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Advancing the Science of Vaccine Safety During the Coronavirus Disease 2019 (COVID-19) Pandemic and Beyond: Launching an International Network of Special Immunization Services

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Within 2 years after the start of the coronavirus disease 2019 (COVID-19) pandemic, novel severe acute respiratory syndrome coronavirus 2 vaccines were developed, rigorously evaluated in large phase 3 trials, and administered to more than 5 billion individuals globally. However, adverse events of special interest (AESIs) have been described post-implementation, including myocarditis after receipt of messenger RNA (mRNA) vaccines and thrombosis with thrombocytopenia syndrome after receipt of adenoviral vector vaccines. AESIs are rare (<1 to 10/100 000 vaccinees) and less frequent than COVID-19 complications, though they have associated morbidity and mortality. The diversity of COVID-19 vaccine platforms (eg, mRNA, viral vector, protein) and rates of AESIs both between and within platforms (eg, higher rate of myocarditis after mRNA-1273 vs BNT162b2 vaccines) present an important opportunity to advance vaccine safety science. The International Network of Special Immunization Services has been formed with experts in vaccine safety, systems biology, and other relevant disciplines to study cases of AESIs and matched controls to uncover the pathogenesis of rare AESIs and inform vaccine development.

Keywords. adverse events following immunization; genomics; systems biology; vaccination.

As illustrated by the ongoing coronavirus disease 2019 (COVID-19) pandemic, vaccines are powerful tools for the control of infectious diseases. In combination with public health measures, effective vaccines have had a major impact on the pandemic, with more than 11 billion severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines administered worldwide as of 4 May 2022 [1]. Large phase 3 clinical trials of SARS-CoV-2 vaccines, each enrolling approximately 40 000 demographically and medically diverse participants, demonstrated high efficacy and acceptable safety profiles [2–4]. However, the high expense of clinical trials and the rarity of adverse events of special interest[1] (AESIs are scientific and medical

concerns specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. For vaccines, they are a subset of adverse events following immunizations [AEFIs]) that occur in <1 per 10 000 vaccinees make them unlikely to be detected prior to widespread use [5,6]. For this reason, robust pharmacovigilance strategies are routinely deployed in many high-income countries in order to continue safety assessments post-authorization and implement new pharmaceuticals, including vaccines [7–9]. These strategies were successful in identifying a limited number of rare AESIs such as anaphylaxis and myocarditis following messenger RNA (mRNA) vaccines, as well as Guillain-Barré syndrome and thrombosis with thrombosis with thrombocytopenia syndrome (TTS) following adenoviral vector vaccines that occur with frequencies of approximately 1 to 10/100 000 vaccinees [9–23]. While such AESIs occur much less frequently than COVID-19 disease complications and the known benefits of immunizations outweigh the known risks [17, 21–23], mass vaccination of billions of people can result in thousands of AESIs and contribute to vaccine hesitancy. Similar dynamic benefit–risk changes have been observed with other vaccines such as pertussis and measles. In several countries,

the control and near elimination of these target diseases by high immunization levels combined with an increasing number and relative prominence of AESIs led paradoxically to a loss of confidence in immunizations via media scares and deliberate spread of disinformation with the subsequent resurgence of disease [24].

The unprecedented vaccine development and implementation campaigns to address the COVID-19 pandemic represent a unique opportunity to advance the science of vaccine safety that may serve as a model for mitigating vaccine risks and stabilizing routine immunization programs more broadly. SARS-CoV-2 vaccines using at least 4 technology platforms have been authorized for emergency use (inactivated viral, mRNA, viral vector, protein), with some subsequently licensed [25, 26]. The safety profiles of these new vaccines, initially described in passive surveillance and subsequently confirmed in population-based epidemiologic studies, are emerging as they are rolled out globally. The differential rates of AESIs observed between (eg, TTS primarily observed after adenoviral vaccines and myocarditis observed primarily after mRNA vaccines [9, 11–20, 22]) and within vaccine technology platforms (eg, higher rate of myocarditis after mRNA-1273 vs BNT162b2 vaccines [9, 17, 27]) enable application of systems biology tools to study the scientific basis for these differences and characterize the pathogenesis of these AESIs. This field of study has been termed "adversomics" by 1 of the authors (G. A. P.) and can lead to a new understanding of AESIs that can improve our ability to mitigate these risks at the population level (eg, developing a safer vaccine) and/or the individual level (eg, identifying AESI risk factors) [28, 29]. To enable gathering of data on enough rare cases of each AESI, and controls, in a timely and efficient way requires a global network that builds on existing infrastructures. Here, we describe these key methodologic domains, key partners, and our vision for engaging them via the newly formed International Network of Special Immunization Services (INSIS) [30].

Key International Network of Special Immunization Services Domains

Tertiary Clinical Immunization Services

The most common mechanism used by national health authorities to monitor vaccine safety is the central collection of "spontaneous" or passive reports of adverse events following immunization (AEFIs; eg, US Vaccine Adverse Event Reporting System) [24]. However, clinically significant AEFIs are so rare that it is difficult for healthcare professionals to provide standardized evaluation, diagnosis, and management for an individual patient's novel AEFI; to recognize new adverse events that are possible AESIs; and for the field of vaccine safety to advance scientifically. In response, tertiary clinical immunization services that bring together subspecialists as needed on challenging AEFI cases were organized in several countries, starting with Italy in 1992 [31], Brazil in 1993 [32], the United Kingdom [33],

the civilian Clinical Immunization Safety Assessment (CISA) [34] and military Vaccine Healthcare Centers Networks in the United States [35], followed by services in Canada [36] and Australia [37].

Precision Vaccinology Principles

Both the severity of COVID-19 as well as risks of vaccine AESIs vary with key demographic features such as age and sex, illustrating the relevance of precision vaccinology principles [38]. These principles will be applied to our effort to characterize AESIs such that collecting sufficient clinical data and biosamples from diverse populations within high-risk groups for a given AESI will be a priority.

Systems Biology

Recent advances in systems biology, integrating data from multi-omics (OMICs) technologies, allow unprecedented understanding of vaccine-induced immunity and correlation of aberrant clinical responses (eg, TTS) with OMICs-based biomarkers and mechanisms. The systems biology approach includes assessment of patient DNA (genomics), RNA (transcriptomics), proteins (proteomics), lipids (lipidomics), antibody and functional antibody markers, flow cytometry, and metabolites (metabolomics). Adversomics, the study of genetic and other host system susceptibility to AESIs at the individual and/or population level, provides a promising approach to gain insight into the immune profile of patients who experience AESIs with SARS-CoV-2 vaccines [28]. Adversomics often uses simultaneous approaches of targeted OMICs assessments, based on the underlying pathophysiology of an AESI (eg, cardiac biomarkers in patients with vaccine-associated myocarditis), and agnostic approaches, casting a broad net to define molecular pathways that are associated with, and contribute to, AESIs. The results of such studies could lead to informing future vaccine discovery and development, predicting susceptibility, and reducing the likelihood of a serious AESI [28, 38]. For example, next-generation sequencing technology has yielded comprehensive information about immune responses to influenza and rubella vaccines [39–41]. Integration of transcriptomics and proteomics has provided new insight into the dynamics of the immune response in early life [42, 43]. These immunogenetic findings provide a new model to better understand the mechanisms and interactions in the immune system and guide new strategies for personalized vaccinology [38].

A challenge in applying adversomics approaches to understanding vaccine safety is gathering high-quality clinical data and appropriate samples from sufficient numbers of well-characterized patients of diverse ancestries for appropriately powered analyses to generate robust results. When TTS and myocarditis emerged as vaccine safety signals, clinical immunization networks, thrombosis networks, and cardiology networks were positioned to identify cases, including collection of data and biosamples, and build cohorts of patients with these

AESIs. In addition, the Global Vaccine Data Network (GVDN) [44], which focuses on using Big Data to evaluate vaccine safety in diverse populations, has initiated genomics studies of patients with post-vaccination TTS and myocarditis identified in several middle- and high-income countries. However, no single country has enough patients with these rare events to conduct a statistically powerful analysis by itself.

Key International Network of Special Immunization Services Partners
Recognizing the need for international, multidisciplinary collaboration to investigate rare AESIs, INSIS was formed in 2020 by Brighton Collaboration members, leading clinical immunization services, systems biology teams, GVDN members, and a member of the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) Working Group on COVID-19 Vaccines Safety Preparedness and WHO Strategic Advisory Group of Experts on Immunization (Figure 1). In 2022, INSIS formed collaborations with sentinel surveillance programs in Africa conducted via the African Leadership in Vaccinology Expertise (ALIVE) Network and Vaccines and Infectious Diseases Analytics (VIDA) Research Unit at the University of the Witwatersrand, Johannesburg, South Africa. INSIS is actively seeking additional collaborators from low-, middle-, and high-income countries around the world.

<u>Tertiary Clinical Immunization Services</u>: Leaders of the Canadian Special Immunization Clinic (SIC) Network [36], Australian AEFI-Clinical Assessment Network

(AEFI-CAN) [37], and Vanderbilt Vaccine Research Program (VVRP) contribute expertise and collaborate with expert subspecialists to develop harmonized protocols for patient investigation and management.

SIC Network: The SIC Network was established in 2013 by infectious disease specialists and allergy immunologists at 12 Canadian sites to standardize and improve management of patients with clinically significant AEFIs [36]. In 2020–2021, the network added adult expert specialists and new sites to improve access for adults with adverse events following SARS-CoV-2 vaccination.

AEFI-CAN was established in Australia in 2013, bringing together state-based immunization clinics to facilitate consistent approaches to the clinical response and causality assessment for serious AEFIs and enable accurate, standardized documentation of significant/unexpected AEFIs, including documenting outcomes and making decisions regarding further vaccination. The national network was expanded in 2021 to include adult colleagues (subject matter experts) as the SARS-CoV-2 vaccines were used across the life course.

VVRP: Based on Nashville, Tennessee, the VVRP was formed in 2001 to conduct clinical and translational research in new vaccines and therapeutics. The VVRP serves as the coordinating center for the US Centers for Disease Control and Prevention (CDC)-funded CISA Project to address vaccine safety issues, conduct clinical

Figure 1. Map of International Network of Special Immunization Services formal collaborating partners. Sites are as follows: 1. Dalhousie U/Special Immunization Clinic Network, Halifax, Nova Scotia, Canada; 2. Precision Vaccines Program/Boston Children's Hospital, Boston, Massachusetts, USA; 3. Mayo Vaccine Research Group, Rochester, Minnesota, USA; 4. Brighton Collaboration, Decatur, Georgia, USA; 5. Global Vaccine Data Network, Auckland, New Zealand; 6. Canadian Pharmacogenomics Network for Drug Safety, Vancouver, British Columbia, Canada; 7. Australian Adverse Events Following Immunization-Clinical Assessment Network, Melbourne and Sydney, Australia; 8. Vanderbilt Vaccine Research Program, Nashville, Tennessee, USA; 9. University of Washington, Seattle, Washington (contact based in New Delhi, India); 10. Vaccines and Infectious Diseases Analytics Research Unit, University of the Witwatersrand, Johannesburg, South Africa; 11. African Leadership in Vaccinology Expertise (ALIVE) Network lead site, University of the Witwatersrand, Johannesburg. ALIVE Network sites: A. Bamako, Mali; B. Navrongo Health Research Centre, Ghana; C. Nigeria (national); D. Gondar, Ethiopia; E. Kilifi, Kenya; F. Malawi (national); G. Maputo City, Mozambique; H. Eswatini (national).

research focused on vaccine safety, and assess complex clinical adverse events following vaccination. In addition, they have coordinated efforts under CDC direction to offer a robust on-call safety consultation service to providers whose patients experience AEFIs after SARS-CoV-2 vaccination.

VIDA Research Unit: Under the University of the Witwatersrand and in collaboration with the Task Force for Global Health and GVDN, the VIDA Research Unit set up 2 sites for the sentinel surveillance of AESIs in South Africa and, with additional funding, hopes to expand to more sites within South Africa. This was done with the hope of strengthening the safety profiles of the SARS-CoV-2 vaccines that were recently introduced and increasing public confidence in the available vaccines.

African Leadership in Vaccinology Expertise Network: ALIVE, the flagship research entity of the University of the Witwatersrand, supported by GVDN, has been awarded a grant by Gavi, the Vaccine Alliance, to coordinate the establishment of active vaccine safety in 8 Advance Market Commitment-92 countries in Africa. Established researchers and clinicians in Mali, Ghana, Nigeria, Ethiopia, Kenya, Malawi, Mozambique, and Eswatini will provide data on AESIs for use by country regulatory authorities, WHO, and GACVS to assess safety signals.

Systems Biology (OMICs) Centers:

Precision Vaccines Program (*PVP*): Based in Boston Children's Hospital (Boston, Massachusetts), the PVP fosters international multidisciplinary collaboration among academia, government, and industry to use advanced technologies, including systems biology and age-specific human in vitro modeling, to develop vaccines tailored to protect vulnerable populations (https://www.childrenshospital.org/research/departments-divisions-programs/departments/pediatrics/precision-vaccines-program, [45]). PVP has established multi-OMICs analytic pipelines, including a proteomics and metabolomics core, as well as a PVP data management and analysis core that enables high-quality integration of clinical, immunologic, and systems biology data [38, 43, 46].

Mayo Vaccine Research Group: The Mayo Vaccine Research Group seeks to improve the health of populations through clinical, laboratory, and epidemiological vaccine research by investigating the immunogenetics and systems biology of vaccine responses (https://www.mayo.edu/research/labs/vaccine-research-group/overview; [47]). The center has facilities and expertise for serology, cell-mediated immunity, and HLA typing for immunogenetic studies, as well as high-throughput assays, such

as transcriptomics and epigenomics analysis supported by a bioinformatics platform [28, 29, 39].

Canadian Pharmacogenomics Network for Drug Safety (CPNDS): The CPNDS is an active surveillance network of 32 academic health centers across Canada, established to uncover the genetic and mechanistic basis of drug responses to improve safety and efficacy of prescription medications (https://www.pharmgkb.org/page/cpnds; [48]). The CPNDS laboratory specializes in pharmacogenomic analysis platforms and next-generation DNA sequencing, supported by bioinformatics and functional and pharmacokinetic validation platforms.

Vaccine Safety Networks:

Brighton Collaboration: The Brighton Collaboration was formed in 2000 to help advance the science of vaccine safety, starting with the development of standardized case definitions for AEFIs. Currently, approximately 100 Brighton guidance documents are available (https://brightoncollaboration.us/; [50]). Since the Brighton Collaboration has approximately 1000 members globally and is a well-recognized "brand" in vaccine safety, it provides a platform for outreach to countries without formal tertiary clinical centers for enrolling patients with target AESIs into INSIS protocols.

Global Vaccine Data Network: The GVDN, based at the University of Auckland (New Zealand), has health data capabilities for safety evaluation in more than 25 countries, including India and low-income countries in Africa, and is leading studies of genetic variants associated with rare AESIs that will complement INSIS-led studies that use multi-OMICs approaches (https://www.globalvaccinedatanetwork.org/).

International Network of Special Immunization Services Approach

INSIS-led studies will generally use a case-control design to identify biomarker risk factors and characterize mechanisms that underlie rare AESIs following vaccination (Figure 2). Well-characterized cases that meet Brighton Collaboration AESI case definitions will be matched to controls who did not develop the AESI after vaccination with vaccines from the same platform. INSIS sites will identify cases and prospectively implement harmonized protocols for detailed clinical data collection and serial blood sampling from cases and controls at comparable time points (eg, for cases: during the acute adverse event and 1–3 months and 6–9 months after the adverse event; for controls: pre-vaccination and 1–3 months and 6–9 months post-vaccination).

Whole blood samples will be collected and processed using standard operating procedures to generate aliquots for downstream systems biology assays (eg, proteomics, metabolomics, RNAseq, epigenomics) [43]. INSIS partners have successfully implemented protocols for fractionation of
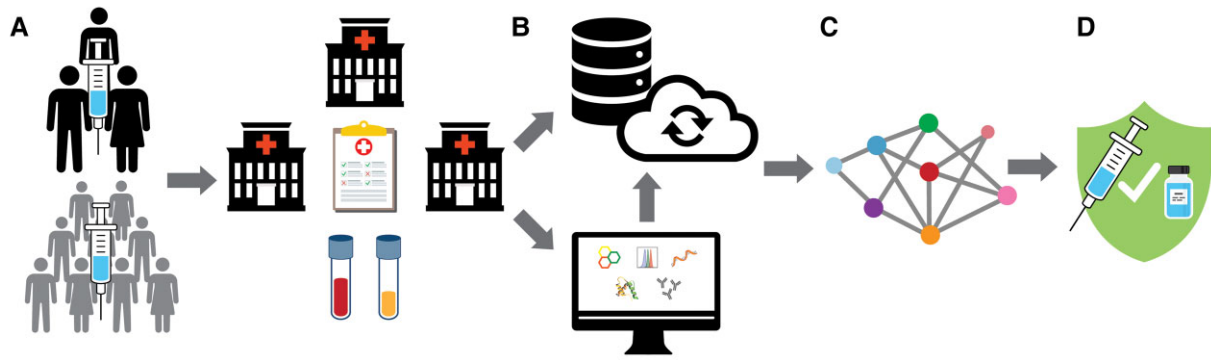
Figure 2. The International Network of Special Immunization Services (INSIS) approach. (*A*), AESI cases and controls undergo standard assessment, and data and sample are collected at INSIS clinical assessment centers. (*B*), Data are transferred to the INSIS central database, and samples are processed at INSIS laboratories for multi-OMICs. (*C*), Integration and analysis of clinical and biological data will generate molecular signatures and biomarkers associated with AESIs. (*D*), Results will inform development of safer vaccines and personalized vaccination strategies. Abbreviation: AESI, adverse event of special interest.

Table 1. Proposed Methods of Investigation of Adverse Events of Special Interest and Expected Outcomes

Proposed Method of Investigation	Expected Outcome
Metabolomics	Assessment of baseline and dynamic (post- vs pre-vaccine) plasma metabolite abundance that correlates with AESI
Proteomics	Assessment of baseline and dynamic (post- vs pre-vaccine) plasma protein abundance that correlates with AESI
Transcriptomics	Assessment of baseline and dynamic (post- vs pre-vaccine) gene transcript abundance that correlates with AESI
Genomics (led by Global Vaccine Data Network)	Genetic variants associated with risk of AESIs

Abbreviation: AESI, adverse event of special interest.

small-volume samples (1–2 mL) in a range of low- and middle-income countries (LMICs) as well as high-income countries [42, 43]. Samples will be transferred to INSIS-affiliated multi-OMICs and systems biology laboratories for centralized processing, with laboratories assigned to conduct specific assays on all INSIS samples to ensure internal validity. A central INSIS REDCap database will capture common data elements on all cases and controls, including demographics, immunization history, past medical history, and details of the AESI and outcomes (cases only), which will be linked to their biological data.

A range of multi-OMICs assays will be used, including proteomics, metabolomics, transcriptomics, epigenomics, and flow-based immunophenotyping, to compare levels of analytes and immune responses within groups over time and between cases and controls to identify differences in basal and post-vaccination levels of analytes (Table 1). Integration of clinical and biological data will be led by bioinformatics experts and conducted using a Data Integration Analysis and Biomarker discovery using Latent cOmponents (DIABLO) on a cloud-based bioinformatic analytic infrastructure [43, 46, 51]. These analyses aim to characterize immunologic signatures associated with rare AESIs and biomarkers associated with increased susceptibility to AESIs, thus allowing us to identify the pathways triggered in these AESIs and individuals at increased risk who may benefit from personalized vaccination strategies (eg, use of a different product or dosing schedule).

INSIS priorities will be informed by a steering committee, a scientific advisory board, the Coalition for Epidemic Preparedness Innovations, and the Safety Platform for Emergency vaccines. Protocols will be shared with partners and results will be shared through traditional dissemination methods, including peer-reviewed publications, as well as via INSIS and institutional websites and traditional and social media. Data will be deposited to public repositories in accordance with funder policies.

DISCUSSION

Global coordination is needed to ensure robust, replicable results that will substantially advance the understanding of rare AESIs and improve safety. As a global standing network for investigation of AESIs, INSIS will connect internationally recognized clinicians and researchers in vaccine safety, adversomics, and public health, while providing a neutral resource for the vaccinology community to compare vaccine responses and safety outcomes between vaccine candidates. Through the Brighton Collaboration, INSIS seeks to develop partnerships with expert clinicians in LMICs to enhance case finding and evaluation globally and to enable assessment of AESIs that arise anywhere in the world. Application of adversomics approaches to studies of rare AESIs will provide insight into the pathophysiology and identify populations at risk, inform prelicensure safety evaluation of new vaccine candidates and platforms, and

enable "reverse engineering" of vaccine platforms to avoid specific pathways that can trigger rare AESIs. The results will also inform international regulatory decision-making regarding benefit–risk assessment of vaccines and support vaccine confidence. As a global network, INSIS has the potential to advance the science and delivery of safe vaccines worldwide beyond what any single national organization or country can do alone.

CONCLUSIONS

The scale and diversity of SARS-CoV-2 vaccination programs across the globe present an unparalleled opportunity to create a multidisciplinary global program such as INSIS in real-time and to reap the benefits now. Understanding mechanisms and risk factors for AESIs is critical to advancing the science of vaccine safety and in supporting vaccine confidence. Such advances can contribute to ending the COVID-19 pandemic, inform next-generation precision vaccine development, provide a scientific basis for safety monitoring of future vaccines, and mitigate future epidemic threats.

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