

COVAX



COVAX is the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator

Workshop Report

COVAX Vaccine Safety Working Group: Developer Needs Workshop

August 31st, 2020

Meeting report prepared by

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Executive summary

On 31st August 2020, COVAX, supported by the Coalition for Epidemic Preparedness Innovations (CEPI), the Global Alliance for Vaccines and Immunizations (GAVI), and the World Health Organization (WHO), hosted a COVID-19 Vaccine Safety Developers Workshop. The main aim was to identify the key vaccine safety issues developers need assistance with.

Co-chairs Dr Ajoke Sobanjo-ter Meulen (Gates Foundation) and Dr Bob Chen (Brighton Collaboration) opened the workshop and welcomed participants.

Dr Jakob Cramer (CEPI) presented an overview of COVAX, the vaccine pillar of the Access to COVID-19 tools (ACT) accelerator. The ACT accelerator was formed in April 2020 as a global collaboration to accelerate development, production, and equitable access to new COVID-19 diagnostics, therapeutics, and vaccines.

Dr Emer Cooke (WHO) gave an overview of WHO's ongoing COVID-19 vaccine safety initiatives. The WHO has been working closely with regulators across the globe since the start of the pandemic, within all three pillars (diagnostics, treatments, and vaccines) of the ACT accelerator, to support regulatory issues, facilitate harmonisation and preparedness, and collaborate to provide a platform for rapid exchange of information. The WHO aims to promote regulatory alignment to facilitate access to quality, safe, and effective products as quickly as possible. On-going WHO COVID-related regulatory activities range from issuing Emergency Use Listing (EUL) to developing guidance for COVID-19 vaccine safety work at global, regional, and national levels.

Dr Kathy Edwards presented an overview of key past studies with notable adverse events following immunisation (AEFI), including the multicentre acellular pertussis vaccine studies, rotavirus vaccine studies, inactivated measles vaccine, dengue vaccines, and post-licensure studies of H1N1 pandemic vaccine. Lessons learned from AEFI surveillance were discussed and how this might relate to COVID-19 vaccine safety.

Results of the Developer Needs Survey were reviewed and a guided discussion about specific needs and other concerns ensued. Developers discussed each milestone in detail, including risk management plan (RMP), post-licensure safety surveillance, Phase II/III, licensure application, WHO prequalification, first-in-human, and communication plan. Specific concerns or needs related to each milestone were identified.

Dr Bob Chen discussed some basics of vaccine safety assessment including how to clarify the causal link between an adverse event and vaccine. He then identified potential cross-cutting COVID-19 vaccine safety assessment issues including comparison of safety data, willingness to contribute data to allow evaluation of safety data on similar new technology platforms across different candidates, tracking of vaccine exposure information, plans for obtaining and using background rates of AEFI and adverse event of special interest (AESI) for post introduction studies, and process for formally declaring a "safety signal" and how this information will be shared/action plan if this should occur.

Dr Steve Black (Brighton Collaboration) summarised the key takeaways from the workshop and Dr Sobanjo-ter Meulen outlined the next steps, including continuing to map relevant resources to enable assessment of post-licensure safety and COVAX alignment with WHO regarding vaccine safety efforts. The meeting was then adjourned and attendees thanked for their participation.

Introduction

On 31st August 2020, 61 vaccine developers, vaccine safety experts, and representatives of major global organisations involved in COVID-19 vaccine development participated in a workshop on vaccine safety hosted by COVAX and supported by CEPI, GAVI, and WHO.

The global COVID-19 pandemic has marked an unprecedented time in vaccine development with new platforms, new actors, developers, and companies, and different target populations. Thus, the topic of vaccine safety has never been more important. The purpose of the workshop was to identify the key vaccine safety issues facing the developers.

COVAX Overview

Dr Jacob Cramer, head of Clinical Development at CEPI, explained that the search for a vaccine against COVID-19 is the most pressing global challenge of our time. Hence, ACT accelerator was formed in April 2020 as a global collaboration between public, private, and social sector organisations to accelerate development, production, and equitable access to new COVID-19 diagnostics, therapeutics, and vaccines. The vaccine pillar of ACT accelerator is also referred to as COVAX.

COVAX has three workstreams including the development and manufacturing of vaccines coordinated by CEPI, procurement and delivery at scale of those vaccines coordinated by GAVI, and policy and allocation led by WHO. The five functional groups included in the developing and manufacturing workstream of COVAX include the following:

- Research, Development, and Manufacturing (R&D&M) Investment Committee which manages the allocation of funds for (R&D) vaccine development and manufacture;
- Technical Review Committee which oversees and progresses development and manufacturing support across Vaccine teams and SWAT teams;
- Vaccine teams which consist of COVAX and vaccine developer representatives;
- SWAT teams which answer specific, critical, cross-developer questions at speed to accelerate COVID-19 vaccine development and manufacturing;
- Regulatory Advisory Group (RAG; co-led by CEPI and WHO) which consists of COVAX representatives and representatives of key regulatory agencies including WHO and discusses, answers, and feeds back questions raised by Vaccine or SWAT teams.

Three SWAT teams have been established to address developers' needs. The first addresses enabling sciences (i.e. animal models, diagnostics, standards, assay validation), the second addresses clinical development and operations, and the third addresses manufacturing (i.e. manufacturing capacity). The clinical development and operations SWAT team have identified three main areas they would like to address and support developers with, including clinical-operational readiness (e.g. trial sites, landscape analysis), vaccine safety (e.g. case definitions for adverse events of special interest [AESIs] and vaccine mediated enhanced disease [VMED]), and clinical science (e.g. adaptive trial design, correlate of protection in clinical trials).

Overview of COVID-19 Vaccine Safety Initiatives – Connecting the Dots

Dr Emer Cooke from WHO provided an overview of COVID-19 vaccine safety initiatives. WHO has been working very closely with regulators across the globe since the start of the

pandemic, within all three pillars (diagnostics, treatments, and vaccines) of the ACT accelerator, to support regulatory issues, facilitate harmonisation and preparedness, and collaborate to provide a platform for rapid exchange of information. It aims to promote regulatory alignment to facilitate access to quality, safe, and effective products as quickly as possible. A summary of on-going WHO COVID-related regulatory activities are listed as follows with some initiatives described in further detail below:

- Issuing Emergency Use Listing (EML) for in vitro diagnostics and preparing EUL for medicines and vaccines, plus risk assessment for medicines;
- Working hand-in-hand with R&D Blueprint and providing guidance on ACT accelerator workstreams;
- Highlighting key technical guidelines for manufacturing;
- Developing guidance and questions & answers for manufacturing, inspection, and testing during COVID-19;
- Close communication with regulators and regulatory networks through regular meetings;
- Providing up-to-date regulatory-focused information by issuing regulatory update newsletters;
- Conducting adverse events analysis on potential treatments to mitigate safety issues;
- Issuing safety alerts on COVID-related substandard and falsified medical products;
- Increasing post-market surveillance in low- and middle-income countries (LMICs);
- Developing best practice guidance (regulatory agility);
- Developing guidance and implementation manuals for COVID-19 vaccine safety work at global, regional, and national levels;
- Assisting work of medical devices, supply-chain, and shortages.

Dr Cooke emphasized that this is an unprecedented time in vaccine development with new platforms, new actors, developers, and companies, and different target populations (i.e. not childhood immunisation). Thus, the topic of vaccine safety has never been more important and alignment from clinical trial phase to post deployment is essential. WHO is launching the Solidarity Vaccine trial to ensure awareness and involvement of regulators. Some guidance has been developed within the guidance framework to help developers of vaccines against COVID-19, including Food and Drug Administration (FDA) guidance on “Development and licensure of vaccines to prevent COVID-19” and a revision of WHO guidance on DNA vaccines. Points to consider on mRNA vaccines are being developed by WHO.

WHO has a time-limited, special procedure called an EUL to evaluate medical products for use during public health emergencies. It is a risk benefit assessment based on pre-specified eligibility criteria and an essential set of available quality, safety, and immunogenicity/efficacy data and programmatic aspects (e.g. cold chain provisions). EUL is used for United Nations procurement decision-making and to support highly impacted countries in their regulatory decision making. The submission must include post monitoring provisions for quality, programmatic and safety/effectiveness.

The RAG, co-led by CEPI and WHO, provides product agnostic advice on specific issues to support the work of the SWAT. In addition, regulatory preparedness and guidance work has been identified as a cross cutting topic. This group, led by WHO, looks at regulatory preparedness and product specific work and provides regulatory guidance and explanations, supports regulatory preparedness (including safety), and performs product specific work (WHO only). This internal WHO group meets on a weekly basis and provides updates to CEPI and GAVI on a regular basis.

Three components will inform countries to formulate the in-country vaccination strategy. These include:

- Strategic Advisory Group of Experts (SAGE), a WHO committee that provides guidance and policy advice on specific candidates (e.g. on vaccination strategies);
- Regulatory, safety and monitoring activities which provides guidance on regulatory issues, safety, and monitoring;
- Allocation framework which sets the frame for overarching public health goals and priorities (candidate independent).

Countries are responsible for the final decision on in-country policy, allocation, and vaccination strategy.

The current safety work of WHO includes deliverables related to product related safety and pharmacovigilance, prerequisites for vaccine safety preparedness, AESIs, and safety communications. In terms of product related safety and pharmacovigilance, specific monitoring requirements will be part of each clinical trial approval and RMPs will be required for each as part of any emergency or other authorization. WHO is also developing product-specific roadmaps, which outline the regulatory pathways and safety monitoring expectations for specific products, in order to be prepared for product-related work. In terms of prerequisites for vaccine safety preparedness, WHO is working on providing guidance to countries and regions about vaccine safety preparedness, including RMPs in authorisations, aligning vaccine safety preparedness, and helping with decision making tools. WHO is involved in work on AESI via their Global Advisory Committee on Vaccine Safety (GACVS) and is developing a roadmap for safety communication including input from behavioural psychologists and with clear responsibilities/role of national regulatory authorities (NRAs).

A dedicated meeting of GACVS was held on 27-28 May to help with preparation for roll out of COVID-19 vaccines. Four main aspects were considered including challenges specific to vaccine safety monitoring particularly in LMICs, systems and capacity required (LMICs) to monitor, assess, and manage known and unknown AEFI in context of COVID-19 vaccines, the elements of a pharmacovigilance preparedness workplan for LMICs ahead of COVID-19 vaccine roll-out, and the proposed approach and roadmap for COVID-19 vaccine risk/benefit communication. The WHO has established four working groups post-GACVS to provide guidance to countries and regions on prerequisites for vaccine safety preparedness that could be adapted to local country contexts as part of vaccine introduction plans.

The WHO is an observer to International Coalition of Medicines Regulatory Authorities (ICMRA) activities which include hosting a technical expert workshop on real world data and observational studies, developing international cohorts, developing pregnancy cohorts, pharmacovigilance network set up to share best practice, methods, plans for pharmacovigilance of COVID-19 vaccines.

Finally, the evaluation of COVID-19 vaccine safety is one of the primary objectives of the WHO Solidarity Vaccine Trial. Safety monitoring will be continuous at all sites, serious adverse events will be monitored and reported at any time after vaccination (by baseline SARS-CoV-2 serostatus where available), AESIs, as required, will be reported by investigators and monitored by the Data Monitoring Committee, and safety monitoring will also consider the possibility that some vaccines may “enhance” the incidence or severity of disease.

Workshop Objectives

Dr Ajoke Sobanjo-ter Meulen emphasized the primary aim of the workshop was to focus on the developer perspective and identify topics/themes of high importance to developers with regards to vaccine safety. Specific objectives include:

- To identify developer needs for meeting global COVID-19 vaccine safety requirements;
- To identify what is needed for licensure and RMPs, both individually and systematically;
- To identify potential key cross-cutting safety issues;
- To gain perspective on potential solutions that COVAX may address following this meeting.

Key Background Presentation: COVID-19 Safety

Dr Kathryn Edwards discussed lessons learned from AEFIs during development of previous vaccines, and how these might relate to COVID-19 vaccine safety.

A head-to-head safety and immunogenicity study comparing 13 acellular and two whole cell pertussis vaccines showed that safety profiles in terms of fever with acellular vaccines were considerably and significantly less than for whole cell vaccines, and more fever was evident with each successive vaccine than with the first. In addition, entire leg swelling >50mm was noted after the fourth and fifth dose with a number of the vaccines. This emphasizes the need to follow the reaction profiles if booster doses are required as the full safety profile might not be evident with the primary vaccination series. Studies of Rotashield rotavirus vaccine and intussusception confirmed the need for a large sample size to study an uncommon event. Low persistence of neutralising antibodies was evident following inactivated measles vaccine resulting in children acquiring measles 5-6 years post-immunisation. A concentration of rash was evident on the right gluteal region, believed to be the site of inactivated measles virus vaccine injection, in these children with some also developing pneumonia. The pathogenesis of this reaction was immune-mediated and suggested non-neutralising antibody that had waned in the five years since vaccine administration was associated with an immune-mediated adverse event. Dengue vaccine studies reported that individuals seronegative for antibody against dengue prior to vaccine administration had an increased rate of hospitalisation and severe dengue disease. This was the result of incomplete neutralisation of the virus with enhanced uptake of sub-optimally optimised particles. Finally, post-licensure studies of H1N1 pandemic vaccine have shown the importance of comprehensive investigation if an adverse event occurs following vaccination. Concurrent infections were detected in patients with neurological illness (e.g. Guillain Barre syndrome) following H1N1 vaccine.

Dr Edwards concluded that vaccine safety must be meticulously assessed as AEFIs do occur. The frequency and potential immune mechanisms associated with AEFI need to be carefully assessed, and background rates of adverse events without vaccination should be determined and compared with rates seen with vaccination. Post-licensure safety assessments will be important to evaluate rare adverse events as well as the possibility of enhanced disease following vaccination.

Review of Results from Developers Needs Survey & Guided Discussion about Specific Needs / Other Concerns

Overview of developer survey

Dr Sobanjo-ter Meulen set the scene for discussions on developer needs by presenting the results of the Developer Needs Survey. The aim was to collect information on developer needs to inform priorities for the Vaccine Safety Working Group and other organisations. High-level topics covered in the survey included experience with vaccine safety topics in the development of novel vaccines, regulatory authorities that developers plan to submit licensure for, COVID-19 vaccines in development (development stage, vaccine constructs, adjuvants), and vaccine development milestones where external guidance is most needed. The survey was sent to developers in advanced Covid-19 vaccine development and other stakeholders including Product Development Partners (PDP), International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and Developing Countries Vaccine Manufacturers Network (DCVMN) representatives, and WHO.

The majority (n=24/29, 82.8%) of survey respondents worked for a vaccine developer. Overall, there was an average level of experience (range 3.0 to 4.1 where 1 is no experience and 5 is significant experience) in licensure applications and RMPs across developers (PDP/other, developers who have never licensed a vaccine before, and developers who have licensed a vaccine) with minor variation. Experience with post-licensure safety and the pre-qualification process varied between developers and related directly to prior experience with licensing vaccines. Developers, even those with previous licensure experience, report a paucity of experience in overall vaccine safety and pharmacovigilance in LMICs.

Of developers who took the survey, 37.5% (n=9/24), 33.3% (n=8/24), and 29.2% (n=7/24) reported their organisation was a member of IFPMA, DCVMN, or neither, respectively. Approximately one third of developers (n=9/24, 37.5%) belonged to an organisation that had previously licensed a vaccine; almost two-thirds (n=15/24, 62.5%) had no previous experience of vaccine licensure. Around half of developers plan to submit licensure for their COVID-19 vaccine(s) in development to either FDA (n=11/24, 45.8%) or European Medicines Agency (EMA; n=14/24, 58.3%) with a quarter submitting to the Chinese FDA (n=6/24, 25%). Over half of developers have more than one COVID-19 vaccine in their portfolio with about a third of respondents developing two candidates. Nucleic acid and subunit/protein vaccines are the most common constructs. All stages of vaccine development are represented; however, most vaccines are in pre-clinical and early stage clinical development. Of those developers with a vaccine that is in Phase III clinical trials, the majority have started working on a RMP.

Key points from the general discussion included:

- Developers reported that discussions had commenced with the IFPMA, but not the DCVMN, regarding relevant information and interactions on COVID-19 vaccine safety they would like to receive/participate in from the IFPMA/DCVMN networks, including their respective pharmacovigilance working groups.
- The DCVMN Pharmacovigilance Working Group has discussed possible contributions of the DCVMN network. It aims to support all DCVMN members that work with COVID-19 vaccines and to develop a harmonised/standardised plan to enable the sharing of information and experience between members. This was also

highlighted to be important within IFPMA, as was the connection between the two networks.

- The value of company subgroups based on their vaccine's construct (e.g. subunit, nucleic acid, etc.) for safety information sharing (including safety surveillance) was highlighted. These subgroups should include all stakeholders (manufacturers, regulatory, academia, mixed private/public groups). Input from different areas will contribute toward a global plan and sharing experience.
- The importance of “big pharma” supporting or sharing best practices with smaller companies that are members of the DCVMN, and vice versa, was highlighted.
- Developers pointed out the importance of understanding the expectations for safety monitoring and how to pragmatically set out to ensure safe and effective use. This will clearly depend on national expectation and the available infrastructure but will be highly complex with the possibility of multiple new vaccines going live in each country. Thus, more of an insight into these issues would enable planning to ensure safe and effective vaccine use.
- The need to recognise the role of social media in vaccine hesitancy was mentioned. A safety signal from one vaccine candidate may influence the acceptance of all vaccine types. Thus, this is an issue for all developers. Safety signals need to be identified promptly but adverse events in the control group also need to be captured and shared. Robust data on the epidemiological baseline is essential to enable interpretation of safety signals. In addition, knowledge of how adverse events following natural infection differ to adverse events in the vaccine group is important.
- The requirement by local regulatory agencies for developers to perform some type of evaluation effectiveness or acquire more data on specific target groups in the post-market period was discussed. It was suggested that potential requirements by local regulatory agencies be discussed between big companies and members of the DCVMN with the aim to harmonise how these post-market requirements are dealt with.
- Some trials of a COVID-19 vaccine will still be ongoing when the product is in emergency use. Concern was raised about how to deal with the emergence of a safety signal during emergency use.
- A discrepancy in timing between countries/regulators already requesting core RMP positions but working groups starting later is an important point that needs consideration.

In the survey, developers were asked to rank vaccine safety development milestones where external guidance is most needed. RMP, post-licensure safety survey, and Phase II/III were identified across all groups (all, developers who have previous licensure experience, and developers who have never licensed a vaccine) as areas where support is needed. Developers with no previous licensing experience also identified licensure application as an area where external guidance is needed.

Risk management plan

Developers who have previous licensure experience ranked RMP as the top milestone where external guidance is required whereas developers with no previous licensure experience ranked RMP fourth. Approximately three-quarters (n=21/29, 72.4%) of developers indicated support needs for execution of RMP in LMICs. Over half of survey respondents identified country-specific planning with health authorities/regulators (n=19/29, 65.5%) and identifying pharmacovigilance needs in post-marketing (n=18/29, 62.1%) as specific topics where external guidance is required. Of developers who need external guidance on setting up multidisciplinary teams and safety governance structure (n=12), seven (58.3%) had previous experience with vaccine licensure while three (25%) had never licensed a vaccine before.

Key points from the risk management plan discussion included:

- Before starting an RMP, developers require direction on what core activities (e.g. enhanced passive surveillance, post-marketing effectiveness studies) the major regulators (US, EU) will require in the post-marketing setting. This is to enable development of protocols and infrastructure to deliver these activities and is seen as quite urgent by developers.
- DCVMN members require training/webinars/guidelines/information sharing for the development of a RMP but also need to understand NRA expectations for the post-market period.
- Some companies have yet to do any safety specification of their product which is also an important section in risk management planning.
- Typically, questions regarding RMP are worked out in direct dialogue between sponsors and regulators. Thus, early and ongoing engagement with relevant regulatory authorities is important. An ICMRA workshop held earlier this year considered some approaches to using real world effectiveness data to help answer some of these questions and was suggested as a potential high-level resource for developers.
- Issues around risk management planning should be raised in a number of fora, including RAG (as it includes a number of regulators) and the ICMRA executive committee, to investigate the possibility of developing a new approach and to move away from the regulator by regulator approach. Agreement from companies to share across regulators will be required. With such agreement, a consolidated approach can be developed. WHO will raise this to assess appetite at a global regulatory level.
- If an AESI is identified, it needs to be followed up by an RMP. This can be challenging in a low resource settings (LMICs) particularly if specialised training in terms of working up that adverse event is required. It has been a challenge to track down and monitor spurious safety signals for meningitis vaccine in low resource settings.

Post-licensure safety surveillance

Post-licensure safety surveillance is a high priority topic with the majority of developers/respondents seeking guidance on this. Interestingly, a higher number of

developers with prior licensing experience than without are seeking guidance on post-licensure safety surveillance. Within the post-licensure safety surveillance milestone, external guidance on availability and accuracy of exposure information (n=18/29, 62.1%), Phase IV study design (n=16/29, 55.2%), and pharmacovigilance capacity were the topics developers reported needing most external guidance on.

Key points from the post-licensure safety surveillance discussion included:

- A common concern in LMICs relates to the sharing of adverse event information with the manufacturers. The local FDA/Centre for Disease Control is often reluctant to share adverse event information, particularly regarding a product exported in the international market such as a potential COVID-19 vaccine. Thus, collecting good post-marketing data for useful benefit risk analysis is a challenge that needs to be addressed.
- There are many countries where regulators are enhancing capacity and are already proactively sharing adverse event information with manufacturers for benefit risk analysis. However, in other countries regulatory authorities do not have the knowledge or capacity to share this information and manufacturers are left with little adverse event data, if any, for useful benefit risk analysis. In the international market, sharing adverse event information between business partners or to WHO is a huge challenge.
- WHO will consider how sharing of adverse event information between regulators and manufacturers can be encouraged and what frameworks can be used. This will require looking across the manufacturers, regulators, and immunisation systems.

Phase II/III

Within the Phase II/III milestone, 51.7% (n=15/29) and 41.4% (n=12/29) of respondents indicated they need external guidance on the monitoring of vaccine-associated immune-mediated enhanced disease (VAED) and AEFI, respectively. In addition, developers identified other specific topics where external guidance is needed ranging from clinical data assessment and management issues to assay development.

Key points from the Phase II/III discussion included:

- Developers with no previous licensure experience did not consider multidisciplinary vaccine safety monitoring teams important. These teams are particularly important in Phase II/III to detect safety issues and can be discussed in DCVMN pharmacovigilance working groups.
- Text message-based reporting was suggested as a possible way to report adverse events, particularly in LMICs where reporting from healthcare providers is likely to overwhelm many healthcare systems given the volume of vaccine administration. Experience of text message-based adverse event reporting in a recent COVID-19 vaccine study and from trials in Africa shows that this method works well and can be used in developing countries. The Brighton Collaboration is in the process of forming

a working group for standardising digital vaccine safety data collection and can soon provide advice in this domain.

- Developers are not readily able to access study protocols including granular detail of operational approaches for safety data collection in the setting of a pandemic. Protocols from ongoing studies are already on their fourth, fifth or sixth round of amendments, learnings have been incorporated, and data collection is improving; however, these are not public documents. A generic protocol developed by PATH is in the public domain and includes some description of safety follow-up including enhanced disease. This protocol is accompanied by a form where developers can add their comments and lessons learnt. The protocol will then be updated accordingly by PATH and made available to developers (<https://www.protocols.io/view/collection-of-protocols-and-guidelines-for-phase-3-bj5pkq5n>).
- Developers currently in clinical trials/those trying to operationalise these studies were encouraged to share experiences/learnings of what is going on in the field and the unique aspects of doing safety data collection in the setting of a pandemic. Access to protocols including disease outcome or safety endpoint definitions, data collection methodology, time windows around outcome definitions, etc. should be non-competitive, standardisable, and shared.

Licensure application

Over half of respondents indicated they need external guidance on FDA (n=15/29, 51.7%) and EMA (n=15/29, 51.7%) requirements within the licensure application milestone. Other topics within the licensure application milestone where respondents need external guidance include clarity on regulatory pathway(s) for emergency use, needs of NRAs in LMICs (in contrast to FDA and EMA), and guidance on submission in LMICs.

Key points from the licensure application discussion included:

- As a third of developers are submitting to the Chinese FDA, so establishing connections/links would be important.
- The issue of co-administration of adjuvanted vaccines, such as COVID-19 and influenza, was raised. There is a knowledge gap in this area at present as efforts are focused on Phase III vaccine development, thus no recommendations regarding coadministration are available. There is concern about prioritisation given uncertainties about the potential side effects of co-administration or the potential impact on COVID-19 vaccine efficacy if it is co-administered. Uncertainty in the perception of risk could have a negative impact on vaccination in general.
- Several companies have used the EMA Article 58 on scientific advice to facilitate WHO prequalification/registration and feedback has been variable. Experiences should be shared to enable companies to learn from each other. It was noted that Article 58 is really intended for products which would not be commercialised in Europe.

WHO prequalification

Within the WHO prequalification milestone, almost three-quarters (n=21/29, 72.4%) of respondents need external guidance on expedited review versus the full approval process. Almost half (n=14/29, 48.3%) of respondents need guidance on the overall process and about a third (n=10/29, 34.5%) need guidance on the preparation of a product summary file. Some additional topics identified include response to WHO questions/concerns, and process and expectations around emergency use.

Key points from the WHO prequalification discussion included:

- With regards to a potential COVID-19 vaccine, WHO is waiting to see if there is sufficient information for prequalification; however, it might be more likely to be EUL. The outcome from a review by a stringent regulatory authority can be used to expedite or do an abridged process. With vaccines that look likely to be successful, WHO will work on a specific roadmap with the developer and regulatory authorities to see how both the EUL or prequalification could be expedited and regulatory approval obtained in countries wanting to use this vaccine. This would be done with the agreement of the manufacturer and regulatory authorities concerned. For the Merck Ebola vaccine, WHO in collaboration with the EMA, involved African regulators in the process, organised a specific workshop to address all questions, and obtained commitment from regulators to use the reliance process for their own reviews. A variation on this will help obtain EUL or prequalification of a promising COVID-19 vaccine.
- Clarification was provided on when prequalification (if there is licensure by the regulatory authority) rather than an EUL (if there is another form of authorisation such as emergency use authorisation) might be appropriate.
- WHO encouraged developers to contact the WHO for help with the prequalification process and for clarification about expectations and timelines. This can be done on a product by product basis. A specific webinar may be provided depending on developer need, but a pre-submission meeting with the WHO prequalification team is likely to be more helpful.
- Transition from EUL to WHO prequalification was discussed. EUL is based on a more limited set of data than prequalification and is likely before any licensure by a stringent regulatory agency. Once there is sufficient data for full licensure, the company is expected to move to full prequalification.

First-in-human

Survey respondents identified choice of animal models (n=13/29, 44.8%), clinical de-risking of vaccine platform/adjuvant (n=8/29, %), and toxicology studies (n=7/29, %) as specific topics they need external guidance on within the first-in-human milestone. Other specific topics identified where guidance is needed include non-human primate and human challenge, how to identify safety concerns in preclinical data, and clinical trial design.

Key points from the first-in-human discussion included:

- The primary issue of concern is the transition from pre-clinical to clinical and the interpretation of safety concerns identified in pre-clinical stage, particularly the use of non-human primate model or considerations around human challenge models in the future. This is a regulatory topic with regards to requirement expectations; there may be candidate-specific and/or vaccine construct platform-specific expectations as to what pre-clinical data and animal model data need to be included in the submission to the regulatory agency to enable entry to first-in-human.
- No companies are known to be actively pursuing human challenge studies at present.
- A discussion ensued of how confident companies are in results from non-human primate studies with regards to enhanced disease. Non-human primate studies thus far have been relatively limited with very short follow-up, and there is concern that studies may require longer follow-up to detect vaccine-enhanced disease. Participants questioned how developers considering moving into first-in-human reassured themselves that vaccine-enhanced disease is not going to be an issue with their vaccine at a later date in the absence of a standardised animal protocol for assessing this.
- Any human challenge model including Good Manufacturing Practices-conformed strains is not expected to be in place within the next 8-12 months. Thus, this would come too late for early stage assessments. Generally healthy adults will be included in these trials and not necessarily the target population or population at risk for COVID-19 disease. Thus, the role of human challenge studies is still under debate and it is not yet clear what role these models might play in vaccine development.

Communication plan

Survey respondents identified communicating benefit/risk profile to stakeholders (n=21/29, 72.4%), addressing vaccine hesitancy (n=18/29, 62.1%), and vaccine labelling (n=11/29, 37.9%) as specific topics within the communication plan milestone where external guidance is needed. Crisis management was identified as an additional topic where guidance is required.

Key points from the communication plan discussion included:

- If manufacturers, developers, public health units, or regulators develop communications in their silos, there is the potential to potentiate rather than clarify issues around vaccine hesitancy. Development of a communication framework (that is above regulators or manufacturers) was suggested. This could be in the form of a communication education strategy prior to the availability of vaccines explaining what a vaccine is, its purpose, and types of vaccines. In addition to a general high-level safety communication, harmonisation of safety labels for respective vaccine constructs in the post-marketing setting was suggested.
- Development of a general high-level safety communication could potentially be supported by the Vaccine Safety Communications Working Group at WHO. A science guide to vaccine safety communication, which is embedded into the global vaccine safety initiative led by WHO, includes content on education and preparedness of the

field in terms of vaccination and is a good start. However, capacity is limited in LMICs and even if a regulator or national immunisation centre is asked to educate with regards to vaccination, manufacturers are often asked to help and at least provide the content. Thus, a partnership is required particularly in low resource settings.

- There is a need for rapid worldwide coordination on safety issues given the speed that safety rumours can spread across countries via social media. Any safety rumour on social media, irrespective of the type of vaccine it relates to, will have an impact on the other vaccine types. Coordination of vaccine communication should be in crisis mode to enable rapid response and not to jeopardise vaccination campaigns.
- Safety data from the control group of all Phase I, II, and III trials should be collated to enable a more robust estimate of the occurrence rate of an adverse event in the control group and thus better interpretation of an adverse event in the vaccine group. However, concern was raised about how to communicate this to the public in a comprehensible way as communicating information about background rates will be too late when adverse events have already started to occur in the post-marketing phase.
- Education prior to the availability of vaccines will enable the public to better understand communications about vaccine safety that are distributed later with the availability of post-marketing data.
- Communication regarding the safety of a specific vaccine is better coming from WHO and other global agencies that do not have a vested interest in one particular company or vaccine.
- It is important to be transparent to the public about AESIs, explaining that data are imperfect, take time to collect, and will evolve but information will be communicated as it is known.
- Vaccine hesitancy is not a single phenomenon and aetiologies vary between regions and groups. This needs to be considered in efforts to understand and reduce hesitancy.
- Two aspects from the WHO perspective include: 1) getting a communication plan ready and running in countries ahead of the roll out strategy where safety issues are communicated in a balanced way for example through training and media presence, and 2) guarding against misinformation by guiding countries/public to sites with the correct information. There are about 80 websites, representing 40 countries and some 35 languages, accredited by WHO which provides correct information on vaccine safety.
- It is also important to communicate information on the benefit of vaccines and substantial efforts are required in this area.

Cross-Cutting Issues

Given the diverse background of developers, Dr Chen discussed some basics of vaccine safety assessment before describing cross-cutting issues.

The issue of defining causality in vaccine safety is complex. An adverse event preceded in time by a vaccine could be the result of the vaccine or it could be coincidental. Vaccines could be the direct and only cause, one of multiple direct causes, a co-factor/indirect cause, or coincidental in an adverse event. Increasingly complex immunisation schedules with simultaneous vaccinations and high vaccine coverage further complicate the issue of causality (i.e. anyone with any disease has been vaccinated). Different ways of clarifying the causal link between an adverse event and vaccine include unique laboratory result (e.g. sequencing mumps virus in a case of aseptic meningitis and showing it is the vaccine strain), unique clinical syndrome (e.g. young military recruit given small pox vaccine develops pericarditis which otherwise is very rare in a young healthy adult), or by an epidemiological study (or large clinical trial). The latter is the most common method to clarify the causal link between an adverse event and vaccine.

Most countries, especially LMICs, have a basic passive reporting system with data available on people who are vaccinated who have the illness/syndrome. To acquire information on those who have been vaccinated but do not have the illness or those who have not been vaccinated but do have the illness, an alternative data source is required (e.g. computerised health insurance database or HDSS databases where vaccination records can be linked to health outcomes and covariates including patient characteristics). These data can also be collected manually but is laborious. The example of rotavirus vaccine and intussusception, where validation studies used a common protocol, is an example of successful pharmacovigilance and a model for COVID-19 whereas narcolepsy following 2009 Pandemrix vaccine is an example of unsuccessful pharmacovigilance where the right data systems were not in place and is to be avoided with COVID-19.

Potential cross-cutting COVID-19 vaccine safety assessment issues include:

- Access to limited post-introduction active surveillance pharmacovigilance capacity for regulator mandated studies;
- Comparison of safety data (overall, by sub-population) in the absence of a head-to-head trial and who will perform the comparison;
- Willingness to contribute data to allow evaluation of safety data on similar new technology platforms across different candidates;
- Since each candidate vaccine will likely be introduced in multiple countries, collating information across countries (including timing of denominator doses administered by location, lot, etc.) in a timely and meaningful way;
- Tracking of vaccine exposure information so if an AEFI occurs, it can be linked accurately, timely, and efficiently;
- Willingness to contribute data to harmonised follow-up studies of vaccine-associated enhanced disease and feasibility of registry for COVID-19 trial placebo recipients who remain unvaccinated;
- Plans for obtaining and using background rates of AEFI and AESI for post introduction studies;
- Process for formally declaring a “safety signal” and how this information will be shared/action plan if this should occur.

Key points from the cross-cutting issues discussion included:

- Real time knowledge of the number of vaccine doses administered by age and gender is critical for the assessment of a potential safety signal. An expectation during the H1N1 pandemic was that manufacturers had access to this information; however, this was not the case and manufacturers were only aware of the total number of doses provided or sold to a particular country. This highlights the need to collaborate with public health institutes or other organisations that do have access. Healthcare databases where manufacturers can potentially access these data are available in the US/Europe; however, these data may not be updated in real time.

Key Takeaways

Dr Steve Black summarised the key takeaways from the workshop as follows:

- Developer needs differ depending on their prior (licensing) experience;
- The top three areas ranked across all developers are: Risk management plan development; Post-licensure safety surveillance; Phase II/III;
- Vaccine safety guidance and support should be tailored to: Specific resource setting; Prior licensing experience; Vaccine platform/adjuvant;
- Several potential cross-cutting safety issues identified;
- Need to establish an information sharing platform across high-income countries and DCVMN developers.

Closing and next steps

Dr Sobanjo-ter Meulen and Dr. Robert Chen thanked attendees for their participation in the workshop and outlined the next steps as follows:

- Meeting report to be shared with workshop participants;
- Continue to map relevant resources to enable assessment of post-licensure safety;
- Discussion in this workshop to inform upcoming WHO workshop on global pharmacovigilance ecosystem;
- COVAX alignment with WHO regarding vaccine safety efforts.