Vaccine Safety Quarterly (VSQ) Fall 2022
Brighton Collaboration 2.0
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What one person can do, a tribute by colleagues
Najwa Khuri-Bulos—leading paediatric care in the Arab world

Kazi, F., & Mushtaq, A. Lancet-infectious disease, June 2022; *22*(6): 778.

Called “Madame Khuri” (a reference to Nobel Laureate Madame Curie) by her late father, Najwa Khuri-Bulos has been a willful dreamer and learner her entire life. “My father would close my books and ‘force’ me to go out and play with the other children. He valued social interaction and play, which he thought were as important as learning from books”, states Khuri-Bulos. Tragically, her father died at the age of 44 from acute myelogenous leukaemia, when Khuri-Bulos was only 10 years old. Her family was left without a breadwinner and they were forced to relocate. Despite these obstacles, Khuri-Bulos was determined to make her father proud. Immersing herself in her studies, Khuri-Bulos received her medical degree from the American University of Beirut, Beirut, Lebanon, in 1968 and graduated with distinctions. She then traveled abroad for residency, studying at various prestigious institutions until completing her residency in paediatrics at Yale University, New Haven, CT, USA. She then attained and completed her fellowship in Infectious Diseases from the University of Colorado Medical Center, Denver, CO, USA. After completing her medical training, Khuri-Bulos returned to the Middle East in order to improve paediatric health care. “I wanted to return to the Arab world after obtaining my board certifications, to give back to the region and its children”, states Khuri-Bulos. Hence, she began teaching at the University of Jordan, Amman, Jordan and eventually became the Chairman of the Department of Pediatrics, amongst many other leadership roles.

Khuri-Bulos states that “in the early days, much of the infectious disease issues were decided by basic scientists, while the clinical aspects of infectious disease decisions were absent”. As a result, Khuri-Bulos has been committed to upgrading teaching curriculums and conducting “opportunistic research”. She states that, in low-income and middle-income countries with high disease burden, waiting for evidence-based decisions might cause unnecessary delay, thus resulting in even more distress for the most vulnerable. Furthermore, she states that when she joined the University of Jordan, she was not afforded dedicated time to conduct research. For those reasons, she proudly states that many of her notable achievements were based upon “personal convictions” and “in-depth study” and were set in motion before some of the data became available. Some of Khuri-Bulos’ accomplishments include introducing an adolescent vaccination programme for diphtheria and the introduction of the combined inactivated and oral poliovirus vaccination programme into the Jordanian immunisation apparatus, before any other nation in the region. Khuri-Bulos cites the adage “the perfect should not be the enemy of the good” to describe her approach to public policy.

Currently, due to the COVID-19 pandemic, Khuri-Bulos has become interested in establishing an Arab Center of Disease Control and Prevention (CDC), as well as advocating for developing the capability to develop vaccines at local level. “The COVID pandemic affected every aspect of our lives starting with health, but also social and economic matters”, states Khuri-Bulos. She states that the pandemic impacted many unrelated conditions such as emergency care, chronic diseases, and specialised care for women, children, and the elderly. Therefore, Khuri-Buros believes that an Arab CDC can help regional countries to be economically and scientifically

self-sufficient in order to implement recommendations to avoid future pandemics. “This continues to be a dream of mine and hopefully will be taken up by the highest level of decision making possible at the next meeting of the Heads of Arab States”, states Khuri-Bulos. Khuri-Bulos also cites the Serum Institute of India as a model for Arab states to emulate in order to mass produce vaccines for their own population. Khuri-Bulos passionately adds that “it is time to work hard at obtaining the public demand for such a regional entity to provide the Arab population of more than 450 million the chance to also be able to harness its scientific and material resources and create a CDC and vaccine making industry”.

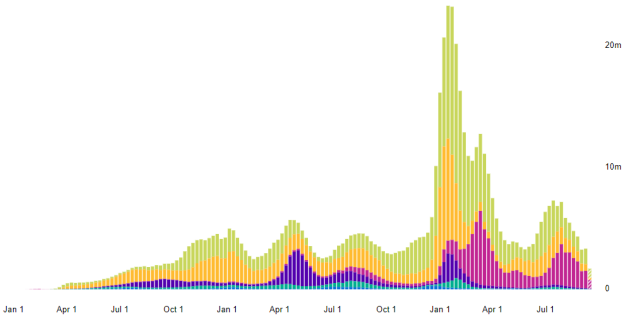
When asked about which of her accomplishments she is proudest of, Khuri-Bulos ö: “I am most proud of having been of help to my department, to my people in Jordan and the Arab world in general, and to our young women who now are able to have a female role model who was not afraid to take the role of leader and founder”. She further states that she takes great pride in knowing that there are four women currently in leadership roles in her department and that the institution's medical school has an equal number of male and female students. Khuri-Bulos has served as a lead member in the International Pediatric Association, a member and chairman of the National Immunization Technical Advisory Groups, with WHO, and a member of the Regional Technical Advisory Group for her region. In closing, Khuri-Bulos reiterates her commitment to being “an explorer and a student in order to become a better investigator and teacher”.

And also a long time contributor to Brighton Collaboration projects. and Science Board member

COVID-19

Quick Links

- COVID-19 Dashboard (Johns Hopkins University)
- COVID-19 vaccine tracker and landscape (WHO)
- Brighton Collaboration: Key Resources for COVID-19 Vaccine Safety Analyses
- Tracking Omicron and Other Coronavirus Variants (CDC)



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. One future scenario proposed is that there will continue to be 2-3 new variants that circulate each year: Covid-19 vaccination-becoming part of the new normal. To date, SARS-CoV-2 infections have been reported in 23 non-human animal species. A recent review of species lumping, its effect on the viral genome and the influence of climate change attempts to link this to virus characteristics.

An external report criticized CDC performance during Covid-19. CDC director Walensky has promised a reorganization, without details. Walensky, citing botched pandemic responses, calls for CDC reorganization.

A rapid Covid-19 test that uses reagent impregnated paper has just become available. Paper strip detects SARS-CoV-2.

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 approved by FDA in July vaccine could also be used as a primary series vaccine for those who are hesitant to receive mRNA vaccines. However, booster uptake has been slow and its role in the Covid-19 vaccine toolbox is unclear.

New SARS-CoV-2 vaccine candidates continue to be developed and studied. Alternative technologies and formulations can help address some shortcomings of currently-available vaccines, including availability to LMIC populations, ease of administration, and improved efficacy against variants (WHO COVID-19 vaccine tracker and landscape). Still, how are vaccine manufacturers and regulatory agencies going to try to keep up with nature? A combination COVID-Flu vaccine developed by Novavax has shown promising immunogenicity in animal studies and early human trials. Combination vaccines could reduce the burden of shots recommended for prevention of seasonal respiratory infections.

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.

Vaccine Safety

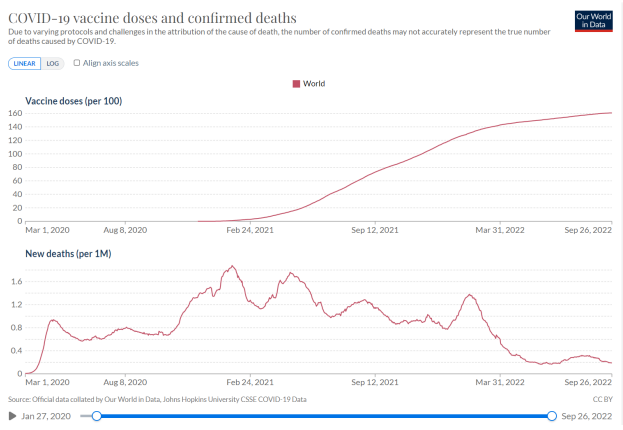
Brighton Collaboration has been involved along with CEPI in developing a list of possible AESIs that may be associated with a COVID-19 vaccine. One early concern was the potential for vaccine-associated enhanced disease. This has been seen with SARS and MERS-CoV vaccines in animal models but remains theoretical for COVID-19 to date. Case definitions and other tools for assessing this and other COVID-19 vaccine AESI's are available here. A review of short term adverse events after a third dose of the Pfizer/BioNTech vaccine found similar or lower reports than after the second dose: Short-term adverse events after the third dose of the BNT. A novel post mRNA booster AE has been reported: Urticaria 12 days after COVID mRNA booster. Another interesting Covid-19 AE has been reported: menstrual cycle changes. Comments to this NYTimes article support this research report. An interesting study of Covid-19 in patients with Kawasaki disease because of the similarity to childhood inflammatory syndrome: Tolerability among patients with Kawasaki Disease.

A study of the association of Covid-19 versus influenza with risk of arterial and venous thrombotic events found higher risk of venous but not arterial thromboembolism within 90 days. Association of COVID-19 vs. influenza with risk of arterial and venous thrombotic events among hospitalized patients.

California has approved a law to punish doctors who promulgate false information.

As usual, rumors about vaccine impacting fertility have surfaced: Widespread misinformation about infertility continues to create vaccine hesitancy.

Vaccines are Effective



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

An evaluation of vaccine effectiveness was done by comparing the odds ratio of symptomatic COVID-19 during the Delta variant predominant phase and the pre Delta phase: Association of COVID-19 vaccination with symptomatic SARS-CoV-2. A recent study estimates the number of infections, hospitalizations and deaths prevented by the vaccines: Estimated Number of COVID-19 Infections, Hospitalizations, and Deaths Prevented Among Vaccinated Persons in the US, December 2020 to September 2021.

Long Covid

After the pandemic subsides, we may still be dealing with adverse health effects among individuals who recovered from acute infections. So-called "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. An intention to study long Covid-19 has been announced. The US now has a research plan for long COVID.

Long Covid: What is it and what are the symptoms? - BBC News

Conditions common 1 to 5 months after positive COVID test - University of Minnesota, Center for Infectious Disease Research and Policy.

Treatment

Two types of therapy are available for Covid treatment. Antivirals, remdesivir, paxlovid, which Inhibit viral replication and antibodies, bebtelovimab, decrease viral load. Dexamethasone and heparin have roles in certain situations. A NIH website provides current guidance for treating non hospitalized and hospitalized patients according to disease severity. Clinical management of adults with covid.

Meanwhile the Ivermectin story continues. Efficacy of ivermectin treatment on disease progression.

The NYTimes maintains a report on progress in drug development.

A fascinating development is that the FDA has withdrawn emergency use authorization of two monoclonal antibody treatments that were less effective against the Omicron variant compared to previous variants.

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 the United States, CDC and MMWR are good sources. WHO provides global information as does the United Kingdom's National Health Service. 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.

Monkeypox

Monkeypox, somewhat misnamed, arose from obscurity in Africa and has been reported in 22 countries with 17,000+ cases in the US. So far most cases are in a limited demographic group. Limited amounts of vaccine are available. There is no known plan to increase supply. FDA has authorized intradermal vaccine administration which uses less vaccine and effectively increases vaccine availability. DelRio has published a short review of monkey pox. Monkeypox in 2022: what clinicians need to know.

Vaccine Intentions

One factor in Covid vaccine hesitancy was supposedly that the vaccine had not received full FDA approval when it was first distributed. A study

compares vaccine uptake before and after full FDA approval and finds little difference.

Parental hesitancy to vaccination children persists in the US, despite final full FDA approval of vaccination for children as young as 5: https://pubmed.ncbi.nlm.nih.gov/35238263/

However, adolescent desires to receive COVID-19 vaccination can influence parental intentions to vaccinate: https://pubmed.ncbi.nlm.nih.gov/35305793/

In Florida anti-vaxers attempted to get representation on the board of a public hospital. Conservatives skeptical of covid vaccine attempt.

A study of geographic variations in vaccine booster uptake shows were additional efforts may be directed: Geographic variations in booster uptake
The NY Times has just published a front page article on vaccine hesitancy. This article is very complete but repeats the bad chemistry about mercury and thimerosal and overemphasizes AEs: The anti vaccine movement.

One commentator has stated that new approaches are needed to approach vaccine hesitancy. More of the same, charts and graphs, will not work.The abysmal covid vaccination rate

How to Discuss Vaccine Hesitancy

Omicron and BA.5: Questions patients may have and how to answerhav

Vaccine safety and false contraindications to vaccines: Training Manual

Theater for vaccine hesitancy setting the stage

A pharmacologist describes how he confronts anti-science sentiment: Confronting anti-science sentiment.

Political vaccinology

Facebook and Instagram Remove Robert Kennedy Jr.'s Nonprofit for Misinformation

Tom Friedan has written an essay on lessons learned, where we are and what may lie ahead: The next COVID wave is probably already here.

Debora Birx, who was a charter member of the White House Covid-19 team, has written a book about the experience: Silent Invasion, by Debora Brix.

Also, the free speech issue: Reducing COVID-19 misinformation while preserving free speech.

But there may be a wider problem of trust in general, including trust in the medical establishment: Maintaining public trust in medical service.

Joe Heller | Copyright 2022 Hellertoon.com

Adverse event surveillance pays off

An unusual form of thrombocytopenia, thrombocytopenia with thrombosis, TTS, was reported early in the COVID-19 immunization campaign. Expert panels thought there was a possible vaccine association but agreed to continue vaccine use with heightened surveillance. Many more cases of TTS have been reported and FDA has limited the indication for Johnson and Johnson COVID-19 vaccine use**.** A case of TTS after Sputnik V vaccination has been reported from Argentina.

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 quarA brief history of vaccinology-googleterly 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 next journal club session will be held Wednesday, October 7 at 9AM GMT-5. Dr. Preeti Sule will present Impact of SARS-CoV-2 vaccination and booster on COVID-19 symptom severity over time in the COVID-OUT trial. To receive the virtual journal club link and to receive journal club announcements, please join the mailing list by completing this Google Form**.**

History

A 1922 essay laments indifference and hostility to smallpox vaccine. JAMA revisits this essay 100 years later.

Also 2 new histories of vaccines:

- A brief history of vaccination (Google).
- The origins of inoculation (J R Soc Med)

Member News

Bob Chen, BC scientific director, was honored at the recent International Society for Pharmacoepidemiology meeting for his work with Covid-19 and 30+ years on vaccine safety. Congratulations, Bob, and thank you for your years of service to the scientific community!

VSQ Readers

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.

Help Wanted

The Brighton Collaboration is recruiting for a **Director of Research.** Please share with potentially interested colleagues.

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 interest.

1. **New-onset autoimmune phenomena post-COVID-19 vaccination**
   Chen Y (ychen@uottawa.ca), et. al. New-onset autoimmune phenomena post-COVID-19 vaccination. Immunology. 2022 April

Abstract: Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to an unprecedented setback for global economy and health. Vaccination is one of the most effective interventions to substantially reduce severe disease and death due to SARS-CoV-2 infection. Vaccination programmes are being rolled out globally, but most of these vaccines have been approved without extensive studies on their side-effects and efficacy. Recently, new-onset autoimmune phenomena after COVID-19 vaccination have been reported increasingly (e.g. immune thrombotic thrombocytopenia, autoimmune liver diseases, Guillain-Barré syndrome, IgA nephropathy, rheumatoid arthritis and systemic lupus erythematosus). Molecular mimicry, the production of particular autoantibodies and the role of certain vaccine adjuvants seem to be substantial contributors to autoimmune phenomena. However, whether the association between COVID-19 vaccine and autoimmune manifestations is coincidental or causal remains to be elucidated. Here, we summarize the emerging evidence about autoimmune manifestations occurring in response to certain COVID-19 vaccines. Although information pertaining to the risk of autoimmune disease as a consequence of vaccination is controversial, we merely propose our current understanding of autoimmune manifestations associated with COVID-19 vaccine. In fact, we do not aim to disavow the overwhelming benefits of mass COVID-19 vaccination in preventing COVID-19 morbidity and mortality. These reports could help guide clinical assessment and management of autoimmune manifestations after COVID-19 vaccination.

2. **Covid-19 vaccines and variants of concern: A review**
   Hadj Hassine I (hadj_hassine_ekbell@yahoo.fr). Covid-19 vaccines and variants of concern: A review. Rev Med Virol. 2022 Jul;32(4):e2313.

Abstract: Since the outbreak of coronavirus disease 2019 (Covid-19) in December 2019, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the number of confirmed infections has risen to more than 242 million worldwide, with nearly 5 million deaths. Currently, nine Covid-19 vaccine candidates based on the original Wuhan-Hu-1 strain are at the forefront of vaccine research. All nine had an efficacy over 50% against symptomatic Covid-19 disease: NVX-CoV2373 (~96%), BNT162b2 (~95%), mRNA-1273 (~94%), Sputnik V (~92%), AZD1222 (~81%), BBIBP-CorV (~79%), Covaxin (~78%), Ad26.CoV.S (~66%) and CoronaVac (~51%). However, vaccine efficacy (VE) can be jeopardised by the rapid emergence and

spread of SARS-CoV-2 variants of concern (VOCs) that could escape from neutralising antibodies and/or cell-mediated immunity. Rare adverse events have also been reported soon after administration of viral vector and mRNA vaccines. Although many Covid-19 vaccines have been developed, additional effective vaccines are still needed to meet the global demand. Promising Covid-19 vaccines such as WIBP-CorV, AD5-nCOV, ZyCoV-D, CVnCoV, EpiVacCorona and ZF2001 have advanced to clinical studies. This review describes the most relevant mutations in the SARS-CoV-2 spike protein, discusses VE against VOCs, presents rare adverse events after Covid-19 vaccination and introduces some promising Covid-19 vaccine candidates.

3. **Safety and Adverse Events Related to Inactivated COVID-19 Vaccines and Novavax;a Systematic Review**
   Dadras O (omiddadras@yahoo.com), et. al. Safety and Adverse Events Related to Inactivated COVID-19 Vaccines and Novavax;a Systematic Review. Arch Acad

Introduction: Knowledge of the safety of vaccines is crucial, both to prevent and cure them and to decrease the public hesitation in receiving vaccines. Therefore, this study aimed to systematically review the adverse events reported for inactivated vaccines and Novavax.

Methods: In this systematic review, the databases of PubMed, Scopus, Cochrane, and Web of Science were searched on September 15, 2021. Then we identified the eligible studies using a two-step title/abstract and full-text screening process. Data on the subjects, studies, and types of adverse events were extracted and entered in a word table, including serious, mild, local, and systemic adverse events as well as the timing of side effects' appearance.

Results: Adverse effects of inactivated coronavirus vaccines side effects were reported from phases 1, 2, and 3 of the vaccine trials. The most common local side effects included injection site pain and swelling, redness, and pruritus. Meanwhile, fatigue, headache, muscle pain, fever, and gastrointestinal symptoms including abdominal pain and diarrhea were among the most common systemic adverse effects.

Conclusion: This systematic review indicates that inactivated COVID-19 vaccines, including Sinovac, Sinopharm, and Bharat Biotech, as well as the protein subunit vaccines (Novavax) can be considered as safe choices due to having milder side effects and fewer severe life-threatening adverse events.

4. **Elevated Histamine Etiology Model for Most Major Vaccine Associated Adverse Events including SARS-CoV-2 Spike Vaccines**

   Ricke DO (Darrell.Ricke@ll.mit.edu). Elevated Histamine Etiology Model for Most Major Vaccine Associated Adverse Events including SARS-CoV-2 Spike Vaccines. Med Hypotheses.

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.

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:

- Myocarditis and Pericarditis: Case Definition Companion Guide
- Vaccines based on the replication-deficient simian adenoviral vector ChAdOx1: Standardized template with key considerations for a risk/benefit assessment
- A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for an inactivated viral vaccine against Chikungunya ,
- A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for the Moderna COVID-19 Vaccine (mRNA-1273)
- Advancing the Science of Vaccine Safety During the Coronavirus Disease 2019 (COVID-19) Pandemic and Beyond: Launching an International Network of Special Immunization Services
- Thrombosis/Thromboembolism Case Definition

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

Brighton Collaboration Science Board Election Announcement

Here is the full list of SB member and their qualifications (click here) as well as their Brighton experience and areas of expertise (click here).

Science Board:

Sonali Kochhar, MD - India
Wan-Ting Huang, MD - Taiwan
Clare Cutland, PhD, MBBCH - South Africa
Nicholas Wood, MBBS, PhD, MPH, FRACP - Australia
Paul Henri Lambert, MD - Switzerland
Azucena Bardaji, MD, MSc, PhD - Spain
Jim Buttery, MD - Australia
Alejandro Cravioto, MD, PhD - Mexico
Matthew Dudley, PhD, MSPH - USA
Jane Gidudu, MD, MPH - USA
Hector Izurieta, MD, PhD - USA
Najwa Khuri-Bulos, MD - Jordan
Denny Kim, MD, MPH - USA
Nicola Klein, MD, PhD - USA
M Top, MD, MSC, FRCPC - Canada
Robert Wise, MD - USA

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