Vaccine Safety Quarterly (VSQ) | Summer 2021

Brighton Collaboration 2.0

Frederick Varricchio, PhD, MD - *Editor in Chief*

Challenges and solutions to COVID-19 vaccine research in a rapidly-changing environment

Nadja A. Vielot, University of North Carolina at Chapel Hill, USA

The Covid-19 Prevention Network (CoVPN) was established by the United States National Institute of Allergy and Infectious Diseases to develop rapid responses to the COVID-19 pandemic. Leveraging existing research networks, including the HIV Vaccine Trials Network, CoVPN has advanced research to develop vaccines and monoclonal antibody therapies to prevent and manage COVID-19 disease.

The multi-site "Prevent COVID U" study (CoVPN 3006) was conceived to estimate the efficacy of the Moderna mRNA COVID-19 vaccine against 1) SARS-CoV-2 infection in college and university students, and 2) transmission of SARS-CoV-2 to close contacts. The Moderna vaccine received Emergency Use Authorization (EUA) by the U.S. Food & Drug Administration on December 18, 2020, based on clinical trial data demonstrating 94% efficacy against severe COVID-19 disease among adults 18 years and older. Data from CoVPN would provide additional information on the incidence of asymptomatic infections after vaccination, and provide an evidence base to inform masking and physical distancing guidelines in a vaccinated population.

The COVID-19 pandemic has been and continues to be a rapidly-evolving situation. From the detection of novel variants to the piecemeal delivery of vaccines across the globe, scientists are racing to keep up. The CoVPN 3006 team is no exception. Here is a summary of the challenges we have faced and the solutions we have implemented to deliver on our objective to understand COVID-19 transmission among young adults.

1. **Originally conceived as a placebo-controlled trial, CoVPN 3006 had to change course once the Moderna COVID-19 vaccine received EUA.** The original CoVPN 3006 design was a three-armed clinical trial to compare the efficacy of the full dose of the Moderna vaccine against a half dose and a placebo. After receiving EUA, it was no longer ethical to withhold vaccine from a control group, and thus the placebo-controlled design was eliminated in favor of a 1:1 randomized two-armed study to compare individuals receiving immediate vaccination to those receiving delayed vaccination (i.e. four months later).

2. **Vaccine rollout in the U.S. happened faster than expected.** In the earliest stages of vaccine rollout, the Moderna and Pfizer mRNA vaccines were recommended only to older adults and those with chronic health conditions. As a result of rapid vaccine production, the introduction of the one-dose Johnson & Johnson/Janssen vaccine on February 27, and President Joe Biden's March 11 declaration that all U.S. residents would become eligible for COVID-19 vaccination by May 1, the pool of eligible unvaccinated individuals began to rapidly decline. Concerns were raised that college students would become eligible for vaccination prior to study launch, and that a delayed vaccination arm was no longer ethical. To accommodate the need for a valid control group in the absence of equipoise, we allowed participants randomized to the delayed vaccination arm to receive vaccination outside of the study if they chose. We would continue to follow them to monitor viral shedding in the nasal passage and viral transmission to close contacts.

3. **Students attending colleges and universities in person and/or living on campus were vaccinated quickly.** At UNC Chapel Hill, which was the first major educational institution in the U.S. to shut down after the start of the Fall 2020 semester, administrators and students alike were eager to vaccinate the roughly 6,000 students who lived in campus housing or attended classes in person. A major campaign provided the J&J/Janssen vaccine to approximately 4,000 UNC students over two weeks in March. By the time our site opened for enrollment on March 31, there were very few unvaccinated students remaining, and many of them already had vaccination appointments pending. The protocol was further adapted to allow students from community colleges and other non-four-year institutions to enroll. Here in Orange County, which is composed largely of UNC Chapel Hill employees and students, 62% of adults are vaccinated as of May 27; coverage is lower in surrounding counties and at institutions that lack robust campus health systems. A subsequent modification opened enrollment to any adult aged 18-29 years. While students were originally targeted due to their tendency to gather in groups, our recruitment goal of 12,000 student enrollees among approximately 30 educational institutions would not be feasible. Finally, the new protocol will allow for a control arm of individuals who declined vaccination, in lieu of withholding or delaying vaccination for those who want it.

Despite many challenges to implementing CoVPN 3006, the information to be gained regarding the incidence of subclinical infections, viral shedding, and transmission risk is invaluable to controlling the COVID-19 pandemic. CoVPN continues to evolve along with the pandemic to provide evidence-based guidance for safe reopening of public spaces and congregations with friends and loved ones. The study will close November 30, 2021 and preliminary results will be available by early 2022.

Left: Sylvia Becker-Dreps, MD, MPH (left) and Nadja A Vielot, PhD (right) are co-Principal Investigators of the UNC Chapel Hill site of CoVPN 3006. Right: Nurse Alison Tiano administers the Moderna COVID-19 vaccine to a CoVPN 3006 participant.

COVID-19

Over 140,000 citations coded COVID-19 are listed in PubMed. Many appear to be from China but from many other countries as well. This is a remarkable achievement in one year. The signs, symptoms, course, and sequelae of this disease are still evolving and probably will continue to do so for some time. 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 many important unknowns such as the duration of antibodies. 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.

In terms of pathophysiology, the virus first binds ACE II (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. Assessment of the frequency and variety of persistent symptoms include fatigue and somnolence, which affect about ⅓ of survivors, so-called "long haulers". 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.

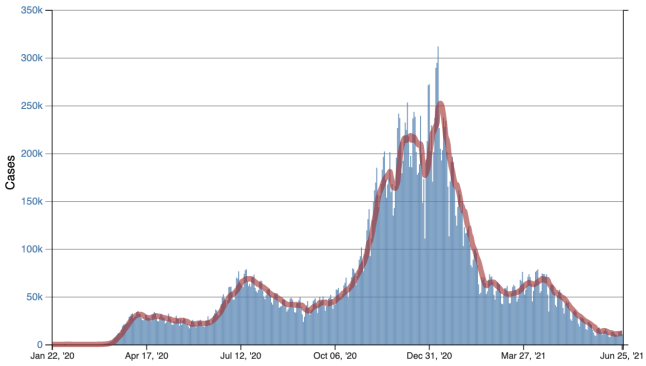
A "new AE" COVID-19 related inflammatory multisystem disorder has been reported and is similar to Kawasaki disease. Its status is currently being discussed.

Mid-December a more contagious mutant was found in the UK. This mutant has already spread widely . Other mutants are South Africa and Brazil which also are now widespread. A double mutant, originally found in India, is spreading widely worldwide . Other localized mutants such as California are being followed. WHO is renaming COVID-19:variants with Greek letters, the UK variant is now Alpha and the Indian variant is Delta. Initial information is 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 and coagulopathy. COVID-19 antibodies have been found in breast milk.

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.

The New York Times continues to publish COVID-19 case counts as well as vaccine administration efforts in the US. There are also detailed diagrams of the COVID-19 genome and mutants Coronavirus variant tracker



Daily Trends in Number of COVID-19 Cases in the United States Reported to CDC

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 approval. It will be available through state health departments. Francis Collins, the NIH director, convened a meeting quickly in April 2020 to discuss drug therapy of COVID-19. This meeting brought together government scientists, regulators, FDA and drug industry leaders. They identified 170 compounds of potential interest. However, progress toward effective therapy has been disappointing to date. A recent publication describes how COVID-19 infection affects host cell processes. This should lead to antiviral drugs.

Articles attesting to the lack of efficacy of hydroxychloroquine continue to appear. The NYTimes maintains a report on progress in drug development. The FDA has just announced a dedicated reporting system for

Covid-19 therapeutics. The Regeneron product that received emergency FDA approval is being used. It is a unique double antibody drug which acts by attaching to COVID-19 virus particles and thereby reducing viral load. 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.

COVID-19 vaccine

Moderna and Pfizer-Biontech (PB) vaccines are used extensively in the US, with about 300M 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. The numbers vary greatly by age, state, political party and religion. The vaccines are now approved for ages 12 and up. Real world data agree with the first trial data as to efficacy in the 90% range. A negative is that the PB requires extreme cold for storage and transport. They both use a novel messenger RNA (mRNA) platform. A third vaccine, Johnson and Johnson-Janssen has recently been approved and is already being used and reported 70-90% success. This vaccine uses a viral vector platform and has advantages in stability and cost and only requires one dose. Use of this vaccine is slowed because of serious problems at one manufacturing facility. Because of the mutants that have appeared, 2nd generation vaccines are already in progress. One goal is to develop a vaccine with broader efficacy. The FDA has already 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 8 vaccines are currently on the world market. This includes vaccines from Russia, China. and india. A Cuban vaccine is in an advanced state of development. The New York Times maintains a list of the status of the 70 odd vaccines in development. About 6 different platforms are being tried. Merck has stopped development of 2 vaccines because of poor efficacy. 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. Of course there are other possible applications of this approach such as in long pursued gene therapy. Moderna reportedly has about 25 products in advanced stages of development.A detailed graphic outline of the production process has also appeared.

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. As of mid February an estimated 130 countries had not received 1 dose. 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. 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 reactogenicity.

TTS is reported after the Astra-Zeneca(AZ) and Johnson and Johnson-Jensen(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. Karin Batty has compiled a detailed account of the TTP situation. 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. 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. A combined Covid-19 influenza test has recently become available.

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.

Vaccine Success

According to the US Centers for Disease Control and Prevention, Cervical cancer due to human papillomavirus (HPV) has decreased in the US due to screening and vaccination but other cancers such as oropharyngeal cancer have increased.

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 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 have been administered in the US with about 60+% coverage . 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".

China and Russia have been exporting their vaccines to other nations. But relatively little is known about these products; possibly contributing to vaccine hesitancy.

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.

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 Cathy Panozzo of Moderna TX and BC member Nadja Vielot of the University of North Carolina.

In observance of the US Independence Day, the July 2 SIG Journal Club will be cancelled. The next meeting will be held in October 2021, with details to come in the next VSQ issue. To join the discussion, please complete this Google Form and we will include you on the mailing list.

History: When anti-vaccine sentiment turned violent: the Montreal Vaccine Riot of 1885

CMAJ Apr 2021, 193(14) E490-E492; doi: 10.1503/cmaj.202820.
Corresponding author: Jonathan M. Berman (Department of Basic Science, New York Institute of Technology College of Osteopathic Medicine at Arkansas State University, Jonesboro, AR, USA)

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?

Political Epidemiology

What I Learned in 33 Years at the C.D.C. (NY Times, Anne Schuchat)
The Biden administration will investigate Trump-era attacks on science (NY Times)
The Era of Vaccine Diplomacy is Here (NY Times)

VSQ Readers

The Spring VSQ was emailed to over 900 readers. An estimate from the returned reader survey shows 30% of readers are from the US followed by Canada and India. Occupations vary from clinical research to statistics to fund raising. 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. **Anxiety-Related Adverse Event Clusters After Janssen COVID-19 Vaccination - Five U.S. Mass Vaccination Sites, April 2021**
   MMWR Morb Mortal Wkly Rep. 2021 May 7;70(18):685-688. doi: 10.15585/mmwr.mm7018e3.
   Corresponding Author: Anne M. Hause (US CDC)

What is already known about this topic?

Syncope and other anxiety-related events can occur after vaccination and have been reported to the Vaccine Adverse Events Reporting System (VAERS) for other vaccines.

What is added by this report?

Five mass vaccination sites reported 64 anxiety-related events, including 17 events of syncope (fainting) after receipt of Janssen COVID-19 vaccine. The reporting rates of syncope to VAERS after Janssen COVID-19 and influenza vaccines (2019–20) were 8.2 and 0.05 per 100,000 doses, respectively.

What are the implications for public health practice?

Vaccine providers should be aware of anxiety-related events after vaccination and observe all COVID-19 vaccine recipients for any adverse reactions for at least 15 minutes after vaccine administration.

2. **Novel vaccine safety issues and areas that would benefit from further research**
   BMJ Glob Health. 2021 May;6(Suppl 2):e003814. doi: 10.1136/bmjgh-2020-003814.
   Corresponding Author: Daniel A. Salmon (Global Disease Epidemiology and Control, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA)

Abstract: Vaccine licensure requires a very high safety standard and vaccines routinely used are very safe. Vaccine safety monitoring prelicensure and postlicensure enables continual assessment to ensure the benefits outweigh the risks and, when safety problems arise, they are quickly identified, characterised and further problems prevented when possible. We review five vaccine safety case studies: (1) dengue vaccine and enhanced dengue disease, (2) pandemic influenza vaccine and narcolepsy, (3) rotavirus vaccine and intussusception, (4) human papillomavirus vaccine and postural orthostatic tachycardia syndrome and complex regional pain syndrome, and (5) RTS,S/adjuvant system 01 malaria vaccine and meningitis, cerebral malaria, female mortality and rebound severe malaria. These case studies were selected because they are recent and varied in the vaccine safety challenges they elucidate. Bringing these case studies together, we develop lessons learned that can be useful for addressing some of the potential safety issues that will inevitably arise with new vaccines.

3. **Evidence-Based Strategies for Clinical Organizations to Address COVID-19 Vaccine Hesitancy**
   Mayo Clin Proc. 2021 Mar;96(3):699-707. doi: 10.1016/j.mayocp.2020.12.024.
   Corresponding author: Robert M. Jacobson (Community Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA)

Abstract: The success of vaccination programs is contingent upon irrefutable scientific safety data combined with high rates of public acceptance and population coverage. Vaccine hesitancy, characterized by lack of confidence in vaccination and/or complacency about vaccination that may lead to delay or refusal of vaccination despite the

availability of services, threatens to undermine the success of coronavirus disease 2019 (COVID-19) vaccination programs. The rapid pace of vaccine development, misinformation in popular and social media, the polarized sociopolitical environment, and the inherent complexities of large-scale vaccination efforts may undermine vaccination confidence and increase complacency about COVID-19 vaccination. Although the experience of recent lethal surges of COVID-19 infections has underscored the value of COVID-19 vaccines, ensuring population uptake of COVID-19 vaccination will require application of multilevel, evidence-based strategies to influence behavior change and address vaccine hesitancy. Recent survey research evaluating public attitudes in the United States toward the COVID-19 vaccine reveals substantial vaccine hesitancy. Building upon efforts at the policy and community level to ensure population access to COVID-19 vaccination, a strong health care system response is critical to address vaccine hesitancy. Drawing on the evidence base in social, behavioral, communication, and implementation science, we review, summarize, and encourage use of interpersonal, individual-level, and organizational interventions within clinical organizations to address this critical gap and improve population adoption of COVID-19 vaccination.

4. Postmarketing safety surveillance of quadrivalent recombinant influenza vaccine: Reports to the vaccine adverse event reporting system.

Vaccine. 2021 Mar26;39(13):1812-1817. doi: 10.1016/j.vaccine.2021.02.052. Epub 2021 Mar 5.
Corresponding author: Emily Jane Woo (Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA)

Abstract: On October 7, 2016, the Food and Drug Administration approved recombinant hemagglutinin quadrivalent influenza vaccine (RIV4) (Spodoptera frugiperda cell line; Flublok Quadrivalent) for active immunization for the prevention of influenza disease in individuals 18 years of age and older. Clinical trials did not reveal any major differences in adverse events or serious adverse events following Flublok Quadrivalent versus standard-dose quadrivalent inactivated influenza vaccine. To improve our understanding of the safety profile of this vaccine, we reviewed and summarized adverse event reports after Flublok Quadrivalent administration to the Vaccine Adverse Event Reporting System (VAERS). Through June 30, 2020, VAERS received 849 reports after RIV4 vaccination. The vast majority (810; 95%) were non-serious. Among serious events, there were 10 cases of Guillain-Barré syndrome, including 5 people who required mechanical ventilation and 2 people who died. Many allergic reactions were reported as non-serious, but required interventions to treat a life-threatening event, e.g., epinephrine, nebulizers, albuterol, glucocorticoids, and supplemental oxygen. Two people experienced a positive rechallenge (i.e., allergic reactions after repeated vaccination with RIV4), including a person who-despite premedication with antihistamines-developed respiratory difficulties, required epinephrine, and was transported to the emergency department. The occurrence of anaphylaxis and other allergic reactions in some individuals may reflect an underlying predisposition to atopy that may manifest itself after an exposure to any drug or vaccine, and does not necessarily suggest that Flublok Quadrivalent is particularly allergenic. Postmarketing safety surveillance will continue to be vital for understanding the benefits and risks of quadrivalent recombinant influenza vaccine.

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 Portugese.

A couple of notable recent publications are:

- Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Protein Vaccines
- Sensorineural Hearing Loss (SNHL) as an Adverse Event Following Immunization (AEFI): Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data
- How to ensure we can track and trace global use of COVID-19 vaccines?

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!

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