Vaccine Safety Quarterly

Brighton Collaboration Community News

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Letter from INSIS

Understanding the Etiologies of Adverse Events Following Immunization via the International Network of Specialist Immunization Services

Karina Top, MD, MS

Vaccine safety has been my primary research focus for over a decade. I established the Canadian Special Immunization Clinic Network with Drs. Gaston De Serres (Laval University) and Scott Halperin (Dalhousie University) in 2013, which I continue to lead. I have also been a member of the Brighton Collaboration since that time and contributed to the development of several case definitions.

In Fall 2020, recognizing the need for global harmonization of investigation and management adverse events of special interest (AESIs) that may arise following implementation of mass COVID-19 vaccination campaigns, Dr. Bob Chen and the Safety Platform for Emergency vACcines (SPEAC) Executive Board convened a brainstorming meeting to discuss international collaboration between specialist immunization clinics that I attended along with Drs. Kathy Edwards and Neal Halsey of the Clinical Immunization Safety Assessment Network. We discussed the need to collect biosamples and the unique opportunity the COVID-19 vaccination campaign presented to investigate causes of AESIs that may arise after vaccine implementation. In December 2020, we held our first meeting of what came to be known as the International Network of Special Immunization Services (INSIS) hosted by SPEAC. The meeting was attended by representatives from clinical vaccine safety networks in the US (CISA, Drs. Edwards, Halsey), Australia (Dr. Nigel Crawford), Italy, Global Vaccine Data Network (Dr. Steve Black), and leading vaccine immunologists and systems biologists from Mayo Clinic (Dr. Greg Poland), *Precision Vaccines Program*, Boston Children's Hospital, (Drs. Ofer Levy, Al Ozonoff), University of Washington (Dr Sonali Kochhar) and the Canadian Pharmacogenomics Network for Drug Safety (Dr. Bruce Carleton). There was strong interest in leveraging the unique opportunity presented by COVID-19 vaccination programs to address gaps in responses to previous vaccine safety signals through applying an "adversomics" approach to understand why and how AESIs developed and who was at risk. Though biosampling and biobanking of patients with AESIs had been attempted in the past with mixed success, it was recognized that such challenges could be overcome through international collaboration to identify and investigate sufficient numbers of well-phenotyped cases and a harmonized approach to data and sample collection.

INSIS grew from there, with regular meetings starting in January 2021 to discuss emerging vaccine safety signals with leading experts in the conditions of interest (e.g., allergist-immunologists, hematologists). We developed harmonized approaches to investigation and management of these conditions, a central database, and protocol

for data and sample collection for downstream multi-OMICs analysis. An initial focus was on anaphylaxis post-vaccination which arose as a signal by January 2021, followed by thrombosis with thrombocytopenia syndrome (TTS), and later myocarditis and pericarditis. We received support from SPEAC and the Coalition for Epidemic Preparedness Innovations (CEPI) for the concept of an international vaccine safety network to investigate underlying mechanisms and biomarker risk factors for AESIs. We began collaborating on a funding proposal to support INSIS multi-OMICs analysis of myocarditis, pericarditis and TTS. In 2022, I was awarded a Canadian Institutes of Health Research-CEPI Leadership Award in Vaccine Research to support enhancing capacity for AESI investigation and harmonized data and sample collection in low- and middle-income countries (LMICs). Through the Global Vaccine Data Network, INSIS began a collaboration with Drs. Clare Cutland, Sana Mahtab and Kimberley Gutu at the University of the Witwatersrand African Leadership in Vaccinology Expertise (ALIVE) network and Wits Vaccine and Infectious Disease Analytics (VIDA) Research Unit. INSIS has sought to expand its membership through its website, publications, and presentations to stakeholders and at international conferences, as well as through outreach to researchers publishing on myocarditis, TTS and other AESIs.

Efforts over the past year have focused on finalizing a longer-term funding agreement with CEPI which was signed recently with the University of Alberta. This funding will support multi-OMICs analysis of samples from cases with myocarditis, pericarditis and TTS following COVID-19 vaccination versus controls to uncover biomarker risk factors and underlying mechanisms of these events. Funding will also support genomics analysis to identify genetic markers of these conditions through a collaboration between the Global Vaccine Data Network and INSIS. For the past several months, INSIS has been working to identify collaborators with cohorts of well-phenotyped cases with biobanked samples from around the world and prioritize OMICs assays to ensure the most rigorous approach, informed by the current state of the evidence.

INSIS continues to grow with now over 70 members including researchers, representatives of SPEAC and the Brighton Collaboration, WHO and other public health organizations, vaccine developers, vaccine safety experts and specialist clinicians. INSIS hosts monthly meetings with guest presentations by leading experts in a range of AESIs reported with COVID-19 vaccination. As COVID-19 vaccination programs mature and the vaccine safety community's focus has begun to shift to other vaccines, the network is now expanding its focus to potential safety signals with novel vaccines (e.g., RSV, Lassa fever) and childhood vaccinations, as well as developing protocols to respond to a new AESI 'X'.

INSIS welcomes expressions of interest from new members who can contact the network via the INSIS Program Manager, Sara Moradipoor: moradipo@ualberta.ca or via info@insisvaccine.org. INSIS is pleased to be participating in the 4th Biennial International Precision Vaccines Congress in Rome, Italy, October 5-6, 2023. We encourage researchers and other stakeholders interested in vaccine adversomics to attend this world-class conference.

Karina Top, MD, MS
Principal Investigator, International Network of Special Immunization Services
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I. UPDATES ON GLOBAL OUTBREAKS

COVID-19

New COVID-19 boosters

The US Food and Drug Administration (FDA) has approved two updated COVID-19 mRNA booster vaccines (Moderna, Pfizer) to protect against the XBB.1.5 subvariant of the Omicron variant, as well as the EG.5 and BA.2.86 subvariants. EG.5 is currently the most common variant detected among new cases in the US, but BA.2.86, is being closely followed for its high potential to mutate.

COVID-19 Research

With the development of novel vaccines comes the duty to rigorously assess vaccine safety. The Brighton Collaboration will continue its collaboration with CEPI to update the list of possible Adverse Events of Special Interest (AESI) (Updated October 2022) that may be associated with a COVID-19 vaccine. Case definitions and other tools for assessing COVID-19 vaccine AESIs are available here.

New safety studies continue to examine the risks of adverse events following COVID-19 vaccination, including Guillain Barre syndrome and Kikuchi Fujimoto disease. Evidence from clinical trials continues to refute the efficacy of ivermectin in treating COVID-19.

Even as the pandemic enters an endemic phase, we may still be dealing with adverse health effects among those who recovered from acute infections. Long COVID-19 continues to affect some individuals long after the virus has been cleared, with up to 200 million cases reported that last a year or more. Long COVID-19 may emerge even after acute Covid appears to have cleared, and may lead to significant activity limitations in the long term. Long COVID-19 and significant activity limitations The National Institutes of Health (NIH) recently established the Office of Long COVID Research and Practice, which plans to implement clinical trials to study the effects of different interventions and treatment modalities in preventing Long COVID-19 under the RECOVER Initiative.

MPOX

Australia modified the Mpox vaccine schedule to conserve the limited vaccine supply. Local adverse events were more frequent after dose 1 of intradermal pre-exposure vaccination and lowest after dose 2 of subcutaneous post-exposure vaccination.

II. VACCINE SAFETY RESEARCH

The BEST Initiative

The US Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) has formed the Biologics Effectiveness and SafeTy (BEST) Initiative to ensure the safety and effectiveness of biological products. BEST uses novel methods such as artificial intelligence and natural language processing to conduct biologics safety surveillance using real-world data. A distributed network and an innovative methods exchange platform are also envisaged. Several publications have already approved. See BEST for a list. A recent publication from BEST evaluated COVID-19 vaccine safety in near-real time using large commercial insurance databases, confirming previously-known safety signals for myocarditis/pericarditis and anaphylaxis following mRNA vaccination. BEST surveillance will continue to identify safety signals of interest that can be explored further. The FDA's approach to studying COVID-19 vaccine safety will be the subject of the October journal club (see below). Check out the BEST Seminar Series for monthly updates on surveillance and real-world data methods.

Adverse Events Monitoring

- Injection site necrosis after 23-valent pneumococcal vaccination
- Ayurvedic medicines cause lead toxicity
- Chemotherapy makes fingerprints disappear; cancer patients go on unprecedented crime sprees? Read about
- 6 unusual side effects of medicines.

III. VACCINATION AND SOCIETY

Vaccination Intentions and Hesitancy

Vaccine decisions may also be altered by personal experiences, Associations between Covid-19 death exposure and Covid-19 vaccine uptake

Combating COVID-19 vaccine hesitancy requires effective communication of the benefits and risks of vaccination. An enhanced communication strategy to promote pertussis vaccination among pregnant people in Milan, Italy could provide insights for COVID-19 vaccination communications. The WHO's "Vaccine safety and false contraindications to vaccines" manual is another helpful tool to understand common misconceptions about vaccination. A contrarian suggestion is that there should be no response to misinformation because a response risks amplifying the misinformation and suggests a moral equivalency between legitimate science and pseudo-science. Unfortunately, several physicians have contributed misinformation on social media, seemingly legitimizing anti-vaccine perspectives that are not based in science.

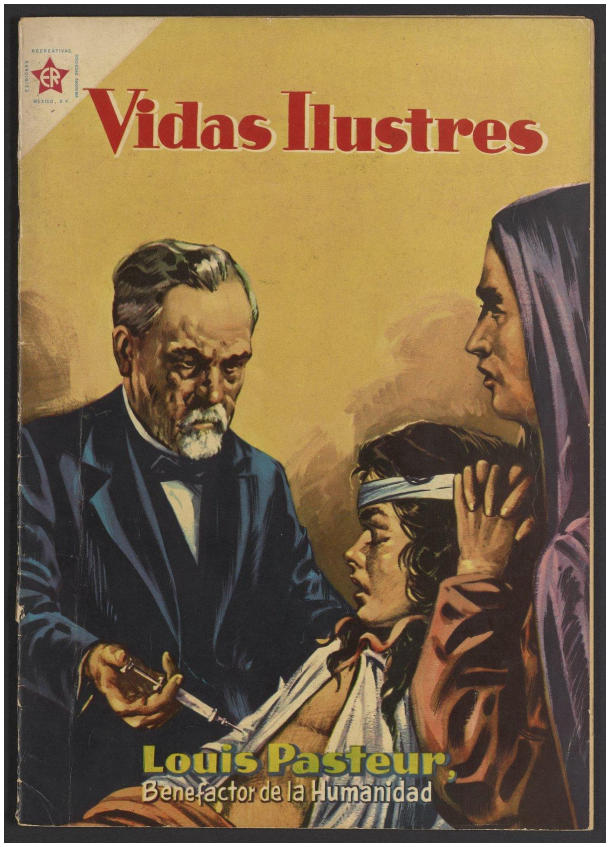
Governmental vaccination mandates, a long-standing strategy for infectious diseases prevention, are facing new challenges with growing vaccine hesitancy. Religious exemptions continue to protect anti-vaccine beliefs and behaviors, and the processes for granting religious exemptions are inconsistent across jurisdictions in the US.

Political Vaccinology

Politics affects COVID-19 mortality: excess death rates due to COVID-19 were higher among Republican voters compared to Democratic voters in the US.

Florida Governor Ron de Santis and Surgeon General Joseph Ladapo continue to oppose COVID-19 vaccination and preventive measures.

History of Vaccination



Louis Pasteur, Benefactor of Humanity | Science History Institute

An 1898 discussion about vaccines and vaccine resistance unfortunately sounds very familiar: An interesting parliamentary debate on vaccination.

Caveat Emptor

Dr. Gregg Semenza, 2019 Nobel Prize Laureate for his work on cellular oxygen regulation, has withdrawn several publications due to concerns of improper reporting of data. The publications had already been cited over 750 times.

The president of Stanford University, Dr. Marc Tessier-Lavigne, withdrew his landmark 2009 paper published in *Nature* describing future directions for Alzheimer's research and treatment, and resigned his position as president but will remain a member of the faculty. Twelve papers related to this research were investigated for fraud and lack of scientific rigor.

Reader, beware! To flex your peer-review skills and learn how to critically assess articles, please join our journal club (details below).

IV. BC MEMBER NEWS & ANNOUNCEMENTS

Brighton Collaboration's website gets a new look

We are excited to share our redesigned website with you. Visit brightoncollaboration.org and find easy-to-navigate resources, including a table of our case definitions, vaccine safety templates, a newsletter archive, and information about our Science Board members.

SPEAC launches new website

The Safety Platform for Emergency vACcines (SPEAC) has launched its new website. Visit speacsafety.net to learn about the CEPI-funded project and access tools including AESI lists, case definition companion guides, guidance documents, and more.

Brighton Collaboration Members attend the BeCOME Conference

The BeCOME (Beyond COVID: the Future of the Real-World Monitoring of Vaccines) Conference was held in Annecy, France, June 11-13.

BeCOME was initiated to create a sustainable forum where experts in Pharmacovigilance and Pharmacoepidemiology from key stakeholders (industry, public health, regulators, academics) can collectively discuss and develop innovations for post-marketing monitoring of benefits and risk of vaccines, leveraging the learnings and keeping the momentum of progress made in response to the COVID emergency.

Future activities in the following workstreams were discussed and prioritized during the meeting: 1) Background Incidence Rates; 2) Safety studies; 3) Pregnancy Surveillance; 4) Vaccine Benefits; 5) Signal Detection; 6) Digital solutions; 7) Low- and Middle-Income Countries.

Ongoing Case Definition Translations

We are excited to announce that the Brighton Collaboration has begun publishing Korean translations for our case definitions and associated companion guides. Some have been available previously in Chinese, Spanish, French, or Portuguese.

Digital Innovations in Vaccine Safety (DIVaS) Working Group

The Brighton website is undergoing renovation and we need help from frequent users to advance requirements and provide design feedback. Please keep your eye out for the new and improved Brighton Collaboration website, which has recently been published in its beta form. Any feedback is appreciated, and please write any positive notes or areas for improvement via email to bc-coordinator@taskforce.org with the subject header: "Beta BC Website Feedback"

Vaccines Journal Club

In collaboration with the International Society for Pharmacoepidemiology (ISPE) Special Interest Group (SIG) on Vaccines, the Brighton Collaboration is pleased to continue the Vaccine Safety Journal Club. Members of both organizations are invited to review and discuss the latest research on vaccine safety, from epidemiological methods to qualitative research. The journal club is co-hosted by SIG Chair Jen Gerber and BC member Nadja Vielot of the University of North Carolina. The next journal club meeting is planned for January 2024. If you are interested in leading a journal club session, please contact nadjavielot@unc.edu.

To receive the virtual journal club link and to receive journal club announcements, please join the mailing list by completing this Google Form.

New Brighton Collaboration Publications

- A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for the Novavax COVID-19 Vaccine (NVX-CoV2373), a recombinant spike protein vaccine with Matrix-M adjuvant to prevent disease caused by SARS-CoV-2 viruses
- A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for the Medigen COVID-19 protein vaccine
- Korean translations of BC case definition publications are now available
- European Medicines Agency Myocarditis Workshop Report (January 2023)
- Sensorineural Hearing Loss: AESI Case Definition Companion Guide
- Anosmia Case Definition

BC Membership

Brighton is looking to expand its membership to strengthen global participation in activities and working groups. Currently, Brighton Collaboration consists of over 1000 members in 108 different countries with the majority of members from the USA, Canada, and India. Please encourage your colleagues to visit our website and join the Brighton Collaboration.

Brighton Collaboration Website

The BC website is continuously updated with BC news and activities. It also has an archive of BC case definitions and publications on the new website. Please send comments on the new website, and keep an eye out for new content and features on the website as we go forward.

Articles and Comments to the VSQ are welcomed and invited

The VSQ is produced by volunteers. But, there are unavoidable expenses for office supplies, etc.
If you would like to help financially with the VSQ, click here and accept our thanks.

We would like to have a series of groups report their work on vaccines, vaccine safety, etc. What have you done? What are you doing? What would you like to do? Contact Editor-in-Chief Fred Varricchio (varricchio@comcast.net) to contribute.

Subscribe to Vaccine Safety Quarterly:

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V. NEW VACCINE SAFETY LITERATURE

A few articles that may be of interest

1. Factors associated with intention for revaccination among patients with adverse events following immunization.

   Muñoz CE, Pham-Huy A, Pernica JM, Boucher FD, De Serres G, Vaudry W, Constantinescu C, Sadarangani M, Bettinger JA, Tapiéro B, Morris SK, McConnell A, Noya F, Halperin SA, Top KA. Vaccine. 2023 Sep 2:

   Objectives: Individuals and healthcare providers may be uncertain about the safety of revaccination after an adverse event following immunization (AEFI). We identified factors associated with physician recommendation for revaccination and participant intention to be revaccinated among patients with adverse events following immunization (AEFIs) assessed in the Canadian Special Immunization Clinic (SIC) Network from 2013 to 2019.

   Conclusion: Physicians appear to use AEFI type and impact to guide recommendations while patients use primarily AEFI impact to form intentions for revaccination. The findings may help inform counselling for patients with AEFIs.

2. Type 1 diabetes, COVID-19 vaccines and short-term safety: Subgroup analysis from the global COVAD study.

   Chatterjee T, Ravichandran N, Nair N, Gracia-Ramos AE, Barman B, Sen P et alCOVAD Study Group. J Diabetes Investig. 2023 Sep 11.

   Aims/introduction: Coronavirus disease 2019 (COVID-19) vaccinations have been proven to be generally safe in healthy populations. However, the data on vaccine safety in patients with type 1 diabetes are scarce. This study aimed to evaluate the frequency and severity of short-term (<7-day) adverse vaccination events (AEs) and their risk factors among type 1 diabetes patients.

   Conclusions: COVID-19 vaccination was safe and well tolerated in patients with type 1 diabetes with similar AE profiles compared with HCs, although severe rashes were more common in type 1 diabetes patients.

3. mRNA COVID-19 Vaccination Does Not ExacerbSymptoms or Trigger Neural Antibody Responses in Multiple Sclerosis.

   Blanco Y, Escudero D, Lleixà C, Llufriu S, Egri N, García RR, et al. Neurol Neuroimmunol Neuroinflamm. 2023 Sep 7;10

   Background and objective: In people with multiple sclerosis (pwMS), concern for potential disease exacerbation or triggering of other autoimmune disorders contributes to vaccine hesitancy. We assessed the humoral and T-cell responses to SARS-CoV-2 after mRNA vaccination, changes in disease activity, and development of antibodies against central or peripheral nervous system antigens.

   Discussion: In this study, mRNA COVID-19 vaccination was safe and did not exacerbate the autoimmune disease nor triggered neural autoantibodies or immune-mediated neurologic disorders. The outcome of patients who developed SARS-CoV-2 infection was favorable.

4. Safety and Immunogenicity of the BNT162b2 Vaccine Coadministered with Seasonal Inactivated Influenza Vaccine in Adults.

   Murdoch L, et al; C4591030 Clinical Trial Group. Infect Dis Ther. 2023 Sep 12.

   Introduction: Vaccination is a critical tool for preventing coronavirus disease 2019 (COVID-19) and influenza illnesses. Coadministration of the COVID-19 vaccine, BNT162b2, with seasonal inactivated influenza vaccine (SIIV) can provide substantial benefits, including streamlining vaccine delivery.

   Conclusions: BNT162b2 coadministered with SIIV elicited immune responses that were noninferior to those elicited by BNT162b2 alone and SIIV alone, and BNT162b2 had an acceptable safety profile when coadministered with SIIV. The results of this study support the coadministration of BNT162b2 and SIIV in adults.

5. Active surveillance of adverse events following COVID-19 vaccines in a tertiary care hospital.

   Cherian, Naveena Mary et al. “Active surveillance of adverse events following COVID-19 vaccines in a tertiary care hospital.” Therapeutic advances in vaccines and immunother

   Background: Vaccination is a safe and effective way to prevent disease and save lives, but it may also produce some undesirable adverse events (AEs)which may affect healthy individuals. Therefore, the monitoring of AE following immunization (AEFIs) is necessary. The objective of this study was to assess the AEs following COVID-19 vaccinations in a tertiary care hospital.

   Methodology: The study was conducted as active vaccine safety surveillance for a period of 6 months among the COVID-19 vaccine beneficiaries of the study site. Active surveillance was conducted via initiating two telephone contacts.

   Results: A total of 2927 enrolled study population completed the study with a response rate of 80.85%. The study identified 902 AEFIs from 614 study populations with an incidence rate of 20.97%. Of which 794 and 79 AEFIs were associated with COVISHIELD™ and COVAXIN®, respectively. The majority of the events were reported among the age group of 18-29 years. Overall, only three events were serious and no deaths were reported among the study population. A total of 75.59% of events had a consistent causal association with vaccination and were categorized as vaccine product-related reactions. The study identified various factors such as gender ($p = 0.019$), age ($p < 0.05$), co-morbid status ($p = 0.032$) and dose number ($p = 0.001$) as potential predictors for development of AEFI.

   Conclusion: The study identified only 0.33% of events as serious, and 99.67% of the study population recovered from the AEFIs, which reveals that COVISHIELD™ and COVAXIN® have a generally favourable safety profile. However, close monitoring is required to identify the potential signals, as the safety data from the clinical trials are limited.

BRIGHTON COLLABORATION LEADERSHIP

Brighton Collaboration Science Board

Here is the full list of SB members and their qualifications as well as their Brighton experience and areas of expertise.

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Anita Renhan-White: Program Manager, Brighton Collaboration

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