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Brighton Collaboration 2.0
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Research and data needs for ongoing evaluation of COVID-19 vaccine safety

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A recent publication by Fraiman, et al. reported the results of a reanalysis of safety data from the two pivotal clinical trials that led to the Emergency Use Authorization (EUA) and eventual licensure of the Moderna and Pfizer mRNA COVID-19 vaccines. The analysis estimated the rates of severe adverse events (SAE) and adverse events of special interest (AESI) that occurred among clinical trial participants, as defined by the Safety Platform for Emergency VACcines (SPEAC), a partnership between the Brighton Collaboration and the Coalition for Epidemic Preparedness Innovations (CEPI).

In brief, the study's findings suggest that both mRNA vaccines are associated with clinically significantly higher rates of SAE and AESI when comparing vaccine recipients to placebo recipients.

Table 2
Serious adverse events.

Trial	Total events (events per 10,000 participants)[a] Vaccine	Placebo	Risk difference per 10,000 participants (95 % CI)[e]	Risk ratio (95 % CI)[e]
Serious adverse events				
Pfizer[b]	127 (67.5)	93 (49.5)	18.0 (1.2 to 34.9)	1.36 (1.02 to 1.83)
Moderna[c,d]	206 (135.7)	195 (128.6)	7.1 (−23.2 to 37.4)	1.06 (0.84 to 1.33)
Combined[f]	333 (98.0)	288 (84.8)	13.2 (-3.2 to 29.6)	1.16 (0.97 to 1.39)
Serious adverse events of special interest				
Pfizer	52 (27.7)	33 (17.6)	10.1 (-0.4 to 20.6)	1.57 (0.98 to 2.54)
Moderna	87 (57.3)	64 (42.2)	15.1 (-3.6 to 33.8)	1.36 (0.93 to 1.99)
Combined[f]	139 (40.9)	97 (28.6)	12.5 (2.1 to 22.9)	1.43 (1.07 to 1.92)

J. Fraiman, J. Erviti, M. Jones et al. Vaccine 40 (2022) 5798–5805.

The results further suggest that the rates of vaccine-associated adverse events exceeded the protective efficacy of the vaccines against COVID-19 hospitalization:

> *"In the Moderna trial, the excess risk of serious AESIs (15.1 per 10,000 participants) was higher than the risk reduction for COVID-19 hospitalization relative to the placebo group (6.4 per 10,000 participants). [3] In the Pfizer trial, the excess risk of serious AESIs (10.1 per 10,000) was higher than the risk reduction for COVID-19 hospitalization relative to the placebo group (2.3 per 10,000 participants)." (Fraiman, et al.)*

One critical limitation of their analysis, which the authors acknowledge in the article, is the absence of publicly-available *individual-level data,* rather than an aggregate count of events across all clinical trial participants, which would allow for more rigorous analysis of SAE/AESI rates within individuals. Notably, it is clear from the aggregate data that some participants experienced multiple SAE/AESI, and the inability to attribute multiple events to a single participant could lead to inflated event rates. On the other hand, the clinical trials used larger denominators and shorter follow-up time for SAE/AESI reporting, which might have underestimated event rates if the reported events were truly associated with vaccination. Regarding the risk-benefit analysis of mRNA vaccination, it is not possible or prudent to conclude from limited clinical trial data that the harms of mRNA COVID-19 vaccination outweigh its benefits. As the authors noted: "...intubation and short hospital stay are not equivalent but both are counted in 'hospitalization' similarly, serious diarrhea and serious stroke

are not equivalent but both are counted in 'SAE'." (Fraiman, et al.) Depending on the severity of the SAE experienced by vaccine recipients and the severity of hospitalization outcomes prevented, one could reasonably conclude that the risk of severe diarrhea is well worth avoiding intubation, but less so that the risk of a stroke is worth avoiding a short hospital stay.

The authors provide access to the study data (which is also publicly available on the US Food and Drug Administration website), and extensive documentation of their analytic methods and correspondence with scientific journals and the FDA defending their conclusions. As truth-seeking scientists, the Brighton Collaboration and VSQ membership appreciate such rigor and transparency, particularly in the context of a global pandemic that demands rapid, yet measured, public health responses.

While potentially controversial, this article is an important contribution to the vaccine safety literature, and emphasizes the need for 1) continued post-licensure monitoring of vaccines and other biologicals and drugs; 2) transparency in the research and dissemination processes to allow for replication of study findings; and 3) complementing evidence from clinical trials with real-world evidence (RWE) generated from real-world data (RWD). Scientific journals are now beginning to require submission of publicly-accessible datasets along with manuscripts, which promotes quality control and replicability of critical evidence for novel pharmaceuticals. Since their rollout in late 2020, over 13 billion COVID-19 vaccine doses have been distributed in over 200 countries, far exceeding the scale and scope of the seminal clinical trials. As such, it is imperative to leverage data from post-licensure surveillance systems, administrative databases, immunization and disease registries, and other available sources to estimate the wider public health impact of COVID-19 vaccination worldwide.

With global estimates of nearly 7 million COVID-19 deaths and 7 million cases, many of them resulting in long-term disability, the rapid development of COVID-19 vaccines across multiple platforms and global regions was a tremendous advance in public health preparedness and response, and the lessons learned from this pandemic can only prepare us better for the next one. The Brighton Collaboration looks forward to its continued relationship with CEPI (see page 6) to expand and improve upon its vaccine safety evaluation efforts, now and in the future.

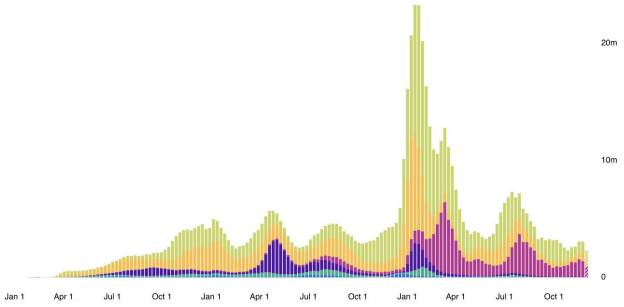
GLOBAL OUTBREAKS

COVID-19

Quick Links

- COVID-19 Dashboard (Johns Hopkins University)
- COVID-19 Vaccine Tracker and Landscape (WHO)
- Coronavirus Drug and Treatment Tracker (NYT)
- Clinical Management of COVID in Adults (NIH)
- Brighton Collaboration: Key Resources for COVID-19 Vaccine Safety Analyses
- Tracking Omicron and Other Coronavirus Variants (CDC)

Omicron and Other Coronavirus Variants



Weekly global trends in COVID-19 cases (click to see full-size graphic).

Control Measures in Flux Across the Globe

The Omicron sub-variants continue to cause most COVID-19 cases, and surveillance is ongoing for emergence of novel variants that evade vaccine-induced immunity. As of the end of November 2022, about 50% of new Covid-19 cases in the US are caused by sub-variants BQ 1 and XBB. As of October 1 the WHO decided these new variants do not rise to a cause of concern. Species jumping, its effect on the viral genome and the influence of climate change attempts to link this to virus characteristics.

Ezekial Emmanuel and other members of US President Joe Biden's COVID response advisory board discuss what needs to be done to prepare for the next epidemic.

In response to nationwide protests, China has relaxed the Covid prevention mandates that comprise its "Zero COVID" policy. The effects on Covid transmission and caseload are to be determined, as the sudden opening of the country causes concern among many.

A rapid Covid-19 test that uses reagent-impregnated paper has been developed as a proof-of-concept that could lead to cheap, easy, accessible, and low-tech Covid diagnosis worldwide.

Long Covid

After the pandemic subsides, we may still be dealing with adverse health effects among individuals who recovered from acute infections. Long Covid continues to affect some individuals long after the virus has been cleared, with up to 200 symptoms lasting a year or more being reported. Weakness appears to be the most common but brain fog is also mentioned frequently. The US has developed a research plan to study long Covid.

COVID-19 Vaccine Rollout and Development

Moderna's and Pfizer's bivalent Omicron-specific booster vaccines have been approved for use in adults in many countries. The Novavax protein-based vaccine approved by the US FDA in July could also be used as a primary series vaccine for those who are hesitant to receive mRNA vaccines. However, booster uptake has been slow, with about 40 million doses administered , US, to date, and its role in the Covid-19 vaccine toolbox is unclear. The new Covid boosters are incredible, and vaccination campaigns continue in the US to increase uptake.

Intranasal COVID-119 vaccines have been approved for use in India and China. These vaccines elicit mucosal immunity, which is expected to prevent

infections that begin in the nose and mouth. Prevention of viral replication in the oral mucosa can also prevent viral transmission of SARS-CoV-2 through droplets or aerosols. However, a US trial of an intranasal Covid-19 vaccine has recently shown disappointing efficacy.

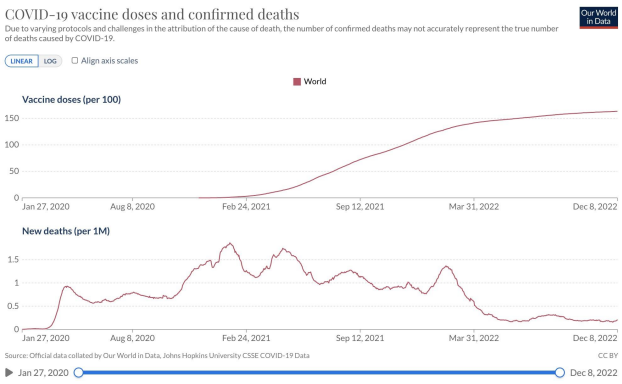
Vaccine Safety

Brighton Collaboration has been involved along with the Coalition for Epidemic Preparedness Innovations (CEPI) in developing a list of possible Adverse Events of Special Interest (AESI) (Updated October 2022) that may be associated with a COVID-19 vaccine. Case definitions and other tools for assessing COVID-19 vaccine AESI's are available here.

The adverse event (AE) profile of the booster vaccine is comparable to that of the monovalent vaccine.

A study on comparative risk of thrombosis with thrombocytopenia found that this AE is more likely with an adenovirus-based vaccine than an mRNA based vaccine. A case of TTS after Sputnik V vaccination has been reported from Argentina.

Vaccine Effectiveness



COVID-19 vaccine doses and confirmed deaths (click to see full-size graphic)

A cost analysis in New York City showed that every dollar spent now on vaccination saves $10 later.

Vaccine Intentions & Hesitancy

Parental hesitancy to vaccinate children persists in the US, despite final full FDA approval of Covid vaccination for children as young as 6 months. Covid-19 vaccine concerns appear to be carrying over to use of traditional childhood vaccines. Opposition to school vaccine mandates has grown since 2019.

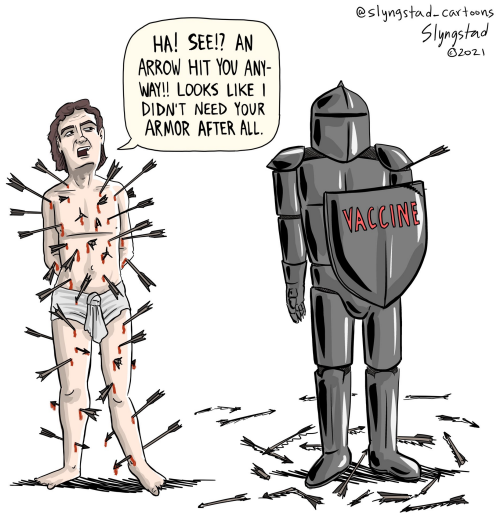
Vaccine hesitancy can be influenced by social, political, economic, and geographic factors, as evidence by a study of Covid vaccine intentions in different language areas of Belgium and among migrant groups in Europe.

Combatting Covid vaccine hesitancy requires effective communication of the benefits and risks of vaccination, and should be tailored to specific audiences depending on the type and amount of information they want. Meta-summaries of Covid vaccine evidence could be an effective communication and education method.

Novel approaches, such as improvisational theater, can build provider skills and confidence to have discussions about vaccine safety with hesitant patients.

Dr. Anthony Fauci will step down from his position as Director of the National Institute of Allergy and Infectious Diseases at the end of 2022. He recently was interviewed about his decades of advising presidents and being a spokesman on important public health concerns, and emphasized the importance of consistency and truth. Anthony fauci a message to the next generation

The WHO's "Vaccine safety and false contraindications to vaccines" manual is another helpful tool to understand common misconceptions about vaccination.



Benjamin Slyngstad | slyngstadcartoons.com

MPOX

Over 80,000 cases of Mpox, formerly known as monkeypox, have been reported in over 100 countries since May 2022. Smallpox vaccine is effective against Mpox infection, but limited amounts of vaccine are available. There is no known plan to increase supply; however, the FDA has authorized intradermal vaccine administration which uses less vaccine and effectively increases vaccine availability.

RESPIRATORY SYNCYTIAL VIRUS

Respirâtory syncytial virus (RSV) has added a third major concern to the winter respiratory virus scene in the US. The "tripledemic" of Covid, seasonal influenza, and RSV threaten hospital surges and emphasize the necessity of Covid and flu vaccination, especially in children. While no vaccine is currently authorized for RSV prevention, vaccine candidates for older adults and for pregnant people have shown promising safety and efficacy profiles in clinical trials.

Political Vaccinology

Congress poised to repeal Covid vaccine mandate.

Vaccines are now an election issue nationwide.

BC MEMBER NEWS & ANNOUNCEMENTS

CEPI-SPEAC Press Release

In its press release on 20 December 2022, CEPI announced that it is renewing and expanding its partnership with the Brighton Collaboration via the Safety Platform for Emergency VACcines (SPEAC) for four more years.

> "The team played a key role during the development and roll-out of COVID-19 vaccines through the Brighton Collaboration's efforts to create harmonized guidelines for collection of data on potential side effects."

On the role the Brighton Collaboration plays in CEPI-SPEAC's efforts on the safety of future vaccines to prevent and respond to pandemics, Dr Melanie Saville, Executive Director of R&D at CEPI, shared the following:

> "Careful safety evaluation is paramount in vaccine development, so access to the Brighton Collaboration's outstanding vaccine safety expertise is crucial to the success of CEPI's vaccine portfolio. SPEAC's expanded scope will be vital to ensuring the safety of CEPI-funded vaccines and platforms over the next 5 years."

Vaccines Journal Club

In collaboration with the International Society for Pharmacoepidemiology (ISPE) Special Interest Group (SIG) on Vaccines, the Brighton Collaboration is pleased to continue the Vaccine Safety Journal Club. Members of both organizations are invited to review and discuss the latest research on vaccine safety, from epidemiological methods to qualitative research. The journal club will take place during SIG meetings via Webex, and will be co-hosted by SIG Chair Jen Gerber and BC member Nadja Vielot of the University of North Carolina.

The January journal club session will be canceled to accommodate holiday travel. We will resume the quarterly journal club meeting in April. To receive the virtual journal club link and to receive journal

club announcements, please join the mailing list by completing this Google Form.

Lasker Award

The 2022 Lasker-Bloomberg Public Service Award was awarded to Dr. Lauren Gardner of Johns Hopkins University, for the development of a dashboard which allowed tracking of Covid-19 cases (see above Quick Links).

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:

- Preterm Birth and Assessment of Gestational Age: Case Definition Companion Guide
- Vaccines based on the replication-deficient simian adenoviral vector ChAdOx1: Standardized template with key considerations for a risk/benefit assessment
- Thrombosis/Thromboembolism Case Definition
- Vaccine-associated enhanced disease (VAED): Case Definition Companion Guide
- Anaphylaxis V2 Case Definition
- Thrombosis and Thromboembolism: Case Definition Companion Guide
- Myocarditis and Pericarditis: Case Definition Companion Guide

Caveat Emptor

There are about 300,000 articles coded Covid-19 in PubMed. Unfortunately, a review found that 138 articles have been withdrawn but some continue to be cited. Withdrawal of articles has increased in recent years.

Passages

Samuel L. Katz, a developer of the measles vaccine, dies at 95.

BC Membership

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

Brighton Collaboration Website

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

Articles and Comments to the VSQ are welcomed and invited

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

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

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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

LITERATURE

There are about 2,400 citations per year in PubMed coded Vaccine Safety. This is increasing by about 200 per month. Here are a few which may be of interest:

1. Information Systems for Vaccine Safety Surveillance. Buttery JP, Clothier H. Hum Vaccin Immunother. 2022 Sep 26:2100173. doi: 10.1080/21645515.2022. 2100173. Online ahead of print. PMID: 36162040 Review.

Abstract: Immunization implementation in the community relies upon post-licensure vaccine safety surveillance to maintain safe vaccination programs and to detect rare AEFI not observed in clinical trials. The increasing availability of electronic health-care related data and correspondence from both health-related providers and internet-based media has revolutionized health-care information. Many and varied forms of health information related to adverse event following immunization (AEFI) are potentially suitable for vaccine safety surveillance. The utilization of these media ranges from more efficient use of electronic spontaneous reporting, automated solicited surveillance methods, screening various electronic health record types, and the utilization of natural language processing techniques to scan enormous amounts of internet-based data for AEFI mentions. Each of these surveillance types have advantages and disadvantages and are often complementary to each other. Most are "hypothesis generating," detecting potential safety signals, where some, such as vaccine safety datalinking, may also serve as "hypothesis testing" to help verify and investigate those potential signals.

2. Genetic predisposition to adverse events in Chinese children aged 3-24 months after diphtheria, tetanus, acellular pertussis and haemophilus influenzae type b combined vaccination. Ma Y Et al.. Expert Rev Vaccines. 2022 Nov 10:1-6. doi: 10.1080/14760584.2022.2144239. Online ahead of print. PMID: 3632895

Background: Post-vaccination safety is a major public health concern. The genetic predisposition on immune response has not been clearly identified. Clarifying whether individual genetic predisposition plays a role on adverse events (AEs) is critical for the prevention of AEs.

Methods: From July 2019 to June 2020, we performed a case-control study among children aged 3-24 months in seven Chinese provinces. Each child received a combination vaccination against diphtheria, tetanus, acellular pertussis, and Haemophilus influenzae type b (DTaP-Hib). Through daily telephone follow-up, we collected AEs within seven days. Oral swab samples were collected to investigate the effects of single nucleotide polymorphisms (SNPs) on the risk of AEs.

Results: 304 participants were included in the study. In univariate analysis, we discovered three protective SNPs (rs452204, OR = 0.67, P = 0.0352; rs9282763 and rs839, OR = 0.64, P = 0.0256) and one risk SNP (rs9610, OR = 2.20, P = 0.0397). In multivariate analysis, the effects of rs452204 and rs839 were found to be stable. The interaction between rs452204 and rs9610 was observed (OR = 7.25, 95% CI: 1.44-36.58, P = 0.0165).

Conclusion: Genetic predisposition was associated with the risk of AEs after DTaP-Hib vaccination, emphasizing the potential application in the prevention of AE.

3. Effectiveness and safety of injectable human papilloma virus vaccine administered as eyedrops. Kim J, Kim E-D, Shin HS, Han SJ, Jamiyansharav M, Yoon SC, Lee JS, Seo KY (SEOKY@yuhs.ac). Vaccine. 2022 Nov 16; S0264-410X(22)01192-6. doi: 10.1016/j.vaccine.2022.09.070. Online ahead of print.

Abstract: Mucosal vaccines have the advantages of ease of administration and the induction of strong mucosal immunity and a systemic immune response. Recently, the eye mucosa has been shown to be an effective and safe alternative vaccination route against influenza, Toxoplasma gondii infection, and hemolytic uremic syndrome in mice. In this study, we showed that the commercially available human papilloma virus (HPV) vaccine, Cervarix, induced significant immune reactions in terms of anti-HPV antigen (Ag)-specific immunoglobulin G (IgG) and IgA antibody production following eyedrop (ED) vaccination in mice. The HPV ED vaccines (EDV) provoked no signs of inflammation within 24 h, as indicated by the inflammatory cytokine mRNA levels and infiltration of mononuclear cells in inoculation sites. Moreover, the morphology of the cornea and retina and intraocular pressure of mice did not change after the HPV EDV. The functions of photoreceptor cells, including rod and cone cells, were normal following the HPV EDV inoculation in mice. These results suggest that Cervarix EDV could be a potent, safe, and effective mucosal vaccine against HPV-associated cancers.

4. Background rates of adverse events of special interest for COVID-19 vaccine safety monitoring in the United States, 2019-2020. Moll K, Azadeh S, (Azadeh.Shoaibi@fda.hhs.gov) et al. Vaccine. 2022 Nov 8;S0264-410X(22)01373-1. doi: 10.1016/j.vaccine.2022.11.003. Online ahead of print.

Abstract: Vaccinees experience no adverse events, mild adverse events, multiple adverse events, or serious adverse events post vaccination. Many of these vaccine adverse events occur with different vaccines with different occurrence frequencies. Many of these adverse events are generally considered as associated with immune responses to the active vaccine components (antigens) and/or to possibly one or more of the vaccine excipients. Most of these vaccine adverse events are self-limiting and resolve within days. Many of these adverse events' symptoms overlap symptoms associated with elevated histamine levels. Based on these observations, the hypothesis that the majority of vaccine associated reactogenicity adverse events are caused by temporal histamine intolerance in vaccinees is proposed. This hypothesis is based on a model of innate immune responses releasing a surge of inflammatory molecules including histamine; this surge is hypothesized to exceed the normal histamine tolerance level for vaccinees with reactogenicity adverse events. Further, these symptoms resolve as histamine levels fall below the vaccinee's tolerance threshold. This model can be evaluated by the detection of elevated histamine levels in vaccinees corresponding to timing of symptoms onset. If confirmed, a direct consequence of this model predicts that some antihistamine treatments, mast cell stabilizers, and possibly diamine oxidase enzyme may reduce the incidence or severity of adverse events experienced by vaccinees post vaccinations for most or all high reactogenicity vaccines including coronavirus disease 2019 (COVID-19) Spike vaccines.

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