A COVID-19 Vaccine Safety Surveillance Strategy for New Zealand

Framework Proposal for discussion

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Context

The COVID-19 pandemic has caused unprecedented havoc globally, with major impact devastating every aspect of society, health, lifestyle and the economy. Although fundamental public health practices remain core to limiting the spread of the pandemic, the development and use of a vaccine is recognized as critical to a path to increasing stability and eventual achievement of a new normality.

The urgency of the pandemic crisis has given rise to extraordinary initiatives in vaccine development, compressing the usually decades long pathway into months to a year or two. Multiple vaccine strategies are in varying stages of development, some of which already are at the point of early Phase III trials. Whilst this accelerated vaccine development will be able to address and identify vaccine safety issues, the trade-off from this approach will be the forgoing of the truly large-scale robust safety studies that have been undertaken historically. Whilst NZ vaccine licensure will be dependent on positive Phase III clinical trial evidence, these will still not be able to identify rare events, or events that may be confined to individuals or groups that were not well represented in phase III international trials. It is unlikely that any Phase III clinical trials will be undertaken in NZ.

Therefore, it is imperative that a NZ COVID-19 vaccine safety surveillance strategy is put in place to identify safety issues with COVID-19 vaccines in use in the broader population to inform decisions about continued use, or to reassure the population of the safety of the vaccine(s) and that its safety is being closely monitored.

NZ operated a highly successful and comprehensive vaccine safety surveillance strategy for the delivery of the new MeNZB vaccine (the Meningococcal Vaccine Strategy – MVS) over the period 2004-2006/7. This approach garnered international interest and accolade for its robust methodology and ability to support decision making and reassure public safety of the vaccine.[1-3]

Unfortunately, once the epidemic was under control, the infrastructure and institutional knowledge and personnel were disbanded and largely lost. However, the approach has been well documented and some of the personnel with system knowledge and elements of the infrastructure are still available, although some of the personnel perform other roles today. Of importance is that there has been significant progress in NZ in electronic approaches to linked datasets and data analysis which will allow more cost effective and efficient surveillance.

The proven MVS approach provides an ideal template on which to base a COVID-19 Vaccine Safety Surveillance Strategy (*decide an appropriate acronym*), customizing it to account for the current era.

A COVID-19 Vaccine Safety Surveillance Strategy for New Zealand

The purpose of the Safety Surveillance Strategy will be to inform Public Health safety decision making about the safety of COVID-19 vaccine(s), how a vaccine's risk-profile may influence its utilization, including potentially withdrawing a vaccine from further roll-out. Overall, a Safety Surveillance Strategy will also serve to reassure the public that stringent monitoring of vaccines that are in use is being undertaken.

Elements of a COVID-19 Safety Surveillance System:

Passive Reporting of Adverse Events Following Immunisation

Spontaneous Reporting Program

New Zealand has had a long and successful history of Adverse Events Following Immunisation (AEFI) monitoring as a component of its Pharmacovigilance system.[4] This is provided through the Centre for

Adverse Reactions Monitoring (CARM) within the New Zealand Pharmacovigilance Centre (NZPhvC) at the University of Otago, which delivers national pharmacovigilance services for the Ministry of Health. CARM is New Zealand's national centre receiving voluntary reports from health professional and the public of AEFI's, as well as adverse reactions to medicines. The CARM system has been in operation since 1965, is well supported with NZ having one of the highest rates per capita of reporting to national monitoring program globally. Vaccines account for about 40% of all reports to CARM. Reports to CARM are reviewed by specialist clinical assessors and are recorded into a national database. Standardized terms are assigned to the events documented in each report using the World Health Organization (WHO) Adverse Reaction Terminology dictionary structured to group related terms by System Organ Class to facilitate pattern identification. The clinical review further determines the severity, seriousness, outcome and the likelihood of causal association to the vaccine for each report in line with WHO protocols. Co-medications and co-morbidity are also recorded.

Enhanced Spontaneous Reporting

Whilst spontaneous reporting has been the cornerstone of NZ's system for over 50 years with high rates of reporting, particularly for vaccines, enhancing spontaneous reporting in the circumstances of new products where there is limited safety information has been applied successfully to gather more data. During the MeNZB vaccination strategy over 2004-6 reporters were encouraged to lower their threshold for reporting of any adverse event to CARM, resulting in a 2-fold increase in vaccine reports over the previous years that were already the highest by double of the next highest country member (Australia), of the WHO Program for International Drug Monitoring of which NZ was a founding member in 1968. These additional reports of the same high quality clinical case narrative classic of NZ AEFI and Adverse Drug Reaction reports to CARM, provide valuable additional data to inform the safety evaluation of the vaccine and illustrates the commitment of NZ Health Professionals to supporting pharmacovigilance.

Enhanced spontaneous reporting of AEFI's both by providers and the public should be encouraged for COVID-19 vaccines to expand the database to support evaluation of the vaccine's safety profile. Enhanced reporting would require further resourcing utilizing the spectrum of communication channels including social media for promotion and marketing to both vaccinators and vaccinees

Active Monitoring of Adverse Events Following Immunisation

KIWIvax

NZ AEFI monitoring has been passive (i.e. reliant on voluntary reporting) and is subject to underreporting. In addition to underreporting, passive reporting systems are further limited by reporting biases and the lack of denominators.

To overcome this, the NZPhvC, working alongside the Immunization Advisory Centre (IMAC), is in the process of finalising the development of KIWIvax, an automated real time SMS-smartphone-based technology system that will enable the identification of AEFI's directly from vaccinees who are actively followed up after vaccination through a series of simple questions initiated from a post vaccination SMS. KIWIvax consists of a program (SMART vax) loaded onto a Medical Practice's computer system and extracts data from the Practice Management System (PMS). Medtech32 currently accounts for approximately 80% of PMS's in NZ.[5] The data from this interaction auto-populates a database which is analysed by customised software that generates a diversity of reports, graphics or customised queries for the purposes of monitoring safety profile of the vaccines monitored.

The development of KIWIvax has become possible due to collegial collaboration between the NZPhvC and the Australian developers of the innovative SMARTvax/AusVaxSafety system, which has achieved uptake across all Australian States and Territories and shown to be successful in monitoring the safety profile of vaccines used in Australia and also in supporting research projects.[6-8]

SMARTvax/AusVaxSafety has been customised to suit the needs for New Zealand vaccine safety monitoring to become a New Zealand SMARTvax/KIWIvax. This development was initiated and well underway prior to the COVID-19 pandemic to support the monitoring of routine schedule and/or other vaccines in use in New Zealand. It is suited to the monitoring of any vaccine and ideally suited to monitor COVID-19 vaccine(s) that may be brought into use.

This approach, discussed in more detail in Appendix 1, sends an SMS message to the vaccinee extracted from the Practice Management System (PMS) of the medical practice where the vaccination was administered by means of a dedicated SMARTvax software application. Medical Practice approval authorises the loading of the SMARTvax software. The message which is sent 3 days after the vaccination event (for routine vaccines), enquires whether there had been an adverse event of any type after the vaccination by simply requiring a 'Yes' or 'No'. For COVID-19 vaccines the timing of the initial message will be revisited according to the vaccine platform type in use. In the event of a 'Yes', the vaccinee is invited to complete a survey by responding to a series of targeted questions/options about the nature of the AEFI. The system also includes an option to report further details relating to events that are of a more serious nature and enable direct follow-up with the vaccinee to establish further detail. Responses are reported back to the Medical Practice's PMS patient file to facilitate clinical follow-up in the event of an event of concern. The SMARTvax software uploads an anonymized copy of the interaction to a cloud-based database which houses the analytical software that enables reports, graphics and queries to be performed. Since the denominators are known (all SMS's sent – 'Yes', 'No' and non-responses), rates of AEFI events can be determined. The SMARTvax at the time of the Cloud database upload also sends a copy of the interaction to the NZPhvC database which complements passive (spontaneous/voluntary/enhanced) reporting to enable a comprehensive overview of all sources of AEFI's to be performed.

KIWIvax offer advantages in reaching the entire vaccine cohort, supporting the automated population of AEFI databases for analysis and can free-up resources that can then be more usefully directed to follow-up serious, clinically significant or unusual AEFI of concern or interest. More than 80% of NZ'ers own a Smartphone.[9] The KIWIvax system provides opportunities to achieve greater efficiencies in resource utilisation and further improve AEFI surveillance. Utilizing this technology will enable far wider reach than the current modalities of reporting which are limited to the conscious decision to report an AEFI online or to a health provider for onward notification to the NZPhvC.

KIWIvax variation for non-PMS systems

SMARTvax has been designed to operate in a PMS Medical Practice environment in interfacing/interrogating PMS-specific structures and data fields. Vaccines that are administered in other clinical settings (Pharmacy or Community Vaccination Clinics), do not use similar computer bound PMS systems or use cloud based software systems. SMARTvax currently is not compatible with non-computer Patient Management Systems. The Australian developers are in the final stages of designing a variation of the way the SMARTvax component of this system operates for application outside of the typical PMS systems used in medical practices. This system is being designed to operate in the context of pharmacy-based or community vaccination clinics, but with the same SMS interaction feeding the Cloud and NZPhvC database. The NZPhvC collaboration with the Australian developers extends to incorporating an appropriately customised variation of this SMARTvax version in New Zealand. This variation will use the core SMS messaging identical to the PMS version, but likely involve the Pharmacy/Community Vaccination Clinics, or in New Zealand the NIR, notifying the NZPhvC of the vaccination including the vaccinee's mobile contact number. The NZPhvC will house the SMARTvax software and initiate the SMS interaction, receive the responses and upload an anonymized copy to the Cloud database.

Hospital surveillance

The Passive and Active safety surveillance elements are likely to provide early real time safety data that due to their targeted focus beyond traditional routine methods may be considered adequate surveillance for NZ's COVID-19 vaccines monitoring. However, it is possible that some AEFI's may be of sufficient severity/seriousness to result in hospital admission or will require Emergency Department consultation. It may also be possible that the vaccine properties/composition could result in unintended events resulting in hospitalisation, not immediately recognised as vaccine-related, but potentially predicted from the anticipated immune response.

By the time NZ will access COVID-19 vaccines for roll-out it is likely that even with the concerns around accelerated Phase III trials there will have been many tens of thousands of trial participants globally

providing a significant baseline of safety reassurance. This, together with safety surveillance data collectively from other countries accounting for probable substantial uptake of vaccine ahead of NZ will provide a further measure of safety reassurance. Despite this, the accelerated development and safety study windows and the diversity of vaccine platforms, the rapid pandemic deployment into population characteristics and underlying conditions potentially not represented in the trials or roll-out elsewhere requires that NZ undertake additional surveillance of hospital attendances for reassuring the safety of the vaccine(s) in use.

It is critical that vaccinees who are hospitalised in a close temporal window following vaccination (timing/duration dependant on the type of vaccine), or who develop an Adverse Event of Special Interest (AESI), which are a subset of AEFI's of particular concern, are carefully reviewed to determine if the admission event may be related to the vaccine. This will further support the early identification of AEFI's of potential concern.

There is expected to be a resource limitation in being able to review every hospital admission to determine if they had received a COVID-19 vaccine within a close temporal window. Whilst we could consider adopting similar approaches from the MeNZB MVS surveillance strategy of the early 2000's which reviewed every hospital attandance who had received a vaccine within the previous 7 days, there are significant challenges to considering the MeNZB approach in the COVID-19 vaccine context:

- The MeNZB MVS hospital surveillance strategy was a highly resource intensive approach with long lead times to training and preparation and focussed on a considerably smaller cohort of vaccinees (sequential geographic rollout and <19 years) than is expected to be the case for COVID-19 vaccine uptake. This would not be feasible for COVID-19 vaccines
- The MVS approach was confined to 3 major hospitals manually reviewing daily/weekly patients admission notes to determine those that met criteria (age/AESI/unusual events) who were then cross checked with the NIR to identify those who had been vaccinated. The logistics of this for COVID-19 vaccines would be immense.
- Manual review of admission notes was required because an ICD diagnostic code was only assigned on discharge, such that if ICD codes were relied upon for case identification, an event of interest could be missed for days or even weeks.
- Unlike the COVID-19 vaccines, the MeNZB vaccine had by comparison only limited Phase III trials, relying on bridging to similar vaccine trials and rollout of related vaccines in other countries. By the time NZ brings COVID-19 vaccines into NZ use, these vaccines will have substantial Phase III safety data already alongside real-world rollout AEFI knowledge.

The key component of the MeNZB Hospital Surveillance Strategy revolved around analysing the AESI's or unusual events which were laboriously identified with great urgency due to the relative absence of safety data by comparison to COVID-19 vaccine(s). A COVID-19 Hospital Surveillance Strategy can still focus on identifying AESIs as a key component, but be less reliant on absolute real time event identification.

The following components of a Hospital Surveillance Strategy for COVID-19 for NZ are possible:

Defining Adverse Events of Special Interest (AESI)

Global initiatives are currently underway to identify AESI's and their associated case definitions. The CEPI organisation (Coalition for Epidemic Preparedness Innovation) has contracted the international Brighton Collaboration to harmonize the safety assessment of COVID-19 vaccines via its Safety Platform for Emergency Vaccines (SPEAC) project.[10] New Zealand vaccinologists are participating in this process, including through the Global Vaccine Safety Data Network project. The current list of AESI's, case definitions and related resources developed to date are included in Appendix 2. This list is likely to be dynamic with the most current list/case definitions expected to be applied in analyses pertaining to AESI's. This list is expected to be a baseline standardised list that NZ surveillance will actively monitor. Historical/background levels of AESI's provide an important baseline from which to determine if vaccine-related AESI's contributes excess risk and is an activity that should be initiated in NZ. The WHO Global Advisory Committee on Vaccine Safety have called for countries to prepare baseline rates of AESIs prior to deploying COVID-19 vaccines.

It will be important to ensure that the definitions of the AESI's can be matched against relevant ICD discharge codes or ICD code groups to enable interrogation to extract cases that meet the AESI definition. An appropriate validation project should be completed to reassure that appropriate ICD codes can be identified to support AESI case extraction.

Establishing historical baselines for AESIs

NZ can utilise the international list of AESIs to set up a monitoring system prior to the entry of vaccines in the country so there is an established historical baseline of population prevalence of these defined events.

Hospital Surveillance Focal Areas

Hospitalisation due to Adverse Events of Special Interest

All hospital attendances that result in an ICD code(s) that aligns with an AESI and regardless of the patient's vaccination status should be identified to support analytical comparisons of observed events against expected/historical levels and between vaccinated and unvaccinated individuals to identify excess events potentially attributable to COVID-19 vaccination. A system supporting rapid regular review/analysis (e.g. weekly/monthly) should be developed and implemented.

Capturing all potential hospital attendances with Adverse Events of Special Interest

Since ICD codes are only assigned on discharge, knowledge of AESI definitions should be promoted amongst clinicians who should be encouraged to identify patients who meet these definitions and that the discharge system ensures that an accurate ICD code is expeditiously assigned. A mechanism for identifying patients who are admitted and managed as a possible AESI, but not yet discharged should be established to include these patients in analyses of Hospital AESI;'s who might otherwise only be identified much later.

Hospitalisation due to other serious and/or unusual events

Clinicians should be encouraged to identify any serious and/or unusual events in vaccine recipients that may help to inform new AESI's. Cases with these criteria should be reviewed to determine the presence of excess numbers, unusual demographic distribution, or an unusual clinical picture.

Mortality monitoring

In order to further support the identification of all possible clinical outcomes of a serious nature that may represent a potential association with the COVID-19 vaccine(s), close to real-time, review of the Mortality Register will be a useful activity. A mechanism should be established to enable NHI data linkage from the National Immunisation Register with the Mortality Register to identify through electronic matching, those deaths that have occurred within 90 days following COVID-19 vaccination.

A weekly/monthly review of the matches should be reviewed by personnel with appropriate expertise and advising those matches with AESI's to an appropriately constituted Mortality/Clinical Review Committee that should be established. The Mortality Review Committee's role will be to determine the presence of a potential pattern of association with vaccination, with reports of any findings of an association to be added to the review of other safety findings.

Vaccine safety surveillance oversight and coordination

In order to provide oversight and coordination across the diverse safety surveillance components, the following structures are proposed: (Figure 1)

COVID-19 Vaccine Safety Surveillance Group

As Medsafe is the Regulatory body within the Ministry of Health legislated to regulate medicines (including vaccines) which embraces safety aspects, there should be an appropriately skilled and resourced group within Medsafe to provide leadership and coordination of the activities and components specific to supporting vaccine safety surveillance elements/components. This COVID Vaccine Safety Surveillance Group should ensure that networks with and access to people with

appropriate skills and expertise are established within the Ministry of Health and/or nationally to support its work. These diverse areas include Public Health/Infectious diseases, Epidemiology, Biostatistics, Database management & analysis, Project management, Training of health personnel (to support surveillance elements), Networking and Communication. Access to expertise and expert advice in Clinical Medicine, Rare diseases, Immunology/Vaccinology or other disciplines of importance to support analysis and review activities will also be required.

This group should serve as the hub towards which all relevant safety data is directed to and accumulated to support analyses that will be used to inform findings of and advice in regard to the safety of COVID-19 vaccines in use in New Zealand to support decision making and communication.

This group will interface with other relevant groups such as the newly constituted COVID-19 Strategy TAG, COVID-19 Vaccine Strategy Group, Science and Technical Advisory Group (STAG), COVID -19 Vaccine Implementation Task Group and the Immunisation Program.

Analytical methods

Whilst descriptive statistics and frequentist approaches are likely to be key methods of characterising the vaccinated population and associated AEFI's/AESI's, strategies such as illustrating observed versus expected numbers of events and risk interval analyses/person-time-at-risk and any other analytical approach is expected. Collaboration with international partners to ensure harmonisation of methods will be important.

Data analysis, Networking and Reporting

Opportunity should be sought within the data management and analytical activities of the group to network and/or collaborate with other experts, individuals or groups in order to strengthen the ability to ensure that all opportunities are utilised to identify issues of safety concern and provide appropriate communication. Expertise from within the New Zealand will include academics/research groups in epidemiology, pharmacoepidemiology, vaccinology, as well as expertise in Immunisation Advisory Centre (IMAC), the ESR. These groups may provide support in communication or undertake independent, complimentary or collaborative research. Regular reports and updates on findings should be produced supporting the science findings from surveillance. These reports also add evidence of transparency and reassure public safety on the findings and rigour of the surveillance system.

International collaboration

Since all countries will be focused on identifying safety issues of concern of the COVID-19 vaccine and many other countries, groups and initiatives are underway, there will be beneficial advantage through networking to identify and/or share findings. Opportunities and mechanisms to engage in collaboration should be actively encouraged. Trans-Tasman collaboration offers advantages due to the existing collegial connections, further strengthened through the use in New Zealand of SMARTvax/KIWIvax, an NZ customised version of the Australian SMARTvax/AusVaxSafety, provides an ideal platform to share/compare data using an almost identical approach. Other international groups include the Global Vaccine Data Network (GVDN), which is co-directed and coordinated from New Zealand as the host country. The GVDN has 17 partner countries across the globe whose focus includes the development of common data models as well as the collective expertise of many of the world's foremost experts in vaccine safety and vaccine pharmacoepidemiology. NZ should also explore collegial relationships with other research groups and initiatives in other countries including the Coalition for Epidemic Preparedness Innovations (CEPI).[11]

MARC – Providing Vaccine Safety Oversight

There is distinct advantage in utilising a group that is outside of Government such as the Medicines Adverse Reactions Committee (MARC) to provide vaccine safety oversight and advice for the new-to-NZ COVID-19 vaccine(s) that will be used on wide scale in NZ. This is especially important in the context of the rapid development and clinical trial processes for the COVID-19 and the need to reassure the NZ public and those that are vaccine hesitant that there is an objective scientific review of the safety evidence of the COVID-19 vaccines that is independent of Government and political influence. MARC is constituted with experts in diverse clinical fields providing advice to Medsafe based on clinical evaluation of safety information presented to it for consideration. It may be appropriate to enhance the spectrum of expert advisors to MARC to specifically support COVID-19 vaccine review for the duration that this may be necessary. This group can review all safety-related surveillance data, request data and provide expert independent advice on the safety of COVID-19 vaccines in use, including the ability to recommend the suspension of any vaccine in use should its findings identify issues of sufficient gravity to warrant such an action to avoid excess vaccine-associated morbidity of concern or morality.

COVID-19 Vaccine Clinical Review Group

It will be essential to have access to clinical expertise to support the review of complex, serious or severe AEFI and those AESI that are attributed to COVID-19 vaccination to determine or asses their causal association to inform vaccine safety evaluation decision-making and advice. Currently a group with such a function for vaccines in current use exists – an informally constituted group of clinicians, pharmacovigilance and regulatory personnel - the Vaccine Safety Expert Advisory Group (VSEAG). This group of peers provides a forum for consideration and discussion of cases of clinical importance, or complexity, their potential further investigation or management, causal association and implications for the vaccinee or use of the vaccine. For COVID-19 vaccines, due to their new technology platforms and COVID-19 disease profiles, an appropriate group should be established, which could include supplementing the VSEAG and formalising it, or establishing a new dedicated COVID-19 Clinical Review Group.

Supporting Pacific Island Neighbours

Whilst the focus of a COVID-19 Vaccine Safety Surveillance Strategy is targeted on developing and implementing a system to ensure the safe use of new vaccines for New Zealanders, our Pacific Island neighbours have less well developed and resourced health systems. Consequently, they may be less able to establish a vaccine safety surveillance system. NZ has expressed its commitment to support access to COVID-19 vaccines for the South Pacific[12] and hence there is a high likelihood that the same or similar COVID-19 vaccines will be delivered to our Pacific neighbours. NZ would be in a good position to assist or facilitate Pacific Island Countries in their vaccine safety surveillance, with use of many of the suggested approaches listed above.

This could be COVID-19 Vaccine Safety Surveillance-specific, or form part of a wider initiative around Medicine Security, including some existing early initiatives on strengthening Pharmacovigilance of Vaccines in Immunisation Programmes and/or Medicines used in these countries. Collaboration with the WHO's Western Pacific Regional Office and its networks should also be encouraged to ensure that any NZ vaccine safety surveillance contribution is complementary to and in alignment with Regional strategies.

The NZPhvC/Otago University has been invited to participate in recent WHO Western Pacific Regional Office (WHO-WPRO) National Regulatory Authority (NRA) workshops since 2018 on Health Systems Strengthening initiatives for the region with special focus on the Pacific Island Countries. A Concept Proposal on Strengthening Pharmacovigilance Systems as a component in support of broader Medicines regulatory Strengthening has gained the interest of WHO-WPRO, Pacific Island Countries (PIC) and MFAT. The NZPhvC/Otago University was invited to present a concept proposal for COVID-19 Vaccine Safety Surveillance for the PIC's at a September 2020 WHO-WPRO NRA meeting. This proposal centered around introducing and establishing Passive Monitoring systems with the support of NZ expertise in Pharmacovigilance/ Vaccine Safety Surveillance based on the model of Health Systems Strengthening

proposal referred to earlier. WHO-WPRO has arranged meetings, workshops and possible implementation strategies and pathways scheduled for November 2020. Through this initiative a pathway to support PIC's and further inform Regional and Global knowledge on the safety of COVOD-19 vaccines will have been established.

Critical Practical Considerations for Developing a COVID-19 Vaccine Safety Surveillance Strategy

- Lead times and infrastructural obstacles

  The MeNZB MVS setting-up in the early 2000's illustrated that long lead times were required to develop and implement its operational components. This was partly due to its novel nature and complexity of establishing the components, but also due to inefficiencies in inter departmental co-operation as well as in resolving legislative and regulatory obstacles to enable the implementation of systems. Initiatives for developing and finalising a NZ COVID-19 Vaccine Safety Surveillance Strategy therefore need to commence urgently to allow sufficient time to address challenges that will inevitably present.

- Adequate resourcing

  The elements presented in this proposal, or any COVID-19 Vaccine Safety Surveillance Strategy, cannot be successfully undertaken as part of ongoing service delivery or operational activities. Not only would any strategy require funding/resourcing of at least some new elements that did not previously exist, or will require resources to be redirected from other areas that in turn would need to be filled to ensure service continuity, but some components will face increased workload that will need additional funding/resource support. An example of the latter pertains to the passive monitoring by CARM for the MeNZB that resulted in a more than 2-fold increase in report workload in a system already operating at the limits of its capacity.

- Institutional knowledge and National Expertise

  Although the members of the MeNZB MVS team were unfortunately disbanded around 2007/8 when the MeNZB epidemic had declined, some key members of this group are still accessible working in other areas of the Ministry of Health. They represent an immense wealth of institutional and practical knowledge on developing, implementing and addressing the operational challenges that were overcome and could be avoided, or provide helpful advice for a COVID-19 vaccine strategy. Key members of this MVS team, or at least the Director of the MVS, would be of indispensable value in being included in developing a COVID-19 Vaccine Safety Surveillance Strategy, the Strategy infrastructure, or at the very least in an advisory role.

  National experts or groups with expertise in areas that can be of value in supporting the elements of an NZ COVID-19 Vaccine Safety Surveillance Strategy should be identified and invited to contribute individually, institutionally, organisationally, or in collaboration with other groups. These include expertise areas such as Epidemiology, Pharmacoepidemiology, Vaccinology, Rare and Infectious Diseases etc.

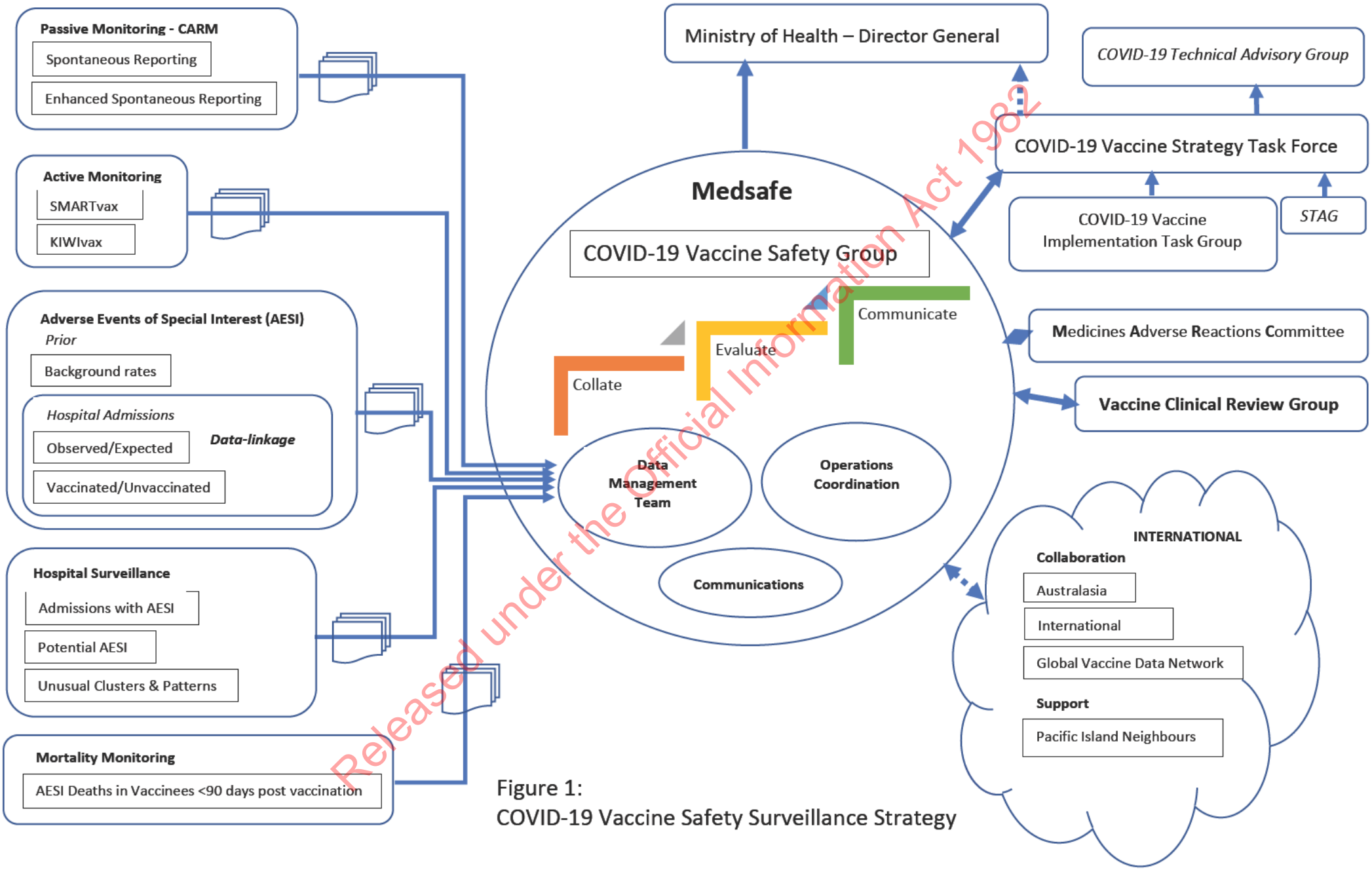

Figure 1:
COVID-19 Vaccine Safety Surveillance Strategy

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Appendix 1

The KIWIvax smartphone based technology to monitor AEFI's

INTRODUCTION

Immunisation is one of the most impactful, effective and successful public health interventions worldwide. Immunisations have saved lives and maintained the health of populations through protection from vaccine preventable diseases. Vaccines in use today have excellent safety profiles, but occasionally Adverse Events Following Immunisation (AEFI) do occur.[13] Most of these AEFI are non-serious, mild and of short duration, but in rare instances serious AEFI's associated with significant health impacts have occurred. Whilst some of these very rare serious effects have been due to the vaccine, most on further review are found to be coincidental. Since vaccines are administered to healthy individuals, especially very young children and often in regions where the diseases they are preventing have become rare or unknown, the public tolerance for any AEFI is extremely low. The family's or vaccinee's fear of the potential for an AEFI can result in reluctance or hesitancy about vaccination and compounded by misinformation, create confusion and anxiety which can affect vaccination uptake. This can lead to unnecessary susceptibility to vaccine preventable diseases that threaten the lives of individuals, or more widely, the community or country.

Surveillance and monitoring of AEFI's is therefore a crucial component of National Immunisation Programme strategy.[14] [15] Immunisation programmes need to be backed by reliable safety monitoring measures and to be able to respond to public concerns about vaccine safety. AEFI monitoring as a component of pharmacovigilance provides information on prevailing patterns of AEFIs, most of which are expected transient local or systemic immune responses that manifest clinically in a small proportion of vaccine recipients. AEFI monitoring also can identify serious, unexpected or unusual AEFIs, all of which can be followed up and investigated to identify whether they are attributed to the vaccine and paving the way for identification of potential safety issues and enabling changes in practice as rapidly as possible. AEFI monitoring informs and supports ongoing Benefit-Risk evaluation of all vaccines and provides reassurance to the public that the safety of vaccines has great importance, translating to maintaining public trust and confidence in the uptake of vaccines.

New Zealand (NZ) has had a long and successful history of AEFI monitoring as a component of its Pharmacovigilance system.[4] This is provided through the Centre for Adverse Reactions Monitoring (CARM) within the New Zealand Pharmacovigilance Centre (NZPhvC) at the University of Otago, which delivers national pharmacovigilance services for the Ministry of Health. NZ AEFI monitoring has been passive (i.e. reliant on voluntary reporting) and is subject to underreporting. In addition to underreporting, passive reporting systems are further limited by reporting biases and the lack of denominators. To overcome this, at the time of introducing the NZ-specific MeNZB vaccine in 2004, NZ introduced a novel Intensive Vaccine Monitoring Programme (IVMP).[3] This included an active monitoring system that involved an automated system that extracted vaccination event details from selected Primary Care medical practice Practice Management Systems (PMS) as well as extracting all vaccinee visits to the medical practice for a 6-week period post-vaccination. This enabled the construction of a post-vaccine event profile. The IVMP was a resource intensive system, not sustainable for long term ongoing monitoring or the monitoring of multiple vaccines. Although Web-based and Smartphone AEFI reporting Apps were brought into use by the Pharmacovigilance system in subsequent years, they remained subject to underreporting, bias and in particular vaccinee awareness that a post-vaccination safety monitoring system was in place.

Recent international approaches to improve ease of reporting have included the use of SMS smartphone technology.[7 8 15-17] This approach sends an SMS message to the vaccinee/caregiver from the PMS from the medical practice where the vaccination was administered. The message which is sent a few days after the vaccination event, enquires whether there had been an adverse event of any type after the vaccination by simply requiring a 'Yes' or 'No'. In the event of a 'Yes' the vaccinee is invited to complete a survey by responding to a series of targeted questions/options about the nature of the AEFI. Responses are recorded in a database and since the denominators known, rates of AEFI events can be determined. Systems also include options to report further details relating to events that are of a more serious nature and enable direct follow-up with the vaccinee to establish further detail. These SMS systems offer advantages in reaching the entire vaccine cohort, supporting the automated population of AEFI databases for analysis and can free-up resources that can then be more usefully directed to follow-up serious, clinically significant or unusual AEFI of concern or interest. More than 80% of NZ'ers own a Smartphone.[9] Utilizing this technology will enable far wider reach than the current modalities of reporting which are limited to the conscious decision to report an AEFI online or to a health provider for onward notification to the NZPhvC.

Adopting SMS smartphone AEFI reporting provides opportunities to achieve greater efficiencies in resource utilisation and further improve AEFI surveillance. This is not only important for the monitoring of current routine childhood, seasonal influenza and travel vaccines in a social environment that is increasingly influenced by vaccine sceptics, but also provides a firm foundation on which to monitor the COVID-19 vaccines on the horizon which will have a very uncertain safety profile. There is an urgency to set up the functionality of such a system prior to the arrival of expected COVID-19 vaccine/s

A SMS smartphone-based monitoring system, SMARTvax, which was initially developed for a medical practice group in Perth, Australia in 2010 to monitor adverse events following the seasonal influenza vaccine[7] achieved great success and has gone on to become the core technology of the nationwide AusVaxSafety implemented in all Australian states and territories.[8 17 18] The utility of SMARTvax as the SMS smartphone interface tool and AusVaxSafety as the overall system analysing the database repository that SMARTvax populates, has repeatedly demonstrated its ability to support diverse vaccine safety studies.[9 11]

In collaboration with the developers of SMARTvax the NZPhvC has initiated the customisation and development of a NZ-specific version of SMARTvax and is working alongside the Immunization Advisory Centre (IMAC) to optimised ensure optimized and culturally sensitive system interfaces. . SMARTvax is known to be compatible with multiple PMS software in use in Australia including Medtech32, the PMS with the largest share in NZ at 80%.[5]
The endpoint will be an NZ SMS smartphone AEFI technology tool supporting 'KIWIvax', an NZ vaccine monitoring approach that would have been demonstrated to be able to interact with the most widely used practice management software application in NZ (Medtech32) and ready for piloting to support NZ AEFI monitoring for any of the national schedule vaccines, and eventually a COVID19 vaccine rollout.

Proposed Operation

KIWIvax system will use the New Zealand-customised version of the SMARTvax tool to interface with the vaccinee/caregiver stimulated by the recording of a vaccine administration in the Practice Management System. The information generated from the interaction will be messaged to the medical practice's PMS and uploaded to the database in the New Zealand Pharmacovigilance Centre (New Zealand's National Centre for the monitoring of adverse reactions) and form part of the national dataset of AEFI's. An anonymised version of the data will be stored on a cloud-based server, which will also hold the software to produce the analytical outputs and dashboard graphics which will form the basis of KIWIvax, a new dynamic, near real-time vaccine monitoring and surveillance system.

The KIWIvax System: (Figure 1)

- SMARTvax will be installed on individual medical practices Practice Management Systems (PMS). Permission and approval will be required by each medical practice.
- Registering of a vaccine administration for a patient in the PMS will at 3 days post-vaccination generate a message to the vaccinee/caregiver with a standard text enquiring if any AEFI has occurred in the period since the vaccination.
- The message will offer 3 possible responses:
    - 'YES' - this will prompt an invitation to a survey with a series of questions and options to choose common AEFI's, some of which will open expandable trees, questions around severity as well as options to provide free text for more detail, or to notify unlisted AEFI's. An optional will also be provided to contact the NZPhvC to discuss the AEFI's with the clinician.
    - 'NO' - will acknowledge that no event occurred and that in the event of a further vaccination there will be further contact.
    - 'OPT OUT' - - will terminate further interaction with an appropriate text message
- All SMS's will form the basis of a denominator for analysis with the various AEFI responses supporting the numerator.
- All data from the interaction will be stored in three locations:
    - on the database of the patient's medical practice from which the SMS originated
    - an upload from the medical practice database:
        - onto an NZPhvC server in line with privacy requirements and subject to the same data security provisions operating in the NZPhvC.
        - of anonymised data to a Cloud-based server housing the analytical software to enable national analyses.
- Data on the Cloud-based server will be analysed to produce NZ-appropriate analysis and graphics that will form the basis of KIWIvax.

SMARTvax development to date

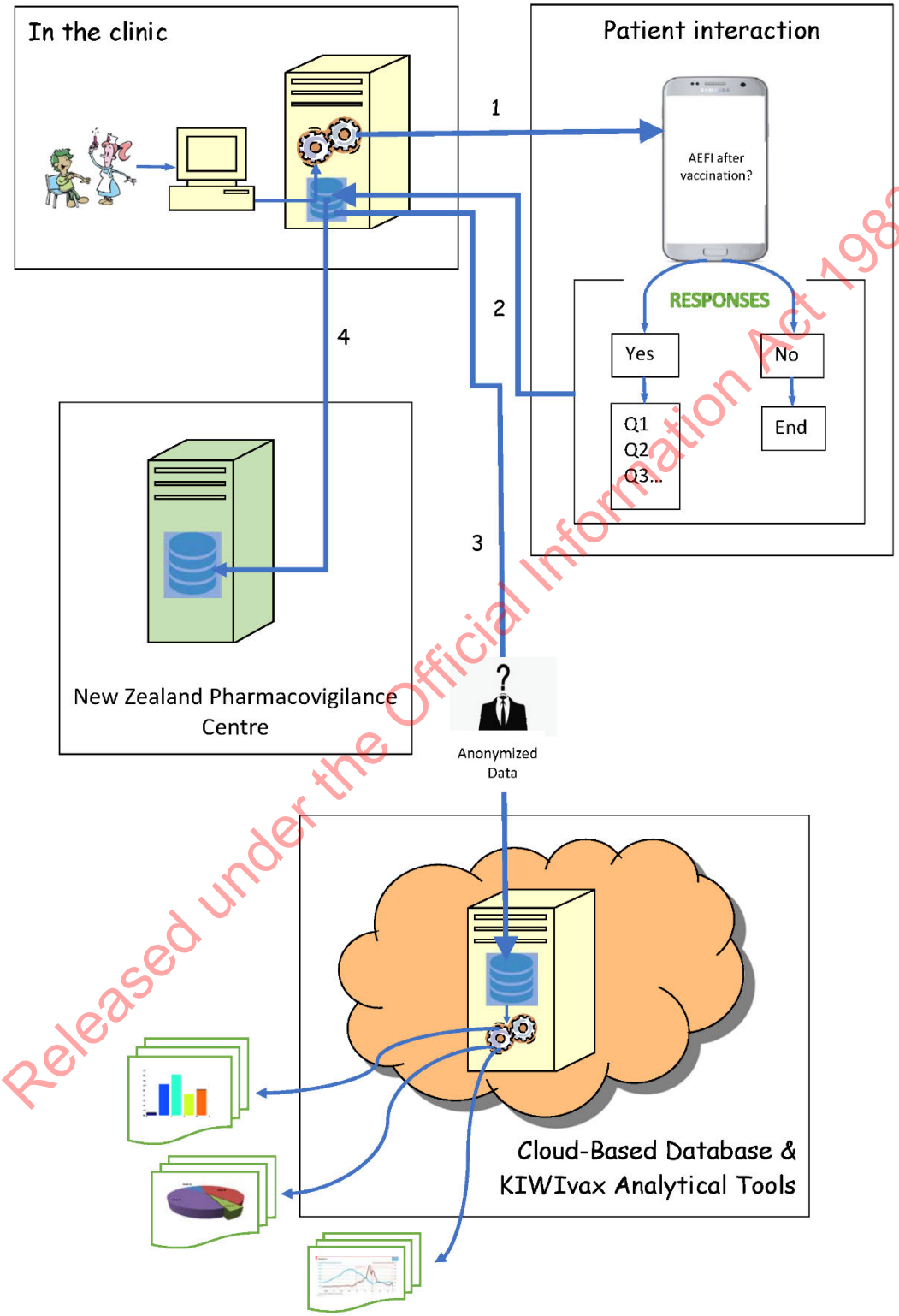
- A collaboration has been established between the NZPhvC and the SMARTvax developers to customise SMARTvax for NZ.
- Confirmed that SMARTvax can interrogate and link to the New Zealand Medtech32 data libraries and identifiers.
- Identified additional NZ-specific data fields that SMARTvax must interrogate, refer to, or incorporate for NZ monitoring.
- Verified that the SMARTvax customisations to initiate SMS messaging and return responses using mobile numbers identified from data fields in a test version of Medtech32 are functional

SMARTvax/KIWIvax development in progress

- Configuration of SMARTvax to upload SMS data interactions from the medical practice PMS to the NZPhvC database
- Configuration of the NZPhvC database to receive incoming uploads from the medical practice and develop protocols for related data management
- Establishing an NZ Cloud-based database to receive and store the data received from the SMARTvax tool interrogation/interaction generated from the medical practice.
- Customisation of the NZ Cloud-based database interrogation analysis and statistical output/dashboards that will become the KIWIvax utility.
- Beta-testing the functionality of the technological tools in a real world medical practice environment for a small number of vaccinees.
- Establishing collaboration with Māori Iwi and Runanga to ensure that the tool and its operations and intended interfaces with vaccinees and providers are culturally appropriate through involvement at appropriate stages in the development of KIWIvax.

- Consideration of ethical aspects that need to be addressed to inform a New Zealand ethics approval in anticipation of a working customised SMARTvax and KIWvax technology being finalised. Two key dimensions of ethics considerations are those of (a) the ethics of interrogating patient level details from the medical practices PMS required by SMARTvax and (b) vaccinee/caregiver opt in/opt out considerations.
- Plan and implement a trial of the KIWIvax system in a real-world environment in a PHO setting for a 3-6 month period to evaluate its functionality, acceptability and utility in supporting vaccine safety surveillance.
- Consider requirements, workload and resource implications for the possible integration of SMARTvax into other non- Medtech32 practice management systems.

Figure 1: KIWIvax Processes and DataFlows



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Appendix 2

COVID-19 vaccine Adverse Events of Special Interest

The rapid development of COVID-19 vaccine candidates and accelerated clinical trial timelines and relatively limited sample sizes exposes risks in being able to fully reassure the safety of these vaccines.[1,2] This highlights the critical importance of vaccine safety surveillance strategies to detect both common and rarer post-vaccination adverse events in the wider real-world exposed population. This is all the more critical since no DNA or RNA vaccines have been licensed in humans to date[2] adding further weight to the need to ensure that the AEFI monitoring for these vaccines is as comprehensive as possible. Potential safety concerns include vaccine-mediated disease enhancement syndrome (observed with other RSV vaccines)[2], as well as other events that may be potentially attributable to the characteristics of the vaccine, the nature of the immune response to the vaccine antigens, or even the disease itself. These events form a distinct subset of AEFI's referred to as Adverse Events of Special Interest (AESI's).

An Adverse Events of Special Interest is defined as:

> *'An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsors product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) but also be warranted.'*[3]

Discussions and consensus groups have highlighted the importance of considering COVID-19 disease enhancement syndrome and the need to identify AESI's. Initiatives are currently underway through SPEAC (Safety Platform for Emergency Vaccines) funded by CEPI[4] (Coalition for Epidemic Preparedness Innovations). SPEAC have developed a Priority List of Adverse Events of Special Interest: COVID-19, organising candidate AESI's in three groups:[3]

1. ***AESI relevant to a broad range of vaccines***

Neurologic	Generalized convulsion Guillain-Barré Syndrome (GBS) Acute disseminated encephalomyelitis (ADEM)
Hematologic	Thrombocytopenia
Immunologic	Anaphylaxis Vasculitides
Other	Serious local/systemic AEFI

2. ***AESI relevant to one or more specific COVID-19 vaccine platforms***

Neurologic	Aseptic meningitis Encephalitis / Encephalomyelitis Transverse myelitis
Immunologic	Arthritis
Other	Myocarditis

3. ***AESI relevant to a specific target disease***

Immunologic	Enhanced disease following immunization Multisystem inflammatory syndrome in children
Respiratory	Acute respiratory distress syndrome (ARDS)
Cardiac	Acute cardiac injury including: • Microangiopathy • Heart failure and cardiogenic shock • Stress cardiomyopathy • Coronary artery disease • Arrhythmia • Myocarditis, pericarditis
Hematologic	Coagulation disorder • Deep vein thrombosis • Pulmonary embolus • Cerebrovascular stroke • Limb ischemia • Hemorrhagic disease
Renal	Acute kidney injury
Gastrointestinal	Liver injury Guillain Barré Syndrome
Neurologic	Anosmia, ageusia Meningoencephalitis Chilblain-like lesions
Dermatologic	Single organ cutaneous vasculitis Erythema multiforme

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