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Brighton Collaboration 2.0

Frederick Varricchio, PhD, MD - *Editor in chief*
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Dear Brightonians,

A year ago, I wrote to you to celebrate the development and approval for emergency use of COVID-19 vaccines in several countries. While these remain amazing accomplishments, the real world events and experience since [e.g.,the emergence of vaccine hesitancy and new variants of concern (Delta and now Omicron), inadequate and inequitable vaccine supply] are humbling, and remain challenging for humankind to address.

One bright spot during the pandemic, however, has been the relative success of post-introduction pharmacovigilance systems in mostly high income countries (HIC) to identify safety signals and then characterize and mitigate the risks [e.g., thrombosis and thrombocytopenia syndrome (TTS) and myocarditis] for benefit/risk decisions in a timely manner.

Like the successes in apparent "rapid" COVID-19 vaccine development, these successes in vaccine safety were possible only after prior long term investment in essential infrastructures; these include 1) standard case definitions for adverse events following immunizations [e.g., the Brighton Collaboration], 2) passive surveillance [e.g., the Vaccine Adverse Event Reporting System (VAERS)], 3) active surveillance [e.g., the Vaccine Safety Datalink (VSD) and VAC4EU project], 4) tertiary clinical centers [e.g., the Clinical Immunization Safety Assessment (CISA) Network], and 5) and well-trained and staffed offices to oversee and integrate data from these complementary sources for presentation to/discussion for policy making at both individual and societal levels.

The pandemic has also allowed funding of additional vaccine safety initiatives like a) European Medicines Agency (EMA)-funded ACCESS (vACcine Covid-19 monitoring readinESS) project; b) Coalition for Epidemic Preparedness Innovation (CEPI)-funded SPEAC (Safety Platform for Emergency vACcines) Project, c) US CDC- funded V-safe, Global Covid Vaccine Safety (GCoVS) project with the Global Vaccine Data Network (GVDN), CARESAFE projects, and many others.

In closing, I want to thank our three outgoing Brighton Collaboration Science Board (SB) members (Kathy Edwards, Dan Salmon and Barbara Law). This has been a busy period for Brighton Collaboration as we transitioned from 1.0 to 2.0, their wisdom and hardwork (especially outgoing SB Chair Barbara Law) is much appreciated. We also welcome our incoming SB members (see page 13) and look forward to a productive 2022 and beyond. We also welcome Nadja Vielot, PhD as associate editor for the VSQ.

Robert (Bob) T. Chen MD MA
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COVID-19

Over 200,000 citations coded COVID-19 are listed in PubMed, about 10,000 more each month. This is a remarkable achievement in two years. The signs, symptoms, course, and sequelae of this disease are still evolving and probably will continue to do so for some time. A male predominance has been noted. An unsolved mystery: why men One estimate is that 25% of COVID-19 papers are appearing on the preprint servers. Presumably much of this work will appear in print journals. There are also numerous webinars sponsored by the AMA and other organizations. One issue of the Journal of American Medical Association had six articles on COVID-19 and dermatology, cardiology, etc. For non-specialists, Carlos del Rio has 15 articles summarizing some parts of the COVID-19 story. His latest article discusses the omicron variant Winter of omicron. Johns Hopkins University maintains a COVID-19 dashboard which provides a daily global update for 30 countries. A recent paper attempts to describe COVID-19 as a multisystem disease. A fourth wave of Covid-19 cases has appeared in Europe. Several governments have strengthened epidemic response rules. This has caused renewed anti vaccine demonstrations Austria imposes lockdown amid.

In terms of pathophysiology, the virus first binds ACE ll (angiotensin converting enzyme) receptors in the nasopharynx. This receptor is present in many organs including the endothelium. It can cause total destruction of the lung but actually affects multiple organ systems. Over 240 patients have received a lung transplant, many double at a cost of about 1M each. Assessment of the frequency and variety of persistent symptoms include fatigue and somnolence, which affect about ⅓ of survivors, so-called “long haulers' '. Short term and long term rates of postacute. The Virginia health department has prepared a chart of frequent long term effects Long term effects of covid 19 virginia dept. Frequent cardiac effects have been reported and coagulopathy has been reported. For the generalist, an article on pathophysiology, transmission, diagnosis and treatment was recently published. A chronology of disease has been proposed. A review of autopsy findings is also available. Interestingly current vaccines do not produce antibodies in the nasopharynx. Therefore COVID-19 can still invade and colonize this area. This continues the ability to spread viruses. Attempts are in progress to produce a vaccine that would be applied to nasally. Such a vaccine would have other practical advantages as well. Trying to Block SARS-CoV-2 Transmission With Intranasal ... - PubMed.

A “new AE” COVID-19 related inflammatory multisystem disorder has been reported and is similar to Kawasaki disease. Its status is currently being discussed.

Delta, a double mutant originally found in India has spread widely worldwide and did account for more than 90% of new infections in the US. Delta is more transmissible than the wild type. As a result, there is a new surge in infections and hospitalizations. About 90% of hospitalized patients are unvaccinated. Breakthrough infections are also reported but these cases are usually milder. An initial summary of breakthrough cases has recently appeared. Initial results say that the current vaccines will give effective protection against these mutants except perhaps the South African. Autoantibodies have been found in some cases and it has been proposed that they could account for some long term symptoms. COVID-19 antibodies have been found in breastmilk. On a molecular basis, it has been found that individuals produce a variety of antibodies to COVID-19, some more potent than others. With this information about “Super Antibodies”, there is an attempt to reverse engineer a vaccine. A new variant, mu, is attracting attention.

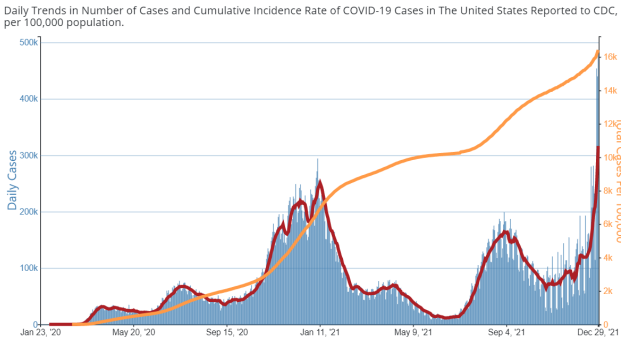
Omicron Variant

A new variant, Omicron, was reported in Southern Africa in late November. It has about 50 mutations from the wild type. It has been identified rapidly in over 70 countries. WHO had an emergency meeting and declared Omicron a subject of great interest. Travel bans from Southern Africa have been rapidly installed. Intense studies are reportedly underway to learn about the transmissibility and current vaccine susceptibility of this new variant. As of mid December Omicron has spread wildly and now accounts for most new cases in the US, which is experiencing record COVID-19 case numbers since the start of the pandemic. Fortunately, Omicron appears to cause less serious disease, and hospitalization and death rates are not increasing concomitantly with infection rates. Efficacy of current vaccines against Omicron is being scrutinized intensely, and clinical trials for new variant-specific COVID vaccines are underway. With a booster dose, mRNA vaccines appear to be effective (Moderna, Pfizer-BioNTech), and the US FDA is considering approving boosters doses for children ages 12-15 to reduce transmission in schools. However, Israel has raised the possibility of a fourth dose. Following new recommendations, the definition of "fully vaccinated" will continue to evolve.

WHO has issued a first report of the world's overall response to COVID-19. This report documents failures at every turn. And the U.S. Congress shows, unintentionally, masks work. However, due to increased transmissibility of Omicron, experts worldwide are recommending the use of medical-grade masks in place of cloth facial coverings that had been recommended to date.

The New York Times continues to publish COVID-19 case counts as well as vaccine administration efforts in the US by state. Not surprisingly there seems to be an inverse relationship between vaccination rates and COVID-19 cases and deaths. There are also detailed diagrams of the COVID-19 genome and mutants in the Coronavirus variant tracker.

In positive news, recent data from South Africa, the country to first identify Omicron, suggests that this current COVID wave has reached a peak as cases have fallen consistently in the last two weeks. While global COVID surveillance and mitigation measures must continue, these trends provide hope that Omicron will pass through quickly in other countries that have dealt with recent surges.



Daily Trends in Number of Cases and Cumulative Incidence Rate of COVID-19 Cases in The United States Reported to CDC, per 100,000 population.

Treatment

Remdesivir has been approved for use in certain cases; however, its effect appears to be modest. Banlanivimab, a monoclonal antibody that blocks attachment of the virus to the ACE2 receptor, received emergency approvalI . To date, progress toward effective therapy has been disappointing. A recent publication describes how COVID-19 infection affects host cell processes. This should lead to antiviral drugs. A federal budget includes several million dollars for research on COVID-19 treatment. Articles attesting to the lack of efficacy of hydroxychloroquine continue to appear. The NYTimes maintains a report on progress in drug development. Also Ivermectin, the worm treatment, continues in the press Toxic effects from ivermectin

The FDA has announced a dedicated reporting system for Covid-19 therapeutics. The Regeneron product, Banlanivimab, received emergency FDA approval and is being used. It is a unique double

antibody drug which acts by attaching to COVID-19 virus particles and thereby reducing viral load. Lilly has a similar product.

Continuing this approach, a group of protein chemists is trying to develop molecules that would be even more efficacious. Another novel idea which has appeared is a bifunctional compound used as nasal spray which would prevent viruses from attaching to the ACE2 receptor. A trial of convalescent serum in the emergency room was halted recently for lack of efficacy.
Pfizer and Merck have just announced drugs that are effective in treating COVID-19. Early results indicate that the Pfizer drug is more effective. Both companies have indicated that they will make their drug available in the third world at greatly reduced price. But in any case there probably will be limited amounts of drugs available in 2021. Both drugs are FDA approved by mid December. The Maryland health department has issued guidelines for the use of these drugs Maryland Board of Physicians.

COVID-19 vaccine

Moderna and Pfizer-BioNTech (PB) vaccines are used extensively in the US, with about 500M total doses to date. Daily doses have fallen greatly to 1M. Municipalities have tried various ideas to encourage vaccination such as mobile immunization sites and even lotteries. Mandates appear to be effective, and the CDC currently recommends concomitant COVID-19 and influenza vaccination during the current flu season. The numbers vary greatly by age, state, political party and religion. The vaccines are now approved for ages 5 and up. Real world data agree with the first trial data as to efficacy in the 90% range.

A booster dose of either mRNA vaccine six months following completion of the initial vaccination series is now generally recommended. Because of the wide variety of COVID vaccines available globally, including different formulations and effectiveness rates, as well as issues with global vaccine distribution, increased attention is being paid to "mixing and matching" vaccines. Whether you have the opportunity to choose your vaccine, or you are limited to what is available, new data compare the immunogenicity of different combinations of vaccine regimens for those seeking booster shots.

Because of variants of concern that have appeared, 2nd generation vaccines are already in progress. BioNTech has announced that a new vaccine for Omicron could be ready in 100 days, early 2022, if necessary. One goal is to develop a vaccine with broader efficacy. The FDA has announced that 2nd generation vaccines will not require the usual large trials. Instead it may be possible to follow some immunological markers in a few hundred people for example. Actually, about 13 vaccines are currently on the world market. This includes vaccines from Russia, China. and india.. The New York Times maintains a list of the status of the 70 odd vaccines in development. About 6 different platforms are being tried. This variety of vaccines being used in many countries makes data interpretation difficult and requires the utmost attention to detail. Even two vaccines that might be thought to be identical, Moderna and PB may have subtle differences and some different effects. There may be other changes in vaccine trials in the future because of experiences during this pandemic. The history of the development of mRNA vaccines is beginning to appear in the popular press. One woman, Kati Kariko, persistently pursued for 10 years her belief that this idea could work. She has recently received the Kovik and Lasker prizes. Of course there are other possible applications of this approach such as in long pursued gene therapy. Moderna reportedly has about 25 products including a flu vaccine in advanced stages of development. A detailed graphic outline of the production process has also appeared. Cdc now reports covid cases and deaths by vax status

Since supplies of vaccines are still limited worldwide, discussions continue concerning the priority of distribution. Furthermore, more

worldwide distribution is being addressed by the COVAX program, Covax cut its 2021 forecast. The NY Times has prepared an estimate of 10 countries that could develop the necessary technology to produce mRNA vaccines. There is a breakdown of what's required, what they have and a timeline Fighting covid with vaccines made President Biden has talked of sending a million doses of vaccine to Africa.

Allergic reactions have appeared as an AE concern since mass vaccinations began. Most individuals were female and had a history of severe allergic reactions. A recent publication reports 66 known anaphylactic reaction cases involving both vaccines and compares them. The NIH has launched a study to determine if people with a history of allergy or a mast cell disorder are at higher risk of systemic allergic reactions to the mRNA vaccines. Other possible vaccine-related AEs continue to be mentioned and are on the lookout such as thrombosis with thrombocytopenia syndrome (TTS), myocarditis and facial-paralysis and Guillain Barré syndrome . A report of the most reported AEs after each mRNA vaccine and each dose is generally consistent with the clinical trial results. The authors point out that although local and systemic AEs are expected and often transient they may have the most immediate effect on patients' perception of the vaccination experience. Therefore, setting a patient's expectations may alleviate some anxiety elicited by post-vaccination

TTS is reported after the Astra-Zeneca (AZ) and Johnson and Johnson-Jansen (JJJ) vaccines. The original review found about 30 cases of TTS after 5M doses of vaccine About 1200 cases of myocarditis have been reported after the mRNA-based vaccines. Most cases are in young men and are relatively mild. A CDC committee has concluded that there is a possible association with the vaccines. In both cases the benefit of the vaccine far exceeds the risk but intense surveillance should continue. The Brighton Collaboration has prepared case-finding definitions of TTP and myocarditis. The definitions are available on the Brighton website.

Brighton Collaboration has been involved along with CEPI in developing a list of possible AEFIs that may be associated with a COVID-19 vaccine. One concern is the potential for enhanced disease. This is theoretical for COVID-19 but has been seen with SARS and MERS-CoV vaccines in animal models.

COVID-19 testing

With little public notice there have been a series of improvements in virus testing. Now there's even a test that can be used at home. A national drug store chain reported that COVID-19 test kits are its best seller. While speed usually compromises accuracy, each has its advantages. Now these tests must be evaluated as to how they perform with the Covid-19 mutant. Some tests require interpretation. A combined Covid-19 influenza test has recently become available. In the United States, as a result of increased travel and gathering during the winter holidays and a surge of infections caused by Omicron, COVID-19 testing resources have been overwhelmed by demand. At-home COVID-19 tests are largely out of stock in pharmacies, and COVID-19 testing centers experience unprecedented wait times.

COVID-19 Vaccine Data Resources

Brighton Collaboration has assembled a COVID-19 vaccine safety resource. Topics include regulatory approvals, risk management plans, usage recommendations, adverse events and databases. This resource is intended for public use by anyone who is interested in COVID-19 vaccine details. Comments and additional sources may be sent to varricchio@comcast.net.

In general, CDC and MMWR are good sources. The CDC/FDA's Vaccine AE Reporting System (VAERS) database is available to the public. The AMA also

maintains a resource of Covid-19 articles, webinars, interviews etc.

Vaccine Hesitancy

Discussion continues concerning how to deal with vaccine misinformation and increase public confidence. The CDC has a 1 page "tip sheet" on frequent vaccine questions and responses. These are available in bulk Should physicians be encouraged to keep some in their waiting areas. Heidi Larson, a London anthropologist, proposes how to deal with false information and build trust. She studies rumors and is founder of the Vaccine Confidence Project. Also see, "the science of changing someone's mind". Duke university medical school has added a course. The US Covid-19 relief law contains funds to work on the effort. Robert Kennedy Jr. has been a prominent vaccine doubter. His granddaughter, a physician, has publicly rebutted his position.

In recognition of the critical importance of COVID-19 vaccines and the need to understand their safety, the CONSIDER (**CO**vid-19 vacci**N**e **S**afety quest**I**ons an**D** h**E**althcare p**R**oviders) working group (WG) was created in September 2020. The CONSIDER WG aims to provide clear, comprehensive answers to questions pertaining to COVID-19 vaccine safety prior to, and during the vaccines roll out to 1) facilitate scientific discussion between stakeholders, including front line health workers with potential vaccine recipients and 2) increase comprehension and transparency of information to facilitate acceptance and uptake. As more questions come to the group's attention or more information becomes available, including on AEFI (from COVID-19 vaccine clinical trials and early experience with vaccine introduction in countries), the answers are being updated and new answers posted here and are cross-referenced on other sites, including on WHO's Vaccine Safety Network (VSN). The Smithsonian museum has just joined the effort to provide quality information and also the history of vaccines and epidemics at the site vaccinesandus.

The UN has announced an effort to make reliable COVID-19 information available to everyone called "Verified". It enables volunteers from around the world to share information. The theory is to enable social organization, people providing information to friends, family, and social contacts. More recently WHO has announced a collaboration with Wikipedia which is known to be frequently consulted by the public for health information. The WHO will make its information available for posting. The WHO also maintains a list of credible vaccine information sources, the Vaccine Safety Network (VSN). This contains primarily government sources but Brighton has just been included.

There have been numerous articles in the press about people, even military, who say that they do not want to be among the first to get the vaccine. Apparently, this is because of a feeling that a vaccine may have been rushed to market. But about 300 million doses have been administered in the US with about 70% having at least one dose. Peter Marks, director of CBER-FDA, has stated that in his experience as an oncologist confidence is best achieved from a relationship with a physician. It is known that a trusted intermediary can have a powerful effect. A recent survey divides the 35% vaccine hesitators into 4 groups: wait and see, high cost of lost time from work, distrust of the system, and 14% "don't believe the threat. A recent article discusses vaccine resistance on a sociological basis. The theory is that some do not consider themselves part of the group and therefore have no obligation to others Vaccine hesitancy is about trust and class. There is also hesitancy about the HPV vaccine The HPV vaccine prevents cancer but. And why do some vaccinated parents hesitate on the same va for their children Why parents hesitate to vaccinate.

The Biden administration has embarked on a new multi-million advertising campaign to promote

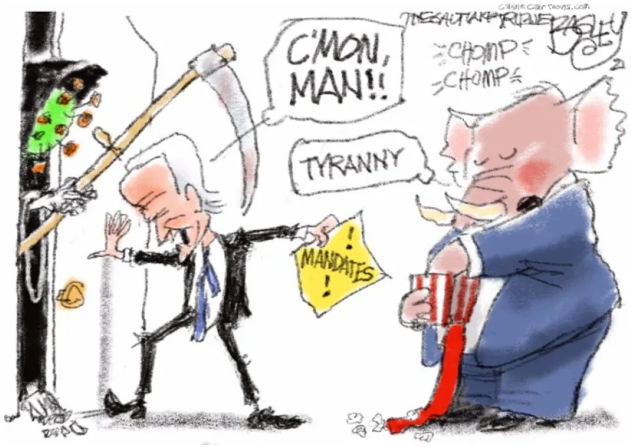
immunization. The CDC Director, Rochelle Walensky, has commented that these days most "scientific" information passes by Twitter. Therefore, responsible sources must use Twitter too. Clearly, consistency is very important. Regrettably there has been widespread resistance to immunization among healthcare workers. Then, there are physicians who have been spreading vaccine misinformation. This has also happened in New Zealand and elsewhere.

Panic and Neglect

Lawrence Gostin has written a commentary on the Anthrax scare of 2001 and the public health response, the state emergency health powers act, and subsequent emergencies up to Covid 19. He concludes that the public health response in the US is one of panic and neglect Twenty years after the anthrax terrorist attacks.

Un Faux Pas

An article entitled "The Safety of Covid-19 Vaccines: We Should Rethink the Policy" appeared in the journal *Vaccines.* This article appeared to be written by people unfamiliar with the subject and also to be a failure of the review process. Three associate editors immediately resigned. The journal retracted the article promptly but not before it had been seen by thousands. The retraction also appears in PubMed. This incident was described in this news piece in the British Medical Journal.



Pat Bagley | Copyright 2021 Cagle Cartoons

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 will take place quarterly during SIG meetings via Webex, and will be co-hosted by SIG Chair Bradley Laton of RTI International and BC member Nadja Vielot of the University of North Carolina.

The next meeting will be held January 5, 2022 at 9:00AM GMT-5. Dr. Rajamohanan K Pillai will lead discussion of the following papers:

Robert W. Frenck, Jr, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. NEJM Jul 15 2021.

Kashif Ali, M.D., et al. Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents. NEJM Aug 11 2021.

We will send a WebEx link ahead of time to those who are currently on the journal club mailing list. To join the mailing list, please complete this Google Form.

History

The Response to Epidemic Disease in Colonial Rhode Island

by Mark Kenneth Gardner

Political Epidemiology

The Era of Vaccine Diplomacy is Here (NY Times)

Two top FDA vaccine regulators resign

In Review, Top FDA Scientists Question Imminent Need for Booster Shot

Opinion|Of Vaccine Mandates and Facing Reality, an economist's point of view

Travel

If you are in England, there is an Edward Jenner House and Museum in Berkeley, England. There is also his temple of vaccinia, a sort of lean-to. Will his museum survive?

VSQ Readers

Happy New Year! Starting in January of 2022, there are 1,140 members of Brighton Collaboration. The fall VSQ was emailed to over 900 readers. About 23% of our membership is from the United States. Canada comes in second with about 8%, and India is in third with almost 7%. All readers are invited to submit comments and articles to the VSQ.

LITERATURE

There are about 2400 citations per year in PubMed coded Vaccine Safety. This is increasing by about 200 per month. I have selected a few which may be of general interest.

1. **COVID-19 Vaccine Safety in Adolescents Aged 12-17 Years - United States, December 14, 2020-July 16, 2021**
   Hause AM (vog.cdc@5eov), et. al. MMWR Morb Mortal Wkly Rep. 2021 Aug 6;70(31):1053-1058. doi: 10.15585/mmwr.mm7031e1.

Abstract: As of July 30, 2021, among the three COVID-19 vaccines authorized for use in the United States, only the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine is authorized for adolescents aged 12-17 years. The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for Pfizer-BioNTech vaccine for use in persons aged ≥16 years on December 11, 2020 (1); the EUA was expanded to include adolescents aged 12-15 years on May 10, 2021 (2), based on results from a Phase 3 clinical trial (3). Beginning in June 2021, cases of myocarditis and myopericarditis (hereafter, myocarditis) after receipt of Pfizer-BioNTech vaccine began to be reported, primarily among young males after receipt of the second dose (4,5). On June 23, 2021, CDC's Advisory Committee on Immunization Practices (ACIP) reviewed available data and concluded that the benefits of COVID-19 vaccination to individual persons and the population outweigh the risks for myocarditis and recommended continued use of the vaccine in persons aged ≥12 years (6). To further characterize safety of the vaccine, adverse events after receipt of Pfizer-BioNTech vaccine reported to the Vaccine Adverse Event Reporting System (VAERS) and adverse events and health impact assessments reported in v-safe (a smartphone-based safety surveillance system) were reviewed for U.S. adolescents aged 12-17 years during December 14, 2020-July 16, 2021. As of July 16, 2021, approximately 8.9 million U.S. adolescents aged 12-17 years had received the Pfizer-BioNTech vaccine.* VAERS received 9,246 reports after Pfizer-BioNTech vaccination in this age group; 90.7% of these were for non-serious adverse events and 9.3% were for serious adverse events, including myocarditis (4.3%). Approximately 129,000 U.S. adolescents aged 12-17 years enrolled in v-safe after Pfizer-BioNTech vaccination; they reported local (63.4%) and systemic (48.9%) reactions with a frequency similar to that reported in preauthorization clinical trials. Systemic reactions were more common after dose 2. CDC and FDA continue to monitor vaccine safety and provide data to ACIP to guide COVID-19 vaccine recommendations.

2. **Antibody responses to the SARS-CoV-2 vaccine in individuals with various inborn errors of immunity**
   Delmonte OM, Notarangelo LD (luigi.notarangelo2@nih.gov), Freeman AF (freemal@mail.nih.gov), et. al. Journal of Allergy and Clinical Immunology, Volume 148, Issue 5, 2021, ISSN 0091-6749. doi: https://doi.org/10.1016/j.jaci.2021.08.016

Background: SARS-CoV-2 vaccination is recommended in patients with inborn errors of immunity (IEIs); however, little is known about immunogenicity and safety in these patients.

Objective: We sought to evaluate the impact of genetic diagnosis, age, and treatment on antibody response to COVID-19 vaccine and related adverse events in a cohort of patients with IEIs.

Methods: Plasma was collected from 22 health care worker controls, 81 patients with IEIs, and 2 patients with thymoma; the plasma was collected before immunization, 1 to 6 days before the second dose of mRNA vaccine, and at a median of 30 days after completion of the immunization schedule with either mRNA vaccine or a single dose of Johnson & Johnson's Janssen vaccine. Anti-spike (anti-S) and anti-nucleocapsid antibody titers were measured by using a luciferase immunoprecipitation systems method. Information on T- and B-cell counts and use of immunosuppressive drugs was extracted from medical records, and information on vaccine-associated adverse events was collected after each dose.

Results: Anti-S antibodies were detected in 27 of 46 patients (58.7%) after 1 dose of mRNA vaccine and in 63 of 74 fully immunized patients (85.1%). A lower rate of seroconversion (7 of 11 [63.6%]) was observed in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Previous use of rituximab and baseline counts of less than 1000 CD3+ T cells/mL and less than 100 CD19+ B cells/mL were associated with lower anti-S IgG levels. No significant adverse events were reported.

Conclusion: Vaccinating patients with IEIs is safe, but immunogenicity is affected by certain therapies and gene defects. These data may guide the counseling of patients with IEIs regarding prevention of SARS-CoV-2 infection and the need for subsequent boosts.

3. A framework for monitoring population immunity to SARS-CoV-2

Lopman BA (404-606-3958), et. al. Ann Epidemiol. 2021 Nov;63:75-78. doi: 10.1016/j.annepidem.2021.08.013. Epub 2021 Aug 21.

Abstract: In the effort to control SARS-CoV-2 transmission, public health agencies in the United States and globally are aiming to increase population immunity. Immunity through vaccination and acquired following recovery from natural infection are the two means to build up population immunity, with vaccination being the safe pathway. However, measuring the contribution to population immunity from vaccination or natural infection is non-trivial. Historical COVID-19 case counts and vaccine coverage are necessary information but are not sufficient to approximate population immunity. Here, we consider the nuances of measuring each and propose an analytical framework for integrating the necessary data on cumulative vaccinations and natural infections at the state and national level. To guide vaccine roll-out and other aspects of control over the coming months, we recommend analytics that combine vaccine coverage with local (e.g. county-level) history of case reports and adjustment for waning antibodies to establish local estimates of population immunity. To do so, the strategic use of minimally-biased serology surveys integrated with vaccine administration data can improve estimates of the aggregate level of immunity to guide

data-driven decisions to re-open safely and prioritize vaccination efforts.

4. **Surveillance for Adverse Events After COVID-19 mRNA Vaccination**
Klein NP (nicola.klein@kp.org), et al. JAMA. 2021;326(14):1390–1399. doi:10.1001/jama.2021.15072

Importance: Safety surveillance of vaccines against COVID-19 is critical to ensure safety, maintain trust, and inform policy.

Objectives: To monitor 23 serious outcomes weekly, using comprehensive health records on a diverse population.

Design, Setting, and Participants: This study represents an interim analysis of safety surveillance data from Vaccine Safety Datalink. The 10 162 227 vaccine-eligible members of 8 participating US health plans were monitored with administrative data updated weekly and supplemented with medical record review for selected outcomes from December 14, 2020, through June 26, 2021.

Exposures: Receipt of BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) COVID-19 vaccination, with a risk interval of 21 days for individuals after vaccine dose 1 or 2 compared with an interval of 22 to 42 days for similar individuals after vaccine dose 1 or 2.

Main Outcomes and Measures: Incidence of serious outcomes, including acute myocardial infarction, Bell palsy, cerebral venous sinus thrombosis, Guillain-Barré syndrome, myocarditis/pericarditis, pulmonary embolism, stroke, and thrombosis with thrombocytopenia syndrome. Incidence of events that occurred among vaccine recipients 1 to 21 days after either dose 1 or 2 of a messenger RNA (mRNA) vaccine was compared with that of vaccinated concurrent comparators who, on the same calendar day, had received their most recent dose 22 to 42 days earlier. Rate ratios (RRs) were estimated by Poisson regression, adjusted for age, sex, race and ethnicity, health plan, and calendar day. For a signal, a 1-sided $P < .0048$ was required to keep type I error below .05 during 2 years of weekly analyses. For 4 additional outcomes, including anaphylaxis, only descriptive analyses were conducted.

Results: A total of 11 845 128 doses of mRNA vaccines (57% BNT162b2; 6 175 813 first doses and 5 669 315 second doses) were administered to 6.2 million individuals (mean age, 49 years; 54% female individuals). The incidence of events per 1 000 000 person-years during the risk vs comparison intervals for ischemic stroke was 1612 vs 1781 (RR, 0.97; 95% CI, 0.87-1.08); for appendicitis, 1179 vs 1345 (RR, 0.82; 95% CI, 0.73-0.93); and for acute myocardial infarction, 935 vs 1030 (RR, 1.02; 95% CI, 0.89-1.18). No vaccine-outcome association met the prespecified requirement for a signal. Incidence of confirmed anaphylaxis was 4.8 (95% CI, 3.2-6.9) per million doses of BNT162b2 and 5.1 (95% CI, 3.3-7.6) per million doses of mRNA-1273.

Conclusions and Relevance: In interim analyses of surveillance of mRNA COVID-19 vaccines, incidence of selected serious outcomes was not significantly higher 1 to 21 days post-vaccination compared with 22 to 42 days post-vaccination. While CIs were wide for many outcomes, surveillance is ongoing.

5. Multisystem Inflammatory Syndrome in Adults after SARS-CoV-2 infection and COVID-19 vaccination

Belay ED (ebelay@cdc.gov), et. al. Clin Infect Dis. 2021 Nov 28:ciab936. doi: 10.1093/cid/ciab936.

Background: Multisystem inflammatory syndrome in adults (MIS-A) was reported in association with the COVID-19 pandemic. MIS-A was included in the list of adverse events to be monitored as part of the emergency use authorizations issued for COVID-19 vaccines.

Methods: Reports of MIS-A patients received by the Centers for Disease Control and Prevention (CDC) after COVID-19 vaccines became available were assessed. Data collected on the patients included clinical and demographic characteristics and their vaccine status. The Vaccine Adverse Events Reporting System (VAERS) was also reviewed for possible cases of MIS-A.

Results: From December 14, 2020 to April 30, 2021, 20 patients who met the case definition for MIS-A were reported to CDC. Their median age was 35 years (range, 21-66 years), and 13 (65%) were male. Overall, 16 (80%) patients had a preceding COVID-19-like illness a median of 26 days (range 11-78 days) before MIS-A onset. All 20 patients had laboratory evidence of SARS-CoV-2 infection. Seven MIS-A patients (35%) received COVID-19 vaccine a median of 10 days (range, 6-45 days) before MIS-A onset; 3 patients received a second dose of COVID-19 vaccine 4, 17, and 22 days before MIS-A onset. Patients with MIS-A predominantly had gastrointestinal and cardiac manifestations and hypotension or shock.

Conclusions: Although 7 patients were reported to have received COVID-19 vaccine, all had evidence of prior SARS-CoV-2 infection. Given the widespread use of COVID-19 vaccines, the lack of reporting of MIS-A associated with vaccination alone, without evidence of underlying SARS-CoV-2 infection, is reassuring.

New Brighton Collaboration Publications

In the recently launched website, newly published Brighton Collaboration articles and tools will be posted in English and some in Chinese, Spanish, French, or Portuguese.

A couple of notable recent publications are:

- *A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for a soluble glycoprotein vaccine to prevent disease caused by Nipah or Hendra viruses*
- *Applicability of the GAIA Maternal and Neonatal Outcome Case Definitions for the Evaluation of Adverse Events Following Vaccination in Pregnancy in High-income Countries.*

New Brighton 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. Comments on the new website to bc-coordinator@taskforce.org, and keep an eye out for new content and features on the website as we go forward

Brighton Collaboration Science Board Election Announcement

The current Brighton Collaboration Science Board (SB) has voted to accept all 16 candidates onto the new Brighton Collaboration Science Board. After consideration of all the candidates and given current unique circumstances, the nominating committee (consisting of the 3 outgoing SB members) proposed that all candidates be appointed to a provisional Science Board for the next two years rather than have an election that would result in only 10 of the 16 being appointed to the board. Click here for the full explanation to not hold elections this year. Here is the full list of SB candidates and their qualifications (click here) as well as their Brighton experience and areas of expertise (click here). The Brighton Collaboration membership voted in support of this change.

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?

If you received this VSQ from a colleague and would like to be added to our mailing list, please complete this form: https://bit.ly/3nPq3tE