adverse reaction caused a pause in the AstraZeneca trial in September 2020 and the J&J vaccine in October 2020.

Finally, Dr Prior made a number of predictions:

- Vaccines will continue to help prevent severe/moderate COVID-19 and reduce hospitalisations.
- The virus will continue to mutate resulting in new variants.
- The current vaccines may be less effective against some of these variants.
- Vaccines will need to be modified to account for new variants
- We may need to receive additional booster vaccines or possibly, annual vaccination.

Post authorization safety monitoring

Dr Daniel Salmon, director of the Institute for Vaccine Safety at John Hopkins Bloomberg School of Public Health, USA explained that the overall goal of post authorization safety monitoring is to ensure the benefits of a vaccine outweigh the risks, both for an individual and for the population. "We have very high standards for vaccine safety largely because we are giving them to healthy people. Additionally, because we are vaccinating very large numbers of people even a small relative risk can have a large attributable risk," he told the webinar. He added that other considerations include optimising the use of limited resources, maintaining public confidence in vaccines and reaching high coverage in order to control the disease.

Dr Salmon said that one of the challenges when it comes to the public perception of vaccine safety is the fallacy that because one event is followed by another then it must be caused by it. "We must be cautious not to presume causality because of a temporal relationship." He said it was important to anticipate the background rates of disease, for example there are 2500 miscarriages and 3000 heart attacks every day in the US. It is also vital to rapidly identify and follow up vaccine safety signals to determine if they are coincidental or causal. "Unfortunately robust science and follow up takes time whereas public concern and rumours can spread globally in seconds."

Although double blind randomised trials are the gold standard for evaluating the safety and efficacy of a vaccine, they do have some limitations. Strict inclusion and exclusion criteria means they can't evaluate adverse events in people excluded from studies. Delayed adverse events may also be missed. Even though some of the COVID-19 vaccine trials were large, with more than 40 000 participants, some of the rarer adverse events may not be identified. Dr Salmon explained that in order for a clinical trial to identify a doubling of a risk from 0.1% to 0.2% then you would need a sample size of 50 000 people. If you were to miss this rare event and vaccinate the US population with one dose this could potentially impact 200 000 people.

Post authorization studies are needed in order to identify these rare adverse events, to look at subpopulations excluded from clinical trials and to address emerging safety issues. Passive surveillance systems can detect signals of unanticipated events that may deserve further follow up. However, these have limitations in that they usually cannot determine if an event is caused by a vaccine or is coincidental. There are also potential biases with under-reporting, incomplete reporting or over-reporting. VAERS (Vaccine Adverse Event Reporting System) is the main passive surveillance system in the US and this accepts reports from anyone. It is designed for detecting signals or generating hypotheses but cannot assess causality.

Active surveillance systems are more effective at assessing a link between vaccines and adverse events, Dr Salmon told the webinar. An example in the US, is the Vaccine Safety Datalink (VSD) which links large healthcare databases from a number of managed care environments. "Size matters – the larger the database for active surveillance then the quicker you can get answers."

Finally, Dr Salmon discussed the pausing of the J&J vaccine rollout in the US following 28 cases of thrombosis with thrombocytopenia syndrome (TTS) reported to VAERS. The pausing may have had an impact on intention to get vaccinated. However, he pointed out that in the US where there are good supplies of two other highly effective vaccines the implications of pausing was much less than it would be in low or middle income countries if there are no alternatives available.

Risk communication

"COVID-19 is not just a health crisis, it is also an information and socioeconomic crisis," Dr Priscilla Rupali, an infectious diseases physician from Christian Medical College, Vellore, India told the webinar. She said that there are a number of possible reasons behind lower levels of vaccine acceptance. Rational decision making is often clouded by biases or emotions. Cultural, religious and political differences can all have an influence.

Dr Rupali said that concerns about vaccine safety can happen when there is overestimating of rare risks and underestimating of common risks. This is compounded because the media tends to over-report negative information. Another factor is that actions tend to be perceived as more harmful than doing nothing. People may also rely on others getting vaccinated to build up herd immunity so feel they don't need to be vaccinated themselves.

"Risk communication and community engagement can break the chains of transmission and mitigate the impact of the pandemic," Dr Rupali told the webinar.

She said people are more likely to be vaccinated if:

- It is convenient, free and easy
- They have confidence in the safety of the vaccine system that delivers it
- Their healthcare professionals recommend it

Dr Rupali said at CMC Vellore hospital they worked hard to combat initial vaccine hesitancy among their 12 000 employees and their dependents and they have succeeded in achieving 90% vaccine uptake. They wrote a list of Frequently Asked Questions before the vaccine was rolled out and this was modified after feedback and then translated into a number of languages. They also held meetings to provide information including levels of vaccine uptake in other countries. The hospital also enabled those vaccinated to become facilitators who encouraged others to get the vaccine.

It is important to allow people to express their anxieties and fears and clarify any misconceptions, Dr Rupali said. Risk communication should acknowledge side effects such as fever and muscle pain. They should communicate that these side effects are transient and actually indicate that the vaccine is working. It was important to summarise the evidence clearly, she added.

Dr Rupali said they had to debunk a lot of myths including that vaccine development was rushed or that the vaccine is unsafe. Other scare stories that had to be debunked were that the vaccines contain a microchip; will alter DNA; contain parts of aborted foetuses; contain parts of animals or cause infertility. She added that UNICEF and WHO have excellent resources to combat vaccine hesitancy.

> **"Risk communication and community engagement can break the chains of transmission and mitigate the impact of the pandemic."**
>
> Dr Priscilla Rupali, infectious diseases physician, Christian Medical College,India

Question and Answer Session

Attendees from all around the world posed valuable questions to the panel about vaccine safety

Are there any safety issues if two different vaccines are used for the first and second dose?

Dr Prior said that trials are ongoing and the full results have not yet been published. But the first results looking at a combination of the Pfizer and AstraZeneca vaccine were published in a letter to the Lancet on May 12. This showed that using the same vaccine for both doses resulted in lower reactogenicity and side effects than if you mixed the vaccines. But even if you used different vaccines it did not result in significant levels of adverse effects.

Dr Patrick Osewe, chief of the Asian Development Bank's health sector group, said this is a big issue for many developing countries who rely on India to supply the AstraZeneca vaccine through the Covax scheme. While some countries held back 50% of their supplies for second doses, others used all their supply as first doses. India, who are tackling their own steep rise in cases, has recently said they will not be able to supply other countries with more vaccines until October. As a result many countries are deciding not to wait that long and are looking at purchasing alternative vaccines, and so will be using a mix and match approach.

If you do have two different vaccines, what is the safe interval between doses?

Dr Prior said that the Lancet study looked at intervals of 12 and 28 weeks. However, we are still waiting for full data to answer this question.

What should we advise mothers who are breast feeding?

Dr Salmon said that in vaccine trials there were women who were pregnant and passive surveillance has not identified any problems with pregnancy or with women who are breast feeding. The US recommendation is that a decision about vaccination for breastfeeding women should be made in consultation with the clinician but breast feeding is not a contraindication to vaccination.

Dr Rupali said that in her clinic if women were in the first six months of breastfeeding they did not give them the vaccine but if they were later than this they could take it.

Dr Prior said he was aware of one study with a cohort of 84 individuals who were breastfeeding and immunised with the Pfizer vaccine and this had not shown up any problems. He added that a factsheet has been put out by the National Institutes of Health related to lactation and COVID vaccination.

There have been reports of thrombosis with thrombocytopenia with the AstraZeneca vaccine, have there been any reports of thrombotic episodes without thrombocytopenia associated with any of the vaccines? If yes, is that a contraindication for the second dose?

Dr Salmon said that there probably have been reports. However, thrombotic events happen all the time but you can't presume an association. He said he was not aware of a contraindication for a second dose but a decision should be carried out in consultation with the physician.

If a patient has a first dose, then gets COVID-19, should the second dose be delayed?

Dr Prior said there is no evidence on this from a clinical trial. However, studies have found vaccine breakthrough events are very rare. Around 1 in 10 000 people receiving the vaccine may get COVID but of these only around 1% have significant disease.

If someone has a first dose of the vaccine then gets COVID-19 is there a chance of a hyperimmune response?

Dr Salmon responded that this has not been studied and there are no data.

Does the Pfizer vaccine protect against the Indian variant?

Dr Prior commented that real world data that is being collected right now suggests that it does.

With the scarcity of vaccines for low income countries, should available vaccines be used in areas with high numbers of cases?

Dr Prior replied that that approach is being used in the UK right now with increased vaccination in those parts of the country with high levels of the B.1.617.2 variant circulating.

How do we know if the levels of immunity after vaccination are adequate?

Dr Prior said that we can't know this yet. He added that there are still many unanswered questions – for example, what is the infective dose for an individual, the most likely route of transmission, and the level of immunity needed for protection.

Dr Salmon agreed that there is an awful lot we still don't know. He said that we need to be forthcoming on what we do and don't know in order to build up trust.

After a non-vaccinated person gets COVID-19 and recovers should they still get the vaccine?

Dr Salmon replied with a definite yes as we don't know how long protection is from natural infection. However, the recommendation on how long to wait varies from country to country.

After completing two doses of vaccination can a woman get pregnant or how long should they wait?

Dr Salmon said he was confident a women can do so straight away but was not aware of any data on this

Is there any vaccine that can be given to a child under 10 years?

Dr Prior said that a trial is ongoing in the US giving the Pfizer vaccine to children as young as 5

For how long is the AstraZeneca vaccine effective?

Dr Prior replied that we still don't know the answer to this and the answer will come from real time data. However, he said we know from previous studies on vaccines using a similar adenovirus platform for SARS and MERS that the protection offered is quite long term

Key learning points

Dr Rupali – We should encourage everyone to take the vaccine as the side effects are very few and this is the way to bring down the mortality and morbidity associated with COVID-19

Dr Salmon – Regarding concerns about the AstraZeneca or J&J vaccine it's all about risks and benefits. If that is the vaccine that is available then the benefits clearly outweigh the risks.

Dr Prior – It's remarkable that 15 months after the first wave of COVID-19 we have a number of vaccines that have been used on a global basis. We have answered some questions but there remains some uncertainty and the answers will only come with time.

About the BMJ and ADB partnership

BMJ and the Asian Development Bank (ADB) launched the **COVID-19 (Coronavirus): ADB Information Centre** to support frontline health professionals manage patients with COVID-19, its relevant differential diagnosis and common comorbidities in real-time, at the point of care.

The Information Centre provides free access to digital health tools such as clinical decision support from BMJ Best Practice, accredited e-learning courses from BMJ Learning as well as patient information leaflets and procedural videos. Evidence on COVID-19 is rapidly changing and frontline healthcare professionals can benefit from trusted, evidence-based and continually updated international guidelines.

Funding: BMJ receives educational funding from the Asian Development Bank to provide free resources on COVID-19 and related diseases in Asia.