Vaccine Safety Quarterly (VSQ) | Spring 2020

Brighton Collaboration 2.0

Frederick Varricchio, PhD, MD - *Editor in Chief* Les Garber - *Style Editor*

Dear Brightonians,

Since the last VSQ in January, much of the world has grappled with emergence of the novel coronavirus, SARS-COV-2, and as we write continued global spread is anticipated. In many countries, hospitals and healthcare workers are overburdened by a surge of COVID-19 cases beyond available capacity and resources, cities have been shut down, schools and offices have transitioned to virtual learning/working environments, international borders allow limited travels, and the global economic market has plummeted. It feels like we are living in a work of science fiction. The new cultural norm, including physical distancing, has left many communities feeling isolated and anxious without the light at the end of this pandemic.

On March 11th, 2020, after careful assessment, the World Health Organization declared COVID-19 as a pandemic. In addition to public health measures such as quarantine, social distancing, and expansion of clinical laboratory testing requirements, Coalition for Epidemic Preparedness and Innovation (CEPI) has funded several programs to develop a vaccine against SARS-COV-2. Brighton Collaboration Safety Platform for Emergency Vaccines (SPEAC), funded by CEPI, have been working in partnership with CEPI to support safety assessment of its vaccine candidates.

Pre-clinical studies of various SARS vaccine candidates have indicated a risk of enhanced disease after challenge with SARS-CoV in previously immunized animals (mice, NHPs). To better understand and hopefully prevent potential enhanced disease during vaccine development against SARS-COV-2, CEPI and SPEAC jointly hosted a global scientific working meeting via webinar on March, 12-13, 2020. The meeting produced a consensus document; this and other meeting proceedings and products are now available to all, especially COVID-19 vaccine developers.

Medical and scientific communities are also providing consolidated resources on COVID-19 under open access (WHO, US CDC, Johns Hopkins Center for Healthy Security [Global Cases Map], ProMED, Worldometers, JAMA, NEJM, the Lancet, BMJ, Nature, IDSA, and Next Strain [SARS-COV-2 genomic sequencing], to name a few).

Other ongoing BC and SPEAC activities on COVID-19 include developing: a) a standardized case definition for enhanced disease post-immunization; b) a list of adverse events of special interest (AESI); and c) standardized safety templates describing key risk-benefit parameters for new vaccine candidates. The BC Viral Vector Vaccine Safety Working Group (V3SWG) had used these templates successfully as a tool -- akin to a pilot's checklist -- to transparently communicate complex information about new viral vector vaccines (e.g., Ebola vaccine) to stakeholders less knowledgeable about biotechnology. As several non-viral vector platforms are being used for SARS-COV-2, the V3SWG is developing new templates for them too.

Wherever you are reading this issue in whatever role you partake in the world amidst this pandemic, remember to take care of yourself as well as those

around you and encourage following WHO and national CDC guidelines and reliance on valid sources.

Please use the Brighton Collaboration for your professional networking in the vaccine safety domain to avoid your isolation. If you didn't receive this newsletter directly and wish to, please enroll.

Stay well,

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THE BRIGHTON WEBSITE

As part of our transition from BC1.0 to BC2.0, we have been working on a new and improved website! The old website will remain operational through May 2020 so that there is no disruption in members' access to the BC Academy feature. The initial version of the new website is already up and running at http://brightoncollaboration.us and http://brightoncollaboration.info, and contains all content from the old site except for some of the content contained solely within the Academy. Once we finalize the Academy portion of the new website (later this year), we will close the old site down and make the original URL the primary URL for the new site as well. We also plan to bring in further web development expertise to make the new website as professional and user friendly as possible. In the meantime, please feel free to provide feedback on content and structure of the new website by emailing the BC coordinator at bc-coordinator[at]taskforce[dot]org, and keep an eye out for new content and features on the website as we go forward!

BC V2.0 SURVEY

There were 88 responses to the reader survey of interests and suggestions. A detailed analysis of the responses is attached. I especially noticed two suggestions. Several indicated a willingness to contribute to the stability of the VSQ. While the VSQ is produced by unpaid volunteers, there are some expenses such as office supplies and occasional computer programs. The next issue will have information about how to contribute if you wish. Also, there was a suggestion that VSQ take a more active role against vaccine misinformation and anti-vaccine issues. Several articles in this issue are a move in that direction.

THE WAKEFIELD AFFAIR

Andrew Wakefield published an infamous paper in 1998 purporting to show an increase in autism after MMR vaccine. The paper was retracted after 6 years, in 2004, and coauthors dissociated themselves. Nevertheless it caused considerable controversy even involving the British Prime Minister and his newborn child at one point We have seen resurgence in vaccine hesitancy with increased social media usage around 2010 and the movie, Vaxxed, directed by Wakefield. To March 2019, the article has been cited 1253 times. The citations have been analyzed by Suelzer, who found the citations are mostly negative. Even after formal retraction of the article in 2010, only 78% of the citations noted the retraction and significant numbers did not document the retraction. The authors find that significant improvements by publishers and others are needed to ensure that retracted articles are adequately documented. I see retracted articles in journals surprisingly often.

VACCINE MISINFORMATION

DeStefano, Bodenstab, and Offit recently published a review of Principal Controversies in Vaccine Safety in the United States. They summarized the evidence on seven of the main vaccine controversies in the US. This includes MMR and autism, thimerosal and neurodevelopmental disorders, vaccine induced Guillain-Barré syndrome (GBS), vaccine induced autoimmune diseases, safety of human papillomavirus vaccine (HPV), aluminum adjuvant induced diseases, and too many vaccines given early in life. The background, allegation, and evidence for each are reviewed. In each, the authors concluded that the current available evidence did not support the allegations. But with GBS, the current calculations indicate a possible increased risk following influenza vaccine but that risk is much less than the risk of GBS after influenza infection. I would add that the authors could be clearer that vaccines never contained actual mercury, Hg, or aluminum, Al, but derivatives thimerosal and aluminum salts such as $AlOH_3$; these are different both chemically and physically. These differences are often ignored by critics. This paper should be useful to anyone in primary care.

INFORMATION SHARING

NIH and FDA have announced a new application, Cure Id, that enables physicians to share information on off-label use of drugs to treat neglected diseases without adequate treatment, especially infectious diseases. The App will also provide a treatment discussion forum. 1500 cases and 18,000 clinical trials have been preloaded. This reminds me of the BC café which has been available already for several years to serve vaccinators with the experience of global colleagues. This new app may not have much to do with vaccines but it will be immensely useful for infectious disease treatment.

ANOTHER VACCINE SUCCESS

The CDC recently reported a 50% decline in adult pneumococcal pneumonia since the introduction of PNEUMOVAX 7 in children in 2000 and PCV13 in children in 2010 and PCV13 in adults in 2014. Therefore, the CDC is no longer recommending PCV13 for all and instead recommends shared decision making for adults. MMWR 68{46}1069.

A NEW ROLE FOR WHO

WHO is actively providing emerging information about the new coronavirus COVID-19. This decision is in response to the quantity of circulating misinformation and conspiracy theories, “cures”, and then “infodemic”. This is being done in collaboration with major websites and social media.

LITERATURE

A PubMed search for Vaccine Safety yields about 20,000 entries. This is increasing by approximately 100 entries per month. I have selected a few recent articles which may be of general interest. Is anyone interested in leading a discussion or journal club on any of these or any other topic?

Dr. Fred Varricchio

1. This survey found that many patients would prefer specific details of side effects and they could decide themselves what is serious. Note that in the US, the definition of vaccine side effects is very different from the usual definition. This latter definition is defined by law and is determined by outcomes such as hospitalization. How is this done in your country?

Title: "I can be the Judge of What's Serious": A Qualitative Pilot Study of Parents' Responses to Messaging About Side Effects of the HPV Vaccine

Maternal Child Health J. 2020 Jan; *published online.* doi:10.1007/s10996-019-02856-8

Corresponding Author: Stephanie A. S. Staras (Department of Health Outcomes and Biomedical Informatics, University of Florida, Gainesville FL, USA)

Introduction: "Parents' concerns about vaccine safety and side effects likely contribute to low rates of [HPV] among adolescents... This study sought to elicit perspectives of parents and providers on the best way to communicate information on vaccine side effects."

Main findings: "Surprisingly, when parents reviewed screen shots of HPV vaccine safety and side effect messages, parents took exception to the expression "no evidence of serious side effects". Parents wanted side effects listed explicitly so they could decide for themselves which side effects were "serious". Parents also felt that the HPV vaccine did have serious side effects, and the wording undermined their trust in the vaccine messaging overall. Providers accepted the phrasing of side effects and did not express concerns that parents would object to the messaging."

2. This paper offers a way of gauging public sentiment about vaccines.

Title: Measuring Vaccine Confidence: Analysis of Data Obtained by a Media Surveillance System Used to Analyse Public Concerns About Vaccines

Lancet Infect Dis. 2013 Jul;13(7):606. doi:10.1016/S1473-3099(13)70108-7

Corresponding Author: Dr. Heidi J. Larson, PhD (Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK)

Introduction: "The intensity, spread, and effects of public opinion about vaccines are growing as new modes of communication speed up information sharing, contributing to vaccine hesitancy, refusals, and disease outbreaks. We aimed to develop a new application of existing surveillance systems to detect and characterise early signs of vaccine issues. We also aimed to develop a typology of concerns and a way to assess the priority of each concern."

Main Findings: "We analysed data from 10,380 reports (from 144 countries) obtained between May 1, 2011, and April 30, 2012. 7,171 (69%) contained positive or neutral content and 3209 (31%) contained negative content. Of the negative reports, 1,977 (24%) were associated with impacts on vaccine programmes and disease outbreaks; 1,726 (21%)

with beliefs, awareness, and perceptions; 1,371 (16%) with vaccine safety; and 1,336 (16%) with vaccine delivery programmes. We were able to disaggregate the data by country and vaccine type, and monitor evolution of events over time and location in specific regions where vaccine concerns were high."

3. This article is important because single antigen measles vaccine is not available in the US.

Title: Adverse Events after MMR or MMRV Vaccine in Infants Under Nine Months Old

Pediatr Infect Dis J. 2016 Aug;35(8):e253-7.

Corresponding Author: Dr. Emily Jane Woo, MD, MPH (Center for Biologics Evaluation and REsearch, Food and Drug Administration, Silver Spring MD, USA)

Introduction: "In the United States, measles is resurging, with more than 700 confirmed cases since January 2014. During measles outbreaks, vaccination as early as at 6 months of age is sometimes recommended for infants who are at risk for exposure."

Main Findings: "This review did not identify any major safety concerns. These findings may facilitate discussions about the risks and benefits of vaccinating infants who are potentially exposed to this life-threatening disease"

4. Article of interest discusses a novel way of delivering injectables and reducing injection site reactions. Authors find it may be particularly useful when multiple injections are needed.

Title: Evaluation of the clinical impact of repeat application of hydrogel-forming microneedle array

Drug Deliv Transl Res. 2020Feb26. doi:10.1007/s13346-020-00727-2

Corresponding Author: Dr. Ryan F. Donnelly (Queen's University School of Pharmacy, Belfast, UK)

Abstract: "Hydrogel-forming microneedle array patches (MAPs) have been proposed as viable clinical tools for patient monitoring purposes, providing an alternative to traditional methods of sample acquisition, such as venepuncture and intradermal sampling. They are also undergoing investigation in the management of non-melanoma skin cancers. In contrast to drug or vaccine delivery, when only a small number of MAP applications would be required, hydrogel MAPs utilised for sampling purposes or for tumour eradication would necessitate regular, repeat applications. Therefore, the current study was designed to address one of the key translational aspects of MAP development, namely patient safety. We demonstrate, for the first time in human volunteers, that repeat MAP application and wear does not lead to prolonged skin reactions or prolonged disruption of skin barrier function. Importantly, concentrations of specific systemic biomarkers of inflammation (C-reactive protein (CRP); tumour necrosis factor-α (TNF-α)); infection (interleukin-1β (IL-1β); allergy (immunoglobulin E (IgE)) and immunity (immunoglobulin G (IgG)) were all recorded over the course of this fixed study period. No biomarker concentrations above the normal, documented adult ranges were recorded over the course of the study, indicating that no systemic reactions had been initiated in volunteers. Building upon the results of this study, which serve to highlight the safety of our hydrogel MAP, we are actively working towards CE marking of our MAP technology as a medical device."

5. Have you ever wondered how long maternal antibodies persist in the newborn?

Title: Measles antibody levels in young infants

Pediatrics December 2019. 144(6) e20190630; doi: 10.1542/peds.2019-0630

Corresponding Author: Michelle Science

Background: "Infants are often assumed to be immune to measles through maternal antibodies transferred during pregnancy and, in many countries, receive their first measles-containing vaccine at 12 to 15 months. Immunity may wane before this time in measles-eliminated settings, placing infants at risk for measles and complications. We investigated humoral immunity to measles in infants <12 months of age in Ontario, Canada."

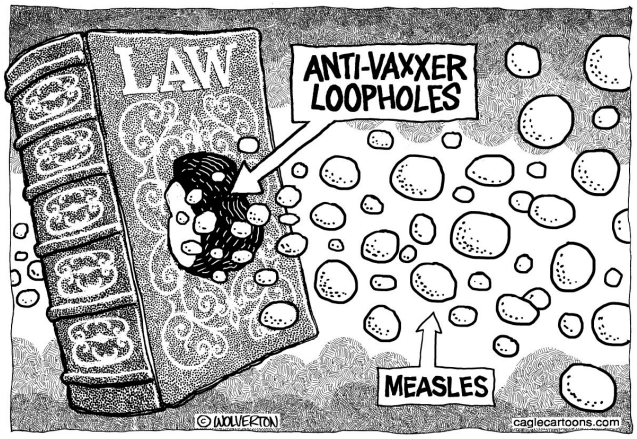
Main Findings: **"**Most infants (n=195) were susceptible to measles by 3 months of age in this elimination setting. Our findings inform important policy discussions relating to the timing of the first dose of measles-containing vaccine and infant postexposure prophylaxis recommendations."

NEW NEWS...

The AMA Morning news recently devoted an issue to some vaccine details in the US.

Vaccine laws continue to be discussed in several state legislatures. In Maine, Tougher Vaccine Rules Are Also On Super Tuesday Ballot (NPR). The law restricting philosophical and religious exemptions was forced onto a statewide vote even before it took effect. The law was upheld by a more than 2:1 vote.

You Are Unvaccinated and Got Sick. These Are Your Odds.



COVID-19 (SARS-COV-2) Update and Resources:

CEPI to fund three programmes to develop vaccines against the novel coronavirus, nCoV-2019

Shielding the Fetus from the Coronavirus

Have Coronavirus and Can't Smell? Harvard Scientists Explain Why

A Heart Attack? No, It was the Coronavirus

The Human Stories of the Coronavirus Pandemic

Contributions to the VSQ are welcomed and invited.

We would like to have a series on groups that work on vaccines, vaccine safety.
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 share your address to bc-coordinator[at]taskforce[dot]org.