Safety by Numbers

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

ISSUE 2 – OCTOBER 2022

Safety of smallpox vaccines administered to prevent monkeypox

With the advent of effective vaccines and medications for COVID-19, the world was beginning to breathe a sigh of relief when a new scourge emerged – monkeypox. The impact of climate change, population growth, and increased globalisation are contributing to the emergence of previously uncommon or new infectious diseases. Monkeypox is not likely to be the last emerging infection, but it comes at a time when the global public health infrastructure has not recovered from the COVID-19 pandemic.

Monkeypox

Monkeypox is a member of the Orthopoxvirus genus along with smallpox, cowpox and camelpox. However, unlike smallpox, its host is not uniquely humans and transmission is seen across a range of other animals including monkeys and rodents such as prairie dogs. The virus has been known since the 1950s when it was discovered in laboratory monkeys in Denmark, but the first human case was not identified until 1970 in the Democratic Republic of the Congo (DRC). It exists in two clades – central African and West African – and has traditionally been associated with animal to human transmission with very limited human-to-human.[1] Mortality rates in Africa for the Central African clade have been reported in up to ten percent of cases with mortality in the West African clade being about half that.[1,2]

More recently, the West African clade has emerged in outbreaks globally among human communities, especially in the USA and Europe with more than 35,000 cases having been reported outside of Africa as of August 2022, with most cases occurring among men who have sex with men. The disease in this current outbreak is generally not serious but the lesions can be very painful. Deaths have been reported outside Africa.[3]

Vaccination for prevention of monkeypox

While there is no specific approved vaccine for monkeypox, animal studies[4,5] have shown that vaccines developed for smallpox are effective in protecting against infection and severe disease with limited human epidemiology supporting these observations.[6-8] Smallpox vaccines that are currently in use, or may become available, include vaccines based upon the original cowpox vaccine developed by Jenner in the 18th century and vaccines using modified vaccinia Ankara (MVA).[9,10]

Live viral vaccines

The live replicating vaccinia virus vaccines, ACAM2000, APSV (Aventis Pasteur Smallpox Vaccine), also known as Wetvax, Elstree-BN, VV Lister CEP, Lister/Elstree-RVIM, and Pourquier vaccine are administered as a single dose delivered percutaneously using a bifurcated needle. The live attenuated replicating vaccinia virus vaccine, LC-16 Kaketsuken/LC16m8, is also a single dose administered using a bifurcated needle.

Live attenuated non-replicating viral vaccines

The live attenuated non-replicating Bavarian Nordic MVA vaccine (Imvanex, Imvamune, Jynneos) is administered in a two-dose schedule, with a minimum interval of four weeks between doses, and injected subcutaneously.

Live recombinant vaccine

A live recombinant smallpox vaccine (VACdelta6) based on genetically modified vaccinia virus has been developed by Russia but there is a dearth of information currently for this vaccine.

Smallpox vaccine safety

The safety of the live replicating ACAM2000 and related vaccines has been well characterised. They can cause disseminated or even fatal infection in immunocompromised hosts and in recipients with eczema. The virus can be transmitted from the vaccination site to other individuals and congenital infection has been reported. Cases of encephalitis have also been reported.[9] However, the most notable side effect has been myocarditis.[11-18] This was estimated by Engler et al. (2015)[15] to occur in about seven per 100,000 healthy vaccinees with subclinical elevations of troponin post vaccination being more common.

Much less is known about the safety of the Bavarian Nordic MVA vaccine[19] as prior to the recent monkeypox outbreak the total usage experience was in about 10,000 individuals in clinical trials, where myocarditis was not seen. However, troponin elevations have been reported.[20,21]

GVDN monitoring activities

Building upon the GVDN existing network infrastructure, a Work Group was convened to develop addendums to protocols developed for COVID-19 vaccine safety monitoring and assessment and begin evaluation of smallpox vaccines being used for monkeypox prevention in September 2022.

Rapid cycle analyses for selected outcomes and development of observed versus expected AESI counts for smallpox vaccines used in the network, and association studies that evaluate the risk of post-vaccination myocarditis, pericarditis, and Guillain-Barré syndrome are underway. Evaluation of smallpox vaccine safety in pregnant women is also included in the maternal COVID-19 immunisation protocol, due for implementation in early 2023.

Limitations in the ability to monitor smallpox vaccine safety emerged early in the Work Group discussions. Smallpox vaccinations are not being recorded on national immunisation registers.

Continued ...

Duty of care and a lost opportunity

Global attention was focused on monkeypox in minority groups outside of Africa who had the highest risk of becoming infected with and transmitting monkeypox, and the risk behaviours associated with transmission. Consultations for monkeypox and availability of smallpox vaccinations were often through sexual health clinics as men who are have sex with men are the highest risk group.

Secrecy around smallpox vaccination, to reduce the risk of stigmatisation, became a priority for many individuals, and some cultures and countries.

To reduce the risk of stigmatisation of the populations most likely to benefit from vaccination and encourage and support them to protect themselves through vaccination, in many countries information on vaccination is recorded locally and is not being included in national vaccine registries.

The newer smallpox vaccines had only been administered to small numbers of individuals before this monkeypox outbreak.

Prior to this monkeypox outbreak, the newer smallpox vaccines had only been administered to a small number of individuals. Only by including these vaccines in registries can the safety of these vaccines be comprehensively assessed.

Recording smallpox vaccinations in registries is necessary to comprehensively assess the safety of these vaccines.

A lack of comprehensive information on the newer smallpox vaccines:

- *Hinders the ability of public health officials to make appropriate recommendations for their use.*
- *Makes it difficult for individuals to make an informed decision regarding receipt of these vaccines.*
- *Has inadvertently discriminated against the groups health professionals wanted to protect.*

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References
References are available on the last page of this newsletter.

Updates from the newsletter collaborating organisations

Vaccine Monitoring Collaboration for Europe

The Vaccine Monitoring Collaboration for Europe (VAC4EU) was established in early 2020 for collaborative monitoring of vaccines in Europe. VAC4EU has become a vibrant community with 25 member organisations across Europe, with many others interested to join. Members collaborate to generate evidence on vaccine effects based on both primary data collection and secondary use of health data. Any public health or research organisation who is not publicly listed can join upon approval by the general assembly. For more information on VAC4EU please visit our website at vac4eu.org and the Zenodo Community www.zenodo.org/communities/vac4eu.

Completed study

Early Covid-19 Vaccine Monitor (ECVM)

Since the previous newsletter, VAC4EU and its members continued work with the European Pharmacoepidemiology & Pharmacovigilance Research Network (EU PE&PV) to complete the ECVM study.

This cohort event monitoring study implemented early active surveillance of primary schemes in six European Union countries, focusing on reactogenicity and non-solicited adverse events of special interest (AESI). An additional cohort study assessed the rates of AESI using four electronic health care data sources, covering a population of 25 million people.

The results show a reactogenicity pattern consistent with clinical trial data and a very low rate of serious adverse events across all the AstraZeneca (AZ), Janssen/Johnson & Johnson (J&J), Pfizer/BioNTech (BNT), and Moderna (MOD) COVID-19 vaccines.

The electronic health care data cohort study assessed rate differences and relative risks of 29 AESI: acute aseptic arthritis, acute coronary artery disease, acute disseminated encephalomyelitis (ADEM), acute kidney injury, acute liver injury, acute respiratory distress syndrome, anaphylaxis, anosmia or ageusia, arrhythmia, Bell's palsy, chilblain-like lesions death, erythema multiforme, Guillain-Barré Syndrome (GBS), generalised convulsion, haemorrhagic stroke, heart failure, ischaemic stroke, meningoencephalitis, microangiopathy, multisystem inflammatory syndrome, myocarditis/pericarditis, myocarditis, narcolepsy, single organ cutaneous vasculitis (SOCV), stress cardiomyopathy, thrombocytopenia, thrombotic thrombocytopenia syndrome (TTS), and venous thromboembolism (VTE).

For most AESI, no excess risk was observed. However, an elevated incident rate ratio (IRR) was found for **anaphylaxis** [AZ, IRR 1.68 (1.37, 2.06)], **erythema multiforme** [MOD, IRR 2.64 (1.25, 5.6)], **GBS** [J&J, IRR 5.65 (1.40, 22.83)], **SOCV** [J&J, IRR 4.39 (1.09, 17.7)], **thrombocytopenia** [MOD, IRR 1.84 (1.07, 3.17)] and [J&J, IRR 2.27 (1.25-4.10)], **TTS** [AZ, IRR 2.98 (1.67, 5.31)] and [J&J, IRR 89.99 (10.30, Inf)], and **VTE** [BNT, IRR 1.11 (1.00, 1.24)] and [MOD, IRR 1.60 (1.40, 1.84)].

The results of both studies were presented at the International Conference for Pharmacoepidemiology (ICPE) or International Society for Pharmacometrics (ISOP) Annual Meeting. The study report is available in the VAC4EU Zenodo community repository and has been submitted for publication.

Ongoing safety and effectiveness studies

COVID-Vaccine-Monitor (CVM)

The CVM cohort monitoring study is a European Medicines Agency (EMA) funded project in collaboration with the EU PE&PV until April 2023, focusing on the continuation and extension of the ECVM study. Twelve countries recruit general and special population vaccine recipients (pregnant and lactating women, children, adolescents, immunocompromised, individuals with a history of allergy, and individuals with prior SARS-CoV-2 infection) through multiple vaccination centres within 48 hours of either their first or booster COVID-19 vaccination. Non-pregnant vaccinees are followed for up to six months from the date of their first vaccination, and individuals who are pregnant are followed until 1.5 months after the end of pregnancy.

Data are collected using the Lareb Intensive Monitoring (LIM) system (general population first dose), the Research Online (RO) tool from UMC Utrecht (booster and special populations), the Croat OpeN data collection system, and the German SafeVac2.0 data collection system.

An interim report describing the monitoring of 550,000 vaccinees, available in the VAC4EU Zenodo community, has already been downloaded 1330 times. Among 7,057 vaccinees in the special populations who reported at least one adverse drug reaction (ADR) following their first vaccination dose, 17 (0.2%) reported at least one serious ADR. In 3,793 vaccinees who reported at least one ADR following the second vaccination dose, nine (0.2%) reported at least one serious ADR. From the total number of vaccinees who reported at least one ADR following the first (N= 7,057) and second (N= 3,793) vaccination dose, 25 (0.4%) and 15 (0.4%) vaccinees reported at least one AESI following the first and second vaccination dose, respectively.

The most reported solicited local ADR among all the COVID-19 vaccine brands, special cohorts, and between first and second dose was pain at the injection site. This is consistent with observations in the general population and with previously published works. Among the solicited systemic ADRs, fatigue, headache, malaise, and myalgia were the most frequently reported events, which is consistent with total populations.

Studies using electronic health record data

The CVM study also created readiness for additional data sources to participate in signal evaluation studies in United Kingdom (CPRD), Norway (Norwegian registers), Spain (BIFAP, FISABIO, SIDIAP data sources), Netherlands (PHARMO), France (SNDS), and Italy (ARS, LAzio, and Pedianet). Registration of COVID-19 vaccines and COVID-19 disease varies across different data sources and geographical areas. Data from the different sources were transformed into the ConcePTION study common data model. Extensive quality checks were undertaken to verify data had been extracted and transformed correctly, and that the data was fit for purpose for COVID-19 studies.

Data sources that were *ready and fit for purpose* are being used to evaluate the myocarditis/pericarditis signal. The updated data clearly show an increased risk of myocarditis in individuals aged under 30 years after the second dose of an mRNA vaccine. Assessment of United Kingdom data alone, where AstraZeneca vaccine was used in younger persons, an elevated risk of myocarditis was also seen after AstraZeneca vaccination. Data were presented at ICPE and ISOP, and a publication has been submitted.

At the request of the Pediatric Committee (PDCO) at the EMA, the CVM project also studied the severity of COVID-19 in children over calendar time. The study was conducted using six data sources in Italy and Spain and included 4,610,927 children. Between 8-10 percent of the paediatric population had one or more risk factors for severe COVID-19 disease, most frequently respiratory disease. Vaccination uptake was quite extensive especially in children 12-17 years of age, in both Spanish and Italian data sources.

The Pfizer/BioNTech vaccine was predominantly used and the Moderna vaccine rarely used in those 12-17 years of age. The Janssen/Johnson & Johnson and AstraZeneca vaccines were rarely used, which is expected since they are not authorised for the paediatric population. Children 5-11 years were vaccinated later, at the end of 2021 and beginning of 2022.

The available data show that the rate of non-severe COVID-19 disease was high in non-vaccinated children, especially for the delta and omicron variants. Vaccination rates were high for 12-17 years of age, but lower in younger ages. Hospitalisations, intensive care unit admission, and death following COVID-19 disease were very rare in each of the age categories, both prior to and after vaccination.

The readiness of data sources will now be used to conduct self-controlled studies on associations that were observed in the ECVM studies. The study report was presented at a PDCO meeting.

COVID-19 Vaccine Effectiveness (CoVE)

The CoVE project is finalising a report on the effectiveness of current homologous and heterologous COVID-19 vaccination schedules in Europe. The study protocol is published on European Union electronic register of Post-Authorisation Studies (EUPAS47725).

PASS studies for vaccine manufacturers

Studies funded by vaccine manufacturers (i.e., Comirnaty PASS & Myocarditis, Spikevax PASS & Myocarditis, Vaxzevria PASS, and Janssen COVID-19 Vaccine PASS) have publicly deposited protocols in the EU PAS register. The studies are conducted according to the EncePP Code of Conduct for scientific independence. Each study also has a Scientific Advisory Board that works directly for VAC4EU to monitor scientific excellence and independence.

Collaboration with GVDN

Global Covid Vaccine Safety (GCoVS) project

VAC4EU is coordinating implementation of three GVDN association studies and the genomics study across its network. The association studies investigate the occurrence of myocarditis/pericarditis, vaccine-induced immune thrombotic thrombocytopenia (VITT), and Guillain-Barré syndrome (GBS) after COVID-19 vaccination. The genomics study investigates the potential genetic contribution towards the occurrence of these three adverse events. Cases will be identified

through hospital and electronic health record data, validated through case review, and a saliva sample collected from the individual for genomic analysis.

Journal club

To stimulate and enjoy scientific debate, VAC4EU organizes a monthly journal club. The vaccine scientific community, members and external persons are welcome to join. Anybody can register on this page https://vac4eu.org/journal-club

Events

VAC4EU was prominent at the International Conference of Pharmacoepidemiology in Copenhagen with its own exposition booth, and successfully contributed to the International Society of Pharmacovigilance Annual Meeting in Verona.

Photo: VAC4EU team at the International Conference of Pharmacoepidemiology

On 19 October 2022, the VAC4EU secretariat and UMC Utrecht study team enjoyed a site visit from the GVDN Lead Epidemiologist and Lead Biostatistician. The meeting was very pleasant and fruitful, with a presentation and discussion of updates on the GCoVS study and development of a strategy and procedures for ongoing collaboration.

In early November, VAC4EU will hold its biannual General Assembly Meeting as an in-person meeting in Barcelona.

Scientific Advisory Board members

VAC4EU operates an independent Scientific Advisory Board (SAB) for advice on ongoing VAC4EU studies. We are seeking to extend our pool of SAB members. If you are interested, please send your curriculum vitae to secretariat@vac4eu.org.

Institute for Vaccine Safety

Established in 1997 at the Johns Hopkins Bloomberg School of Public Health, the Institute for Vaccine Safety (IVS) mission is to provide 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.

Integral to their mission is to prevent disease using the safest vaccines possible. Towards attainment of this goal, the IVS:

- Provide a forum for dissemination of data regarding specific issues concerning the safety of immunisation.
- Offer systematic reviews of a broad range of vaccine safety issues with clear causality conclusions.
- Conduct methodological and empirical research on post-licensure vaccine safety evaluation.
- Investigate safety questions where insufficient data are available to provide definitive conclusions.
- Undertake individual research projects to obtain specific information regarding vaccine safety when existing information about the safety of a specific vaccine is insufficient or flawed.

Coming soon LetsTalkShots.com

Just like LetsTalkCOVIDVaccines but dedicated to all the other routine vaccines other than COVID! Information tailored to the user's language, vaccine intent, vaccine concerns, and demographics will cover the most common concerns about vaccines across the lifespan – maternal, infant, childhood, adolescent, adult, and elderly.

Partner sites, public health, and community organisations can contact Professor Daniel Salmon, 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.

Brighton Collaboration

Even with a twenty-year history of developing case definition protocols, the COVID-19 pandemic posed a challenge to the Brighton Collaboration (BC). However, through the Coalition for Epidemic Preparedness Innovation (CEPI) funded Safety Platform for Emergency vACcines (SPEAC) project, the BC was able to meet the need by developing case definitions for myocarditis, pericarditis, thrombosis with thrombocytopenia syndrome (TTS) also referred to as vaccine-induced immune thrombotic thrombocytopenia (VITT), vaccine-mediated enhanced disease (VMED), thrombosis, and anosmia, amongst others.

These case definitions, along with definitions that were developed earlier, provided critical tools to assist vaccine developers and public health agencies evaluate possible COVID-19 vaccine related safety signals. Case definitions are published in the journal *Vaccine* and are also available on their website.

The website also features all BC activities, has information of potential interest on vaccine safety and adverse event surveillance, and their newsletter.

The Vaccine Safety Quarterly (VSQ) newsletter includes general interest items, vaccine development, adverse events, journal club announcements, and literature abstracts of possible general interest. For further information, please email Varricchio@comcast.net.

Bob Chen recognised by the ISPE

On 27 August 2022, the International Society of Pharmacoepidemiology (ISPE) awarded Dr Bob Chen, Scientific Director of the Brighton Collaboration, a special award for "Contributions to Public Health Associated with the COVID-19 Pandemic" at its 38th annual meeting in Copenhagen, Denmark.

Photo: Dr Robert T. Chen MD MA FISPE, with his award for "Contributions to Public Health Associated with the COVID-19 Pandemic"

Dr Chen's long-standing commitment to vaccine safety and extensive contributions are outlined in his award nomination.

The ISPE is an international organisation dedicated to the science that applies epidemiologic approaches to studying the use, effectiveness, value, and safety of pharmaceuticals.

Vaccine Confidence Project

The purpose of the Vaccine Confidence Project (VCP) is to monitor public confidence in immunisation programmes by listening for early signals of public distrust and questioning. They developed the Vaccine Confidence Index™ (VCI), an information surveillance system and tool for mapping confidence, which allows for early detection of and response to public concerns about vaccines, and determination of the risk level of public concerns in terms of their potential to disrupt vaccine programmes and uptake.

Over the last 10 years, the VCP has embraced opportunities all around the world to build and sustain confidence in vaccines and immunisation. The VCP insights have helped inform the strategies and designs for immunisation programmes to aid allocation of human and financial resources for and with the communities they serve.

In their recently published New England Journal of Medicine paper *The Vaccine-Hesitant Moment* , Heidi Larson, Emmanuela Gakidou, and Christopher Murray highlight:

> *Vaccine hesitancy is a state of indecision and uncertainty about vaccination before a decision is made to act (or not act). It represents a time of vulnerability and opportunity. Multiple surveys that were conducted to examine the sentiments concerning coronavirus disease 19 (COVID-19) vaccination have exposed new levels of volatility around vaccine hesitancy, particularly when the hesitancy is powered by digital media platforms. Spikes in vaccine hesitancy often coincide with new information, new policies, or newly reported vaccine risks.*
>
> *Some of the variability is due to factors such as a decline in the public's trust of experts, preferences for alternative health, political polarization, and belief-based extremism. In this review, we use the examples of hesitancy regarding the measles-mumps-rubella (MMR), human papillomavirus (HPV), and Covid-19 vaccines to look at the multifaceted issues that fuel vaccine hesitancy. Each of these examples is part of a larger, complex story.*

The full article Larson HJ, Gakidou E, Murray CJL. The vaccine-hesitant moment. N Eng J Med. 2022:387(1):58–65 can be read on the Journal website.

Global Vaccine Data Network

Founded in 2019, the multinational, investigator-led Global Vaccine Data Network (GVDN) has 23 partners across 19 countries, representing more than 250 million people. With a focus on rare events and analysis and evaluation of data held in large clinical databases, the GVDN aims to investigate vaccine safety concerns and evaluate vaccine effectiveness to facilitate risk/benefit analyses and discussion.

Rapid growth

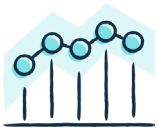
The GVDN is growing rapidly, primarily through expansion of our vaccine safety projects and the addition of key people to lead and support delivery our programme of work.

We were delighted to announce appointment of Professor Jim Buttery as our third Co-Director, joining Associate Professor Helen Petousis-Harris and Emeritus Professor Steven Black in leading the GVDN.

Based in Melbourne, Australia, Jim is affiliated with the Murdoch Children's Research Institute and Royal Children's Hospital. He brings to this directorship a wealth of expertise in vaccine safety, infectious diseases epidemiology, and child health informatics along with his international collaborative relationships as a member of the Brighton Collaboration Science Board and the Advisory Committee on Vaccines for the Australian Therapeutic Goods Administration.

In August, the award of additional funding for the Global Covid Vaccine Safety (GCoVS) project by the Centers for Disease Control and Prevention of the U.S. Department of Health and Human Services enabled extension of existing studies to 2026, the addition of new sites contributing to the suite of studies, an expansion of our epidemiology and biostatistics team, and increased our capacity to develop and disseminate a greater portfolio of communication assets to help partner sites communicate vaccine safety findings locally.

Global COVID Vaccine Safety project, first outputs



Coming soon through an interactive dashboard on the GVDN website, data on the background rates for 13 adverse events of special interest (AESI) from 10 GVDN countries/sites following the GVDN *Background rates of adverse events of special interest following COVID-19 vaccination study protocol*.

In early 2023, we anticipate publication of the observed vs. expected dashboard with data from multiple sites that implemented the GVDN *Observed vs. expected analyses of COVID-19 vaccine adverse events of special interest study protocol*.

Implementation of common protocols across multiple global sites provides a harmonised approach to data collection, collation, and analyses, and allows aggregation of data for meta-analyses.

GVDN relationship building

It is wonderful to have the means to connect the dots so effectively via virtual links across time zones and continents. However, taking the chance to connect in person, when possible, adds incredible value and makes for even more effective ongoing virtual collaborations.

In September, our Lead Epidemiologist, Janine Paynter, and Lead Biostatistician, Yannan Jiang, attended the *16th Vaccine Congress* in Italy. They were able to visit several GVDN partner sites en route and in the region to meet some of our collaborators in person. This was an invaluable

opportunity for relationship building that has further strengthened the scientific partnerships across these sites including the Institut National de la Santé et de la Recherche Médicale (France), Statens Serum Institut (Denmark), VAC4EU (Netherlands), Finnish Institute for Health and Welfare (Finland), Public Health Scotland, UK Health Security Agency (England), and the University of British Columbia (Canada).

Photo: Centre Janine Paynter (left) and Yannan Jiang (right), clockwise from left Petteri Hovi (Finland); Zoe Granger and Lucy Cullen (Scotland); Pascale Tubert-Bitter, Anne Thiébaut, and Sylvie Escolano, (France); Anders Hviid (Denmark)

While in India, Jim Buttery caught up with Narendra Arora and members of his multidisciplinary team. He was introduced to their impressive breadth of research vision, discussed practical aspects of implementing active hospital-based surveillance of AESIs following COVID-19 vaccination, and visited Palwal Hospital.

The team at the Global Coordinating Centre in Auckland would be delighted to host any of our GVDN partners and collaborators who have an opportunity travel to New Zealand.

Unravelling the genetics of adverse events following immunisation

A blog by Bruce Carleton, B.Pharm, Pharm.D, FCP, FISPE

Serious adverse effects are real and rare

Any adverse outcome from vaccine use is a concern to everyone, from vaccine manufacturers to the people who experience them. Vaccines in a way are like cars – incredibly safe and effective, but not without some risk. We don't worry as much about collisions in automobiles as we should, and driver inattention is a significant contributor. In both cases, the risk of vaccine adverse events and collisions are to be expected and need to be understood. One of the purposes of the work of the GVDN is to find out, when an adverse event occurs, what the reason for it is and what the risk is, compared with no vaccine. My work in GVDN is to ask this same question but find out what genetic factors contribute to adverse events.

We are all 99.9% genetically identical, but this still means there are millions of genetic differences between us.

What role might genetic variation play in the development of vaccine-induced adverse events?

The method we will use to explore this I have been studying the genomic contribution to adverse drug reactions for nearly 20 years and started as soon as the technology was cheap enough to begin to consider genomic screening within the constraints of tight research budgets. We used case-control observational trial methods (where people who have an adverse event to a drug are compared with people who received the same drug but did not have the event). A good review of this method can he found in *Epidemiology for the uninitiated*.[1]

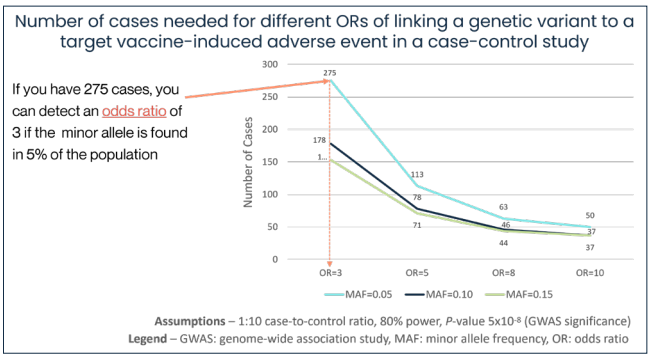
When we study vaccine safety, it is very important to make sure the cases of adverse events are real and related to the drug or vaccine. For example, if a person has chest pain and difficulty breathing, we need to differentiate between a stress event and a heart-related event such as myocarditis. Here is where the clinical notes detailing the symptoms, and laboratory and other medical test results are very important. We start with the most rigorously defined cases of adverse events and find patients who were also exposed to the drug but without the reaction. We then compare the genetic profiles between the two groups. This approach has been surprisingly successful at identifying highly associated (odds ratios ≥ 3, essentially 3x), biologically plausible genomic risk factors for a variety of serious adverse drug reactions.[2-4]

Genetic studies need power

Many genetic studies are underpowered, in part because serious adverse effects are rare. Genome-wide association studies (GWAS) require statistical significance levels that reflect the large number of genetic variants to be examined. Normally, a probability value (*P*-value) of 0.05 is considered statistically significant, in that the result is probably correct 95% of the time. However, for these genomic studies, instead of *P*-values <0.05, we set an initial *P*-value at $5x10^{-8}$ or p = 0.00000005!

The frequency of the genetic variant, called the minor allele, is also an important consideration. If the minor allele frequency (MAF) is too low, you may never find it. Generally, I would set the expected MAF in a population at 5, 10 or 15%. This means it is common enough to find, but not rare enough that you may never find it. This has worked well in drug adverse event studies. Controls (patients without the adverse event) are matched to cases (patients with the adverse event) in large numbers to improve statistical power. From these assumptions you can see in Figure 1 that the numbers of cases needed to find something truly significant are not unreasonable to achieve.

Figure 1: Power and sample size calculation



Finding the cause is the first step in finding a treatment

These biomarkers have stood up to further validation work in the drug arena by using pharmacokinetic, cell- or animal-based functional models. One specific approach we have used was recently published in *Circulation*. Peripheral blood was drawn from patients who have a genetic variant that confers protection against cardiotoxicity. Stem cells were isolated and grown into cardiomyocytes which could then be exposed in vitro to the cardiotoxic drug (doxorubicin) to validate the strong association between gene and adverse drug reaction demonstrated in earlier published research.

This work has taken the genetic findings from a robust statistical association through to drug discovery. With this human cell-tested data, a clinical trial of an approved drug, repurposed to protect against doxorubicin cardiotoxicity, is now being planned.

Such models can show that a strong association between a gene and drug outcome are more than a mere observed association; they provide biological evidence that helps to identify the mechanistic basis of the adverse reaction and ultimately point to potential solutions for safer products and practices (such as who might be best to avoid that particular drug).

Our plan is to do the same thing with vaccines and adverse events following immunisation by using case-control methods to identify genomic factors that are highly associated with the adverse outcome. We will then use this evidence to identify the biology that underlies the mechanism of a specific vaccine-induced harm.

Such information can then be used to better understand the reaction, how to prevent it and how we might treat it. Finding the cause is also the first step for creating safer vaccines. How do you solve a safety problem if you don't know the cause?

Key points

- Ordinarily, vaccines are very safe. Rarely, vaccines can cause serious adverse events.
- For some types of adverse drug and vaccine events genetic variants that place some individuals at risk have been identified.
- Modern techniques have made it possible to study the genetics underpinning these events.
  These compare people with and without the adverse event that have all been exposed to the drug or vaccine.
- This is a great step towards the development of even safer vaccines.

References are available below.

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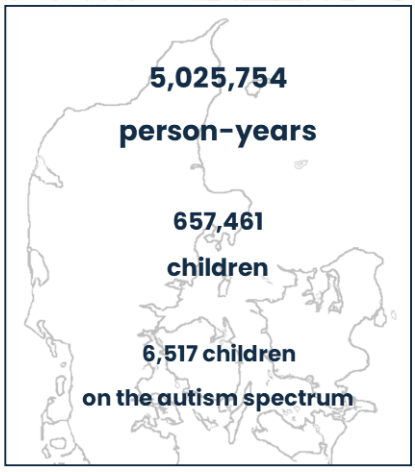
This blog was originally published on the GVDN website at https://www.globalvaccinedatanetwork.org/blog

... by Numbers



Published in 2019, one of the largest single country studies on MMR vaccine and autism[1] included:

» 657,461 children born in Denmark,

» 5,025,754 person-years of follow-up,

» 6,517 children diagnosed with autism.

No association was found between autism and MMR vaccination status, even among children at higher risk of developing the condition.

Key point
No association was found between autism and MMR vaccination status.

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