Vaccine Safety Quarterly (VSQ) Summer 2023
Brighton Collaboration 2.0
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Politics Affects Health

1. **The Lancet** has a new series on Political Science and Health to discuss:
    1. Why some issues become international concern;
    2. Politics of universal health coverage, and;
    3. How global health diplomacy works.

2. In the US, statewide incidence of COVID-19 cases and deaths varied up to almost 4-fold across the country, independent of prevalence of COVID-19 risk factors, according to a recent Lancet article. Worse COVID-19 outcomes were positively associated with the percentage of 2020 Trump voters in each state. Nobel Prize-winning economist Paul Krugman expounded upon these trends in a New York Times opinion piece, connecting high COVID-19 death rates in Republican-leaning states with failure to expand Medicaid and low COVID-19 vaccination rates.

3. Lawrence Gostin, JD reviews how recent Supreme Court decisions affect public health. "The Supreme Court 2021-2022 decisions are impacting the government's ability to act in the public interest and undermining safeguards for groups that have been historically marginalized." He specifically addresses public health powers, false and misleading scientific information, abortion rights, LGBTQ+ rights, Medicaid, health equity, environmental health, and firearm safety, Thus weakens public health with health and equity on the line. The supreme court is harming public health, and Gostin opines that this trend will continue.

4. A recent court decision undercuts the US Affordable Care Act mandate for cost-free coverage of preventive services including contraception, some vaccines, many screenings and pre-exposure prophylaxis for HIV. These are recommendations of the US preventive services task force.

5. The decision by a federal court in Texas, USA to overturn the Food and Drug Administration's (FDA) approval of mifepristone, a medication used since 2000 to safely and effectively terminate early-stage pregnancies, is part of a growing trend of courts deciding they are better equipped than health agencies to answer scientific questions. In an opinion piece published in JAMA Network, the authors call for reform to protect the FDA's scientific process and the very basis of science based medicine. Legal appeals of this decision are continuing.

GLOBAL OUTBREAKS

COVID-19 endemicity

The WHO has ended the COVID-19 emergency declaration as of May 5. This is because the disease is now an established and ongoing health issue and doesn't meet the definition of emergency. They caution that the pandemic persists and that control measures should continue. WHO reported 3.3 million new cases worldwide in March, and the composition of the COVID-19 vaccine for Fall 2023 is still being discussed based on the circulation of novel variants and sub-variants. Peter Marks of the US FDA has described the need for a distinctly improved generation of COVID-19 vaccines which would offer longer protection and greater protection against variants, and an FDA panel unanimously agreed that booster vaccines for Fall 2023 should include only the dominant circulating variant, XBB. As of May 2023, the WHO has made the following vaccine-specific recommendations for primary and booster series vaccination: Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process.

Vaccine Safety

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

New safety studies continue to examine the risks of adverse events following COVID-19 vaccination, including retinal vascular occlusion, Bell's palsy, and diabetes.

Even after the pandemic subsides, we may still be dealing with adverse health effects among individuals who recovered from acute infections. Long COVID-19 continues to affect some individuals long after the virus has been cleared, with up to 200 symptoms lasting a year or more being reported. An attempt at a case definition of long COVID-19 has just been published.

Vaccine Intentions & Hesitancy

Parents' decision to have children vaccinated parallels their acceptance of vaccines for themselves according to the study, "Parental Factors Affecting Decision to Vaccinate Their Daughters." Another study found that prior negative experiences with vaccines and expectations of harm from COVID-19 vaccines are associated with experience of adverse events, suggesting that managing expectations can reduce the perception of normal post-vaccination sensations as vaccine harms.

Vaccine hesitancy can be influenced by social, political, economic, and geographic factors, as evidenced by a study of COVID-19 vaccine intentions in different language areas of Belgium and among migrant groups in Europe. COVID-19 vaccine concerns appear to be carrying over to use of traditional childhood vaccines. Opposition to school vaccine mandates has grown since 2019.

Combating COVID-19 vaccine hesitancy requires effective communication of the benefits and risks of vaccination, as well as financial incentives should be tailored to specific audiences depending on the type and amount of information they want. 9 Meta-summaries of COVID-19 vaccine evidence could be an effective communication and education method.

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

More generally exists the need to maintain confidence in conventional medicine: Building patient trust to

support medication adherence. It is known that as many as 50% of prescriptions are never filled for a variety of reasons, among them cost.

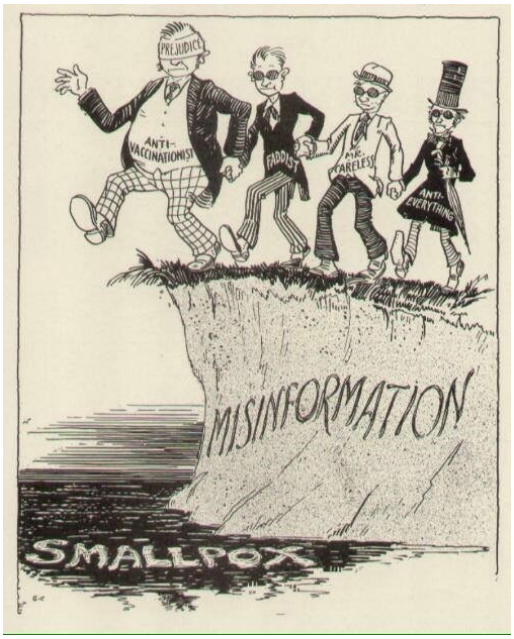
A journalist critiques Anthony Fauci's approach to COVID-19 communications.

The BEST Initiative

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

On vaccine humor

While vaccine safety is no laughing matter, we at the Brighton Collaboration enjoy the odd political cartoon, casting a sardonic eye toward anti-vaccine sentiment. Often, these cartoons have been around for nearly a century, proving that the battle against disinformation and political obstruction is long and hard. Take this (uncredited) depression-era example:



In addition to providing a laugh and/or an eye-roll, vaccination cartoons are a novel source of data reflecting public opinion on vaccines. A group of Canadian researchers reviewed over 2,000 cartoons pertaining to COVID-19 that were published in Canadian newspapers between January 2020 and August 2022, and conducted thematic analysis of nearly 400 cartoons pertaining to COVID-19 vaccination. The study found a shift in attitudes toward COVID-19 vaccines over time, from initial enthusiasm for vaccination to displeasure with vaccination mandates and perceived discrimination against unvaccinated persons. Humor goes both ways, apparently! In any case, we hope you enjoy our minor attempt at comic relief, and we look forward to sharing cartoons in every VSQ issue.

MPOX

WHO has declared that Mpox is no longer a global emergency.

Political Vaccinology

Physicians say an Idaho house bill to criminalize administering mRNA vaccines would be an attack on the medical profession.

We were helpless: Despair at the CDC as the COVID-19 pandemic grew.

BC MEMBER NEWS & ANNOUNCEMENTS

Brighton Collaboration Members attend the BeCOME Conference

The BeCOME (Beyond COVID: the Future of the Real-World Monitoring of Vaccines) Conference was held in Annecy, France, June 11-13, 2023.

Brighton Collaboration's Scientific Director, Dr. Bob Chen, and several past and current Science Board members were in attendance.

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

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

Ongoing Case Definition Translations

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

Digital Innovations in Vaccine Safety (DIVaS) Working Group

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

Vaccines Journal Club

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

The next journal club session will be planned for October 2023, during which we will discuss the interesting exchange between Fraiman and colleagues and the Global Vaccine Data Network on mRNA

COVID-19 vaccine safety. **We especially invite any FDA-affiliated readers to comment on the FDA's approach to surveillance and evaluating COVID-19 vaccine safety.** To receive the virtual journal club link and to receive journal club announcements, please join the mailing list by completing this Google Form.

New Brighton Collaboration Publications

- A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for the Medigen COVID-19 protein vaccine
- Korean translations of BC case definition publications are now available
- European Medicines Agency Myocarditis Workshop Report (January 2023)
- Sensorineural Hearing Loss: AESI Case Definition Companion Guide
- Anosmia Case Definition

Caveat Emptor

There are about 360,000 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. Preprints have increasingly been used to disseminate research results; however, there is no peer review of preprints. Furthermore, a review of preprints and their subsequent publication status found that 23% of preprints were not published in peer-reviewed journals after 12 months, and unpublished preprints tended to have more bias and "spin" than published preprints. Reader, beware! To flex your peer-review skills and learn how to critically assess articles, please join our journal club (details below).

BC Membership

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

Brighton Collaboration Website

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

Articles and Comments to the VSQ are welcomed and invited

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

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

Subscribe to Vaccine Safety Quarterly:

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/3nPq3

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. **Post-authorization safety surveillance of Ad.26.COV2.S vaccine: Reports to the Vaccine Adverse Event Reporting System and v-safe, February 2021-February 2022.** Woo, Emily Jane et al. Vaccine

Background: On 2/27/2021, FDA authorized Janssen COVID-19 Vaccine (Ad.26.COV2.S) for use in individuals 18 years of age and older. Vaccine safety was monitored using the Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system, and v-safe, a smartphone-based surveillance system. Methods: VAERS and v-safe data from 2/27/2021-2/28/2022 were analyzed. Descriptive analyses included sex, age, race/ethnicity, seriousness, AEs of special interest (AESIs), and cause of death. For prespecified AESIs, reporting rates were calculated using the total number of doses of Ad26.COV2.S administered. For myopericarditis, observed-to-expected (O/E) analysis was performed based on the number verified cases, vaccine administration data, and published background rates. Proportions of v-safe participants reporting local and systemic reactions, as well as health impacts, were calculated.

Results: During the analytic period, 17,018,042 doses of Ad26.COV2.S were administered in the United States, and VAERS received 67,995 reports of AEs after Ad26.COV2.S vaccination. Most AEs (59,750; 87.9%) were non-serious and were similar to those observed during clinical trials. Serious AEs included COVID-19 disease, coagulopathy (including thrombosis with thrombocytopenia syndrome; TTS), myocardial infarction, Bell's Palsy, and Guillain-Barré syndrome (GBS). Among AESIs, reporting rates per million doses of Ad26.COV2.S administered ranged from 0.06 for multisystem inflammatory syndrome in children to 263.43 for COVID-19 disease. O/E analysis revealed elevated reporting rate ratios (RRs) for myopericarditis; among adults ages 18-64 years, the RR was 3.19 (95% CI 2.00, 4.83) within 7 days and 1.79 (95% CI 1.26, 2.46) within 21 days of vaccination. Of 416,384 Ad26.COV2.S recipients enrolled into v-safe, 60.9% reported local symptoms (e.g. injection site pain) and 75.9% reported systemic symptoms (e.g., fatigue, headache). One-third of participants (141,334; 33.9%) reported a health impact, but only 1.4% sought medical care. Conclusion: Our review confirmed previously established safety risks for TTS and GBS and identified a potential safety concern for myocarditis.

2. **Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants.** M Kampmann, B. et al . (2023). New England Journal of Medicine

BACKGROUND: Whether vaccination during pregnancy could reduce the burden of respiratory syncytial virus (RSV)–associated lower respiratory tract illness in newborns and infants is uncertain.

METHODS: In this phase 3, double-blind trial conducted in 18 countries, we randomly assigned, in a 1:1 ratio, pregnant women at 24 through 36 weeks' gestation to receive a single intramuscular injection of 120 µg of a bivalent RSV prefusion F protein–based (RSVpreF) vaccine or placebo. The two primary efficacy end points were medically attended severe RSV-associated lower respiratory tract illness and medically attended RSV-associated lower respiratory tract illness in infants within 90, 120, 150, and 180 days after birth. A lower boundary of the confidence interval for vaccine efficacy (99.5%

confidence interval [CI] at 90 days; 97.58% CI at later intervals) greater than 20% was considered to meet the success criterion for vaccine efficacy with respect to the primary end points.

RESULTS: At this prespecified interim analysis, the success criterion for vaccine efficacy was met with respect to one primary end point. Overall, 3682 maternal participants received vaccine and 3676 received placebo; 3570 and 3558 infants, respectively, were evaluated. Medically attended severe lower respiratory tract illness occurred within 90 days after birth in 6 infants of women in the vaccine group and 33 infants of women in the placebo group (vaccine efficacy, 81.8%; 99.5% CI, 40.6 to 96.3); 19 cases and 62 cases, respectively, occurred within 180 days after birth (vaccine efficacy, 69.4%; 97.58% CI, 44.3 to 84.1). Medically attended RSV-associated lower respiratory tract illness occurred within 90 days after birth in 24 infants of women in the vaccine group and 56 infants of women in the placebo group (vaccine efficacy, 57.1%; 99.5% CI, 14.7 to 79.8); these results did not meet the statistical success criterion. No safety signals were detected in maternal participants or in infants and toddlers up to 24 months of age. The incidences of adverse events reported within 1 month after injection or within 1 month after birth were similar in the vaccine group (13.8% of women and 37.1% of infants) and the placebo group (13.1% and 34.5%, respectively).

CONCLUSIONS: RSVpreF vaccine administered during pregnancy was effective against medically attended severe RSV-associated lower respiratory tract illness in infants, and no safety concerns were identified. (Funded by Pfizer; MATISSE ClinicalTrials.gov number, NCT04424316. opens in new tab.)

3. **Safety of co-administration of mRNA COVID-19 and seasonal inactivated influenza vaccines in the vaccine adverse event reporting system (VAERS) during July 1, 2021-June 30, 2022.** Moro et ai. Vaccine. 2023 Mar 10;41(11):1859-1863.

Background: COVID-19 vaccines may be co-administered with other recommended vaccines, including seasonal influenza vaccines. However, few studies have evaluated the safety of co-administration of mRNA COVID-19 and seasonal influenza vaccines.

Methods: We searched the VAERS database for reports of adverse events (AEs) following co-administration of mRNA COVID-19 and seasonal influenza vaccines and following a first booster dose mRNA COVID-19 vaccine alone, during July 1, 2021-June 30, 2022. We assessed the characteristics of these reports and described the most frequently reported MedDRA preferred terms (PTs). Clinicians reviewed available medical records for serious reports and reports of adverse events of special interest (AESI) and categorized the main diagnosis by system organ class.

Results: From July 1, 2021 through June 30, 2022, VAERS received 2,449 reports of adverse events following co-administration of mRNA COVID-19 and seasonal influenza vaccines. Median age of vaccinees was 48 years (IQR: 31, 66); 387 (15.8%) were classified as serious. Most reports (1,713; 69.3%) described co-administration of a first booster dose of an mRNA COVID-19 vaccine with seasonal influenza vaccine. The most common AEs among non-serious reports were injection site

reactions (193; 14.5%), headache (181; 13.6%), and pain (171; 12.8%). The most common AEs among reports classified as serious were dyspnea (38; 14.9%), COVID-19 infection (32; 12.6%), and chest pain (27; 10.6%).

Discussion: This review of reports to VAERS following co-administration of mRNA COVID-19 and seasonal influenza vaccines did not reveal any unusual or unexpected patterns of AEs. Increased reporting of certain events (e.g., COVID-19 disease) was expected. CDC will continue to monitor the safety of co-administration of mRNA COVID-19 and seasonal influenza vaccines, including co-administration involving bivalent mRNA COVID-19 booster vaccines that have been recommended for people ages ≥ 6 months in the United States.

4. **COVID-19 vaccines adverse events: potential molecular mechanisms.** Lamprino et al. Immunol Res. 2023 Jun;71(3):356

Abstract: COVID-19 is an infectious disease caused by a single-stranded RNA (ssRNA) virus, known as SARS-CoV-2. The disease, since its first outbreak in Wuhan, China, in December 2019, has led to a global pandemic. The pharmaceutical industry has developed several vaccines, of different vector technologies, against the virus. Of note, among these vaccines, seven have been fully approved by WHO. However, despite the benefits of COVID-19 vaccination, some rare adverse effects have been reported and have been associated with the use of the vaccines developed against SARS-CoV-2, especially those based on mRNA and non-replicating viral vector technology. Rare adverse events reported include allergic and anaphylactic reactions, thrombosis and thrombocytopenia, myocarditis, Bell's palsy, transient myelitis, Guillain-Barre syndrome, recurrences of herpes-zoster, autoimmunity flares, epilepsy, and tachycardia. In this review, we discuss the potential molecular mechanisms leading to these rare adverse events of interest and we also attempt an association with the various vaccine components and platforms. A better understanding of the underlying mechanisms, according to which the vaccines cause side effects, in conjunction with the identification of the vaccine components and/or platforms that are responsible for these reactions, in terms of pharmacovigilance, could probably enable the improvement of future vaccines against COVID-19 and/or even other pathological conditions.

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