

Safety by Numbers

... A newsletter highlighting collaboration and data to support vaccine safety communication

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Post-Authorisation vaccine safety risk assessment is key to combatting vaccine hesitancy

Vaccine hesitancy continues to threaten public health

Vaccine hesitancy has been a growing threat to global public health, as declared by the World Health Organization, for years predating the COVID-19 pandemic. Despite decades of evidence proving that vaccines are critical to controlling devastating diseases around the world, nearly 50% (94 out of 204) of the countries and territories analysed by the Global Burden of Disease Study recorded decreasing coverage for the third diphtheria/tetanus/pertussis vaccination over the preceding 10 years. Similar patterns have been observed with other vaccines. What's more, only 11 countries were estimated to have reached the Global Vaccine Action Plan target of at least 90% coverage for nine of 11 vaccines assessed. Vaccine hesitancy related to the COVID-19 vaccine has followed this concerning trend, and despite broad access to very safe and effective vaccines, our collective ability to control this pandemic has been hampered by vaccine hesitancy in many countries.

Effective communication efforts require timely robust data

The complex causes of this vaccine hesitancy trend have been in play for many years, and appropriate solutions to address this trend are equally complex. Historically, the vaccine authorisation process has been in place to ensure that the benefits of vaccination outweigh the risks. However, increased and coordinated data collection and analysis globally are needed to provide comprehensive surveillance and monitoring of vaccines to assess their safety once they are used in larger populations, to characterise uncommon risks, and to identify adverse reactions that occur in subpopulations who are excluded from or inadequately represented in clinical trials.

Responding quickly to vaccine safety scares (real or perceived) can prevent a data and communication vacuum

A key contributing factor to vaccine hesitancy are coincidental adverse events following immunisation whose only link with vaccination is timing. These events, often broadcast quickly and aggressively through the news and social media, can ignite public anxiety and derail immunisation programs. Key to counter-acting these real or perceived vaccine safety scares is post-authorisation safety monitoring, which has not always been executed in a timely or comprehensive manner, sometimes resulting in a loss of vaccine confidence and uptake. Rigorous and efficient post-authorisation

vaccine safety risk assessment is one of several needed solutions to pre-empt or mitigate vaccine hesitancy.

Historical examples serve to illustrate the vital role that vaccine safety signal investigations can play in facilitating or hindering efforts to control diseases

Today we recognise the polio vaccination program to be a success story that resulted in the elimination of polio in most parts of the world as we near eradication. However, it is important to note that the launch of the polio vaccine program in 1955 in the United States was accompanied by reports of paralysis following vaccination. The recently formed Epidemic Intelligence Service (EIS) at the Centers for Disease Control and Prevention (CDC) was able to rapidly investigate these post-polio vaccine paralysis cases through an outbreak investigation approach. It was quickly identified that some vaccine batches were not fully inactivated and had caused wild type polio. After a brief pause to the vaccine program and following a rapid investigation—which centred around robust and rigorous science, objectivity of risk assessment, and transparency—the program quickly resumed. Soon after, the U.S. regulators developed basic manufacturing and authorisation guidelines addressing such issues as lot consistency. The swift response to this polio vaccine safety event is a model showing the positive impact of timely vaccine safety risk assessment, which in this case resulted in the resumption and success of the polio vaccine program. However, instead of dispatching a small army of EIS Officers to manually search for new cases of paralysis among recent vaccinees as was done in 1956, we need to do be able to conduct similar rapid investigations of vaccine safety issues using latest digital tools.

Unlike the previous example, there also exist many instances in which a lack of efficient safety risk assessment mechanisms has contributed to significant harm to global public health. One such example is the perceived link between vaccines and autism spectrum disorder (ASD). A 2019 U.S. survey found that among adults aged 30–49, 13% reported that they believed that vaccines cause autism and an additional 43% were unsure. This has resulted in increased outbreaks of previously controlled diseases, such as measles, due to a decline in immunisation. Europe has seen large outbreaks of measles, and the United States almost lost its elimination of measles status as cases increased in communities where vaccination rates are low.

As of 2019, there have been 16 well conducted epidemiological studies—conducted in various countries

and using different methods—exploring an association between autism and receipt of MMR vaccine, thimerosal in vaccines, and simultaneous vaccination with multiple vaccines. None of these studies found an association between vaccines and autism. Despite these results, concerns over the link between vaccines and autism persist, which begs the question: How effective is science at combatting vaccine hesitancy after all?

The answer to this question, in this particular example, requires a look at the timing of the controversies and the studies. Andrew Wakefield's flawed case series in the *Lancet* in February 1998 marks the beginning of the broader public controversy linking vaccines to autism. At the time, following the publication of this flawed study, there was no rigorous scientific study available saying otherwise. In fact, it took 15 months for the first study to be published showing no evidence of a link between the MMR vaccine and autism. And it was nearly two more years before the next study with the same results was published. This time lapse proved to be devastating for vaccination programs worldwide. And the damage is still being felt nearly two and half decades later.

The ability to answer important vaccine safety questions quickly and credibly is critical but requires investment

Pre-existing infrastructure to support quick and efficient vaccine safety risk assessment is critical. Studies, collaborations, and publications assessing vaccine adverse events are an important part of addressing vaccine hesitancy, but without robust infrastructure in

place to quickly assess and disseminate these findings, they can be significantly delayed causing additional challenges to global vaccine programs.

In the absence of such infrastructure, we may miss critical evidence suggesting certain uncommon risks from vaccines. However, absence of evidence does not mean evidence of absence. And without such infrastructure, we not only limit our ability to quickly collect the data necessary to fully understand the risks of vaccines generally, but also to clearly identify the particular and unique risks of certain vaccines to certain populations groups. This knowledge is paramount to securing public trust *and* public health.

Collaborative and comprehensive infrastructure is the key to our ability to address vaccine concerns quickly and with scientific rigor. As we have learned from the pandemic and other historical events, we risk jeopardising public trust in vaccines, and therefore public health generally, if we do not make strong investments in the processes and systems necessary to quickly inform policy, practice, and communications around vaccine safety.

Investment in global vaccine risk assessment infrastructure is critical to combatting vaccine hesitancy and rebuilding public trust in vaccines.

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Updates from the newsletter collaborating organisations

Global Vaccine Data Network™

The Global Vaccine Data Network™ (GVDN™), a multinational, investigator-led network, was founded in 2019 with 21 partner sites across 17 countries. They now have 23 partners across 19 countries, representing more than 250 million people, and continue to expand. The aims of the GVDN™ are to:

- Evaluate vaccine safety concerns through analysis and evaluation of large clinical databases, focusing on rare events
- Evaluate vaccine effectiveness to facilitate risk/benefit analyses
- Coordinate a response to concerns regarding vaccines, such as vaccine hesitancy

In April 2021, the GVDN™ was funded by the U.S. Centers for Disease Control and Prevention (CDC) to conduct the Global COVID Vaccine Safety (GCoVS) project,^a with the GVDN™ Global Coordinating Centre in New Zealand supporting 17 global data partners to evaluate and compare COVID-19 vaccine safety. This project includes several components:

- Develop background rates for adverse events of special interest for each partner site and display these on a publicly available dashboard
- Conduct observed over expected assessments for selected adverse events of special interest
- Conduct association studies for events that have been identified as likely associated with specific types of COVID-19 vaccines
 - Myocarditis and pericarditis
 - Thrombosis with thrombocytopenia syndrome/vaccine-induced immune thrombotic thrombocytopenia (TTS/VITT)
 - Guillain-Barré syndrome (GBS)
- Assess risk of vaccine mediated enhanced disease following COVID-19 vaccines
- Assess COVID-19 vaccine safety in pregnancy
- Conduct genomic assessments for cases and controls for myocarditis, TTS/VITT, and GBS
- Develop communications and resources to support vaccine confidence

The first outputs are expected from mid-2022 and will be available on our website globalvaccinatedatane트워크.org.

Genomics of COVID-19 Vaccine-Induced

Adverse Events

The GCoV project affords a unique opportunity to examine genetic contribution towards vaccine-induced adverse events. Genetic contributions to serious and life-threatening drug reactions have seen genetic information incorporated into 800 drug labels worldwide by regulators. Genomic investigations will try to identify who is at risk of a specific adverse event as well as lead to a better understanding of the biological or pathophysiological basis of adverse events.

The Genomics of COVID-19 Vaccine-Induced Adverse Events project is one of the GCoV project^a activities and is being led by Dr Bruce Carleton. Myocarditis and/or pericarditis, TTS/VITT, and GBS are the globally reported adverse events following COVID-19 vaccination being focused on.

Participants are being sought from around the world. A saliva sample that can be sent by courier is required for DNA analysis.

Partner sites and researchers interested in collaborating in this project can contact Dr Bruce Carleton by email for further information, bcarleton@popi.ubc.ca.

Individuals interested in participating can also email Dr Carleton to self-refer.

ALIVE-GAVI alliance

The GVDNTM is a technical partner for the active surveillance of COVID-19 vaccine safety in eight African Leadership in Vaccinology Expertise (ALIVE) countries led by Shabir Madhi and funded by GAVI.

Across these countries over 147 million people have received at least one COVID-19 vaccination.^b Using hospital case-based monitoring, the project will estimate the risk of pre-defined adverse events of special interest (AESIs) with acute onset and a short period of increased risk following COVID-19 vaccination using a self-controlled risk interval (SCRI) study design.

The GVDNTM has provided assistance with development of screening and case report forms using the REDCap platform and will assist with descriptive and statistical analysis of the data. Data from the participating countries will be included in the GVDNTM database for pooled analysis on the association of COVID-19 vaccines and risk for myocarditis and pericarditis, TTS/VITT, and GBS by age, gender, race, and vaccine type and manufacturer.

Notes

a. This project is supported by the Centers for Disease Control and Prevention (CDC) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award totalling US\$5,643,515 with 100% percentage funded by CDC/HHS. The contents are those of the author and do not necessarily represent the official views of, nor an endorsement, by CDC/HHS, or the U.S. Government. For more information, please visit [cdc.gov](https://www.cdc.gov).

b. Mathieu, E., Ritchie, H., Ortiz-Ospina, E. et al. A global database of COVID-19 vaccinations (Internet). Updated 2022 April 10, cited 2022 April 28. Available from <https://ourworldindata.org/covid-vaccinations>.

Vaccine Monitoring Collaboration for Europe

The Vaccine Monitoring Collaboration for Europe (VAC4EU) was established early 2020 following the successful **ADVANCE** project, which designed and tested an ecosystem for collaborative monitoring of vaccines in Europe. VAC4EU was prepared to embark on the preparation for and safety monitoring of COVID-19 vaccines that was requested by the European Medicines Agency (EMA), vaccine manufacturers, and other organisations.

VAC4EU has become a vibrant community with 24 member organisations who are collaborating in Europe to generate evidence on vaccine effects based on both primary data collection and secondary use of health data. VAC4EU is also an active member of the GVDNTM. For this newsletter we aim to give an overview of the COVID-19 vaccine studies finished and ongoing work in which VAC4EU coordinates or participates.

Completed studies

VAC4EU worked with the European Pharmacovigilance and Pharmacoepidemiology (EU PE&PV) Research Network in the **ACCESS** (vaccine Covid19 monitoring readin**ESS**) project, funded by EMA.

ACCESS aimed to prepare a European infrastructure to monitor COVID-19 vaccines. It generated:

- Event definition and code lists for AESI and corresponding background rates across 10 data sources in Europe. Definitions, code lists, report and data are publicly available with more than 3000 views and 1000 downloads in the VAC4EU Zenodo community doi.org/10.5281/zenodo.5255870.
- Eight template protocols for coverage, effectiveness, and safety studies on the European Union electronic Register of Post-Authorisation Studies (**EU PAS Register**) and **VAC4EU website**.
- Interactive dashboard of incidence rates of AESI on the **VAC4EU website**.

VAC4EU also worked with the EU PE&PV Research Network in the **ECVM** (Early Covid-19 Vaccine Monitor) project, partially funded by EMA. This project aimed to monitor incidence of adverse events related to COVID-19 vaccines using both electronic health record data and cohort event monitoring of self-reported adverse reactions in vaccinated persons.

- Cohort event monitoring was conducted in seven countries (NL, DE, UK, FR, BE, IT, CR) using the Lareb Intensive Monitoring app. This part included more than >117,000 vaccinated persons who are monitored for six months. Report and publication are submitted.
- Safety monitoring of 33 adverse events of special interest (AESI) was conducted with four EHR data sources capturing 25 million subjects (NL, UK, IT, ES) using a cohort design. Results were shared monthly with EMA on a dashboard, publications are submitted.

Ongoing studies

The **CVM (COVID-19 Vaccine Monitor)** project, in collaboration with EU PE&PV Research Network and also funded by EMA, runs until 2023. The project is to prepare for and perform rapid assessment of the association of AESI following COVID-19 vaccination. There are several components:

- Cohort event monitoring is ongoing in 10 countries for first dose, booster dose or special populations, e.g., prior COVID-19, children pregnancy, lactation, immunocompromised. Safety information on more than 550,000 vaccinees has been reported to EMA.
- Rapid hypothesis testing studies using cohort and self-controlled risk-interval (SCRI) design on signals using electronic health record data in nine data sources in Europe, data has been submitted to EMA on multi-inflammatory syndrome and myocarditis/pericarditis.

The **CVE (COVID-19 Vaccine Effectiveness)** project began in April 2022, funded by EMA with the aim to analyse effectiveness of homologous and heterologous COVID-19 vaccinations in Southern, Central and/or Eastern Europe.

Studies funded by vaccine manufacturers

- Comirnaty PASS & myocarditis study
- Spikevax PASS & myocarditis study
- Vaxzevria PASS
- Janssen COVID-19 vaccine PASS

Collaboration with GVDN

- VAC4EU is a partner in the GVDN.
- VAC4EU shared the background rate protocol and data for use by GVDN.
- VAC4EU is participating with four member organisations in UK, ES and NL in the GVDN association studies on myocarditis, thrombosis with thrombocytopenia syndrome (TTS) and Guillain-Barré syndrome (GBS), as well as in the vaccine adversomics studies.

Journal club

To stimulate and enjoy scientific debate, VAC4EU organises a monthly journal club, for the vaccine scientific community, members and external persons are welcome to join. Please register on this page: vac4eu.org/journal-club.

Scientific Advisory Board (SAB) members

VAC4EU operates an independent SAB for advice on ongoing VAC4EU studies. We seek to extend our pool of SAB members. If you are interested, please send your CV to secretariat@vac4eu.org.

Institute for Vaccine Safety

The Institute for Vaccine Safety (IVS) was established in 1997 in the [Department of International Health](#) at the Johns Hopkins University School of Public Health - now the Johns Hopkins Bloomberg School of Public Health. Their mission is to provide an independent assessment of vaccines and vaccine safety to help guide decision makers and educate physicians, the public and the media about key issues surrounding the safety of vaccines. Systematic reviews of a broad range of vaccine safety issues with clear causality conclusions are available on the IVS website at vaccinesafety.edu.

Integral to achievement of their goal to prevent disease using the safest vaccines possible, the Institute for Vaccine Safety:

- provides a forum for dissemination of data regarding specific issues concerning the safety of immunisations,
- investigates safety questions where insufficient data are available to provide definitive conclusions,
- conducts methodological and empirical research on post-licensure vaccine safety evaluation, and
- undertakes individual research projects to obtain specific information regarding vaccine safety when existing information about the safety of a specific vaccine is insufficient or flawed.

LetsTalk COVID Vaccines



LetsTalkCovidVaccines.com, a website developed and managed by the IVS, provides personal stories and information-based animation tailored to users' COVID-19 vaccine intentions, concerns, and demographics.

Resources are currently available in English and Spanish and focused on COVID-19 vaccines but will soon be expanded to include resources in French and vaccines across the lifespan.

Partner sites, public health, and community organisations can contact Professor Daniel Salmon, the Director of the IVS, via email, dsalmon1@jhu.edu, to discuss development of resources with stories and information tailored for their community, country or region.

Did you know ...

To identify a two-fold risk of a vaccine-associated event that occurs once in 100,000 people, 4.7 million people need to have received the vaccine.¹

1. Appendix A: Sample Size Tables. In: Strom BL, Kimmel SE, Hennessy S, editors. *Pharmacoepidemiology*. 5th ed. West Sussex: John Wiley & Sons; 2012. p. 904–20.

Brighton Collaboration

The Brighton Collaboration (BC), launched in 2000, is a non-profit global network with the goal of advancing the science of vaccine safety. It is named after the city in England where the idea to develop standardised case definitions (and eventually other internationally accepted standards, tiered by the level of evidence) for study of adverse events following immunisation (AEFI) was first formulated and a group of volunteers coalesced to bring this vision to fruition.

The "Brightonians" currently number >1000 from 108 countries; ~60% high Income/~40% low- and middle-income countries (LMIC). From 2000–2018, the BC secretariat was hosted by the Children's Hospital in Basel, Switzerland; it relocated in 2019 as a programme of the Task Force for Global Health in Decatur, Georgia.

The standardisation of the periodic table of elements by Mendeleev in 1869 allowed the fields of chemistry and physics to subsequently advance scientifically. Analogously, the various BC working groups have been developing the various standard "vocabularies" needed to advance the science of vaccine safety since 2000. Currently ~95 BC standard case definitions, guidelines, and templates have been developed and published. Several former or existing BC Science Board members are leading various vaccine safety initiatives globally.

Some of the other major initiatives undertaken by BC along are listed [here](#), they include:

- The Safety Platform for Emergency vACcines ([SPEAC](#)) Project supports the emerging Coalition for Epidemic Preparedness Innovations (CEPI) portfolio by creating capacity and solutions for harmonised safety assessment of CEPI vaccines
- The [CARESAFE](#) project builds on existing Centers for Disease Control and Prevention (CDC) and Task Force for Global Health/Brighton Collaboration platforms and technical expertise to work with LMIC to pilot several approaches to strengthen their capacity for pharmacovigilance of COVID-19 vaccine adverse events following immunisation (AEFI)/of special interest (AESI).
- The International Network of Special Immunization Services ([INSIS](#)) to address knowledge gaps in our understanding of the causes of AESIs, risk factors for developing AESIs, and determine the best way to immunise individuals with prior AESIs or risk factors for developing AESIs.
- [GAIA](#) Network for Global Alignment of Immunisation safety Assessment in pregnancy.
- Systematic Observational Method for Narcolepsy and Influenza Immunization Assessment ([SOMNIA](#)).
- Global Research in Paediatrics ([GRIP](#))
- Viral Vector Vaccines Safety Working Group (V3SWG); renamed as the Benefit-Risk Assessment of Vaccines by TechnoLOGY ([BRAVATO](#)) Working Group develops harmonised guidelines and templates for assessing/addressing potential safety issues of concern for new vaccine candidates.
- The Vaccine Safety Quarterly ([VSQ](#)) newsletter.

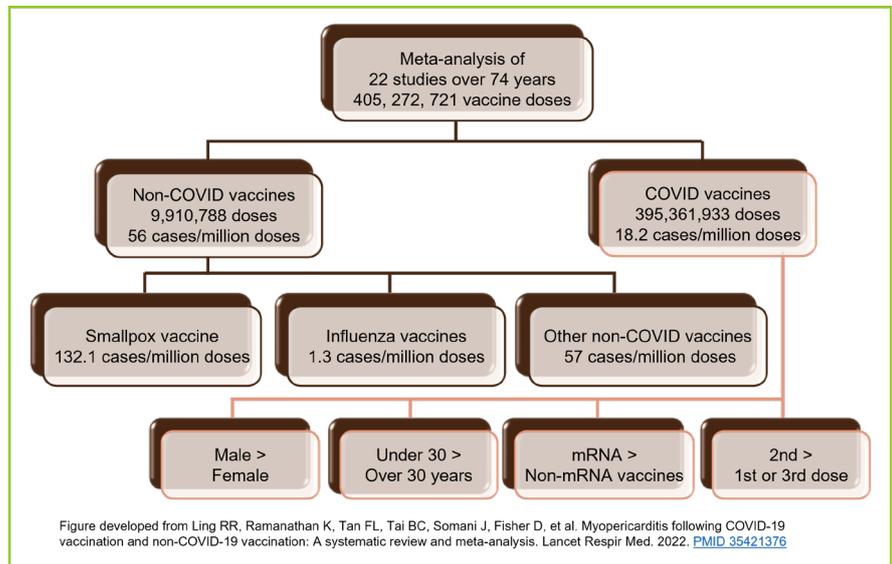
... by Numbers

Reports of myopericarditis onset following vaccination

A new systematic review and meta-analysis of reports of myocarditis or pericarditis (myopericarditis) onset in temporal relation to any vaccination provides perspective on this topic. The review includes observational studies published from 1 January 1947 to 31 December 2020 and events spontaneously reported to four passive surveillance systems. The reporting rate was not significantly different to the reporting rate temporal to receipt of any other vaccination except smallpox vaccine.

Smallpox vaccination is still used for laboratory workers and healthcare providers, and some military personnel in the U.S., at risk of exposure to orthopoxviruses (smallpox and monkeypox). As the current monkeypox outbreak evolves, the WHO has emphasised the importance of effective surveillance, investigation, and management of monkeypox outbreaks in countries that are not endemic for the disease to prevent ongoing spread.

Although not currently advised, roll-out of smallpox vaccination for more risk groups and populations may become necessary to contain monkeypox outbreaks not manageable with contact tracing and isolation. Rigorous monitoring the safety of smallpox vaccines, especially with the known association of increased myopericarditis risk will be a critical and an important component in vaccine communications and confidence.



Key points

The reporting rates of myopericarditis onset after vaccination were:

- 18.2 cases per million COVID vaccine doses
- 56 cases per million non-COVID/non-smallpox vaccine doses
- 132 cases per million smallpox vaccine doses