Vaccine Safety Quarterly (VSQ) | Fall 2020

Brighton Collaboration 2.0

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The Brighton Collaboration Standardized Templates for Collection of Key Information for Benefit-Risk Assessment of Vaccines by Technology (BRAVATO; formerly V3SWG)

Safe and effective vaccines against SARS-CoV-2 are widely seen as the best long term solution for the COVD-19 pandemic. As of September 4, 2020, 234 COVID-19 vaccines are currently under development, 31 of which are in Phase 1 or Phase 2 human trials and eight in Phase 3. The remainder are in preclinical studies. The candidate vaccines use a wide range of both established and novel technologies. Established technologies comprise those for which successful human vaccines exist and include inactivated whole virus, live attenuated virus, viral vectored or antigenic viral proteins produced by recombinant DNA technology. Novel technologies include platforms for which no licensed human vaccines exist, including nucleic acid (RNA and DNA) vaccines. Several vaccines using these novel technologies are among the most advanced of the COVID19 vaccine candidates, already in Phase 2 or 3 trials.

Unfortunately, concerns about vaccine hesitancy of COVID19 vaccines are already emerging. Some of the hesitancy arises from concerns of whether any "shortcuts", especially in assessments of safety, might be undertaken as the typically decade(s) long vaccine development timeline is compressed to a hoped for 12-18 months or less. Another factor may be the well-known public perception of greater risk with new "exotic" or "dreaded" technologies.

The Brighton Collaboration's BRAVATO (Benefit-Risk Assessment of Vaccines by Technology), formerly the Viral Vector Vaccines Safety or V3SWG, Working Group has developed standard templates for benefit-risk assessment of vaccine technologies for the main COVID-19 platforms. The templates aim to increase the comparability and transparency of information, provide a checklist-like tool for managing potential complex risks, and increase scientific literacy and discussion among stakeholders of otherwise highly technical information.

The nucleic acid (DNA and RNA), protein, and inactivated viral vector vaccines templates have been recently published in Vaccine, and the templates for viral vector vaccines (Version 2.0), and live attenuated viral vaccines will be published in the near future.

These templates provide a detailed and standardized description of the platform or vaccine and highlight safety considerations for each platform or vaccine, culminating in a summarized risk assessment.

V3SWG's viral vaccine vector template was the first of the templates to be developed; the second version collects information on the characteristics of 1) the wild type virus from which the vector is derived; 2) the viral vector itself before incorporation of the foreign antigen; and 3) the final recombinant

viral vector vaccine studied in animals and humans, toxicology and potency, with an overall adverse effect and risk assessment.

Presentation of the completed viral vaccine vector template for the Ebola vaccine template to the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) in June 5-6, 2019 resulted in GACVS endorsing the template for use in review of other Ebola vaccines "as it offers a structured approach to evaluating safety." Accordingly, completed templates describing adenovirus 26 and modified variant Ankara (MVA) vector Ebola vaccines were discussed at the December 4-5, 2019 GAVCS meeting with similar endorsement for future use.

After presentation of the new template,s relevant to COVID19 vaccines, at its May 27-28, 2020 meeting, the GACVS recommended "any review of the safety of new vaccines be based on the appropriate Brighton Collaboration standardized templates for benefit–risk assessment of vaccines (by technology platforms) which offers a structured approach to evaluating safety,when available and approved. . GACVS advised that templates be pilot-tested in a number of scenarios and then adapted accordingly."

The templates are living documents and the latest version of the templates are available on Brighton Collaboration website. The templates are currently being utilized by the Coalition for Epidemic Preparedness Innovations (CEPI) funded vaccine developers for a wide range of pathogens via diverse platforms.

We hope that other vaccine developers will follow, especially those whose candidates will soon enter human trials with stakeholders who would benefit from clear communications of the benefit-risk information in the templates.

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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 (www.brightoncollaboration.org) will remain operational through December 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@taskforce.org, and keep an eye out for new content and features on the website as we go forward!

COVID-19

Over 47,000 citations coded COVID-19 are listed in PubMed. Many appear to be from China but from many other countries as well. The signs, symptoms, course, and sequelae of this disease are still evolving and probably will continue to do so for some time. Johns Hopkins University maintains a COVID-19 dashboard which provides a daily global update.

In terms of pathophysiology, the virus first binds ACE ll (angiotensin converting enzyme) receptors in the nasopharynx but persists longer in the lower respiratory tract. It can cause total destruction of the lung but actually affects multiple organ systems. Longer term effects include fatigue and somnolence. Frequent cardiac effects have been reported. The total number of cases and deaths continue to increase with possible recundrences in some areas. For the generalist an article on pathophysiology, transmission, diagnosis and treatment was recently published. A "new AE" COVID-19 related inflammatory multisystem disorder has been reported and is similar to Kawasaki disease. Its status is currently being discussed. One very important issue still unanswered is how long antibodies to Covid-19 will persist (Emerg Infect Dis. 2020 Nov). The answer to this also affects calculations about herd immunity (re: Gallo).

It is noteworthy that Francis Collins, NIH director, convened a meeting quickly in April 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 to date drug therapy is still focused on Remdesivir.

Of general interest is a story about how one biotech company rapidly turned significant attention and effort toward developing a Covid-19 treatment. That company, Regeneron, has a product starting a phase 3 trial.

COVID-19 vaccine

Over 200 possible vaccines are reportedly in some stage of development. Some are in clinical trials. The London School of Public Health maintains a website with details of stage of development and vaccine type. But there is also a report that some trials are progressing slower than planned because of lack of supplies and patient recruitment. There has been much discussion about how a vaccine should be efficiently and fairly distributed. It has even been suggested that it might be advantageous to distribute a vaccine with moderate efficacy on an interim basis. Also more than one vaccine may be necessary to quickly satisfy global demand. Some groundwork and planning have been done in anticipation of the availability of the vaccine.

Thinking ahead 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. At least six different platform technologies are being used in the attempt to develop this vaccine; many of which are new (See first article)

Some other thoughts on enhanced resistance to COVID 19 have resurfaced. One is that immunization against one virus may stimulate the immune enough to spill over to help protect against another virus. There is a 1960 russian study which says that polio vaccine can protect against other viruses for one month.

Remarkably 9 potential covid-19 vaccine manufacturers have signed a public pledge to maintain high standards to ensure that any vaccine they manufacture will be safe and efficacious.

There have been numerous articles in the press about people who say that they don't want to be among the first to get a vaccine when one becomes

available. Apparently this is because of a feeling that a vaccine may be rushed to market. Poor efficacy would be unfortunate because it could give individuals a false sense of confidence and undermine confidence in vaccines in general. There are also reports of individuals concocting their own "vaccines" and not only giving it to themselves but also to others!

JOURNAL CLUB

In collaboration with the International Society for Pharmacoepidemiology (ISPE) Special Interest Group (SIG) on Vaccines, the Brighton Collaboration is pleased to launch 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 Vice-Chair Cathy Panozzo, Harvard and BC member Nadja Vielot, U of No Carolina.

The inaugural journal club will be held **October 7, 2020 at 9:00am EDT**. We will discuss "Alternative observational designs to estimate the effectiveness of one dose of oral cholera vaccine in Lusaka, Zambia" by Ferreras et al.

To join the discussion, please complete this Google Form and we will include you on the mailing list.

VACCINE MISINFORMATION

An article in a business paper, Bloomberg, describes a physician who has made a personal mission to counter anti vaxxers online.

Doubters are not new of course. A recent article describes Galileo's approach but probably is not useful. Last month a headline stated that Americans still trust the CDC on coronavirus. But I was disappointed to read that actually it was only 65% approval.

Dubé outlined approaches to improving communication to the public and reviewed materials available in Canada. They made specific suggestions for improvement such as: 1) targeting an audience and establishing trust, 2) providing balanced information, risks and benefits, 3) giving facts first before myths, 4) using visual aids, and 5) testing materials first. The CDC has 1 page "tipsheets" on frequent vaccine questions and responses. These are available in bulk should physicians be encouraged to keep some in their waiting areas.

The UN has just 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 networks. Has anyone read about this already?

RISK OF SUBDELTOID BURSITIS FOLLOWING INFLUENZA VACCINATION

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The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The Institute of Medicine published a report in 2012 that concluded that there was evidence supporting a causal relationship between the injection of a vaccine and subdeltoid bursitis. Since then, the Vaccine Injury Compensation Program has received an increasing number of claims for alleged shoulder injuries. However, the incidence and risk of bursitis following vaccination was not known. The CDC conducted a study to address this question. A population-based study was done using the Vaccine Safety Datalink (VSD), which drew upon health care encounter data for more than 10 million members of 7 U.S. health care organizations. The study focused on the risk associated with influenza vaccine, because most prior case reports involved influenza vaccine, which is the most common type of vaccine given in the United States with more than 160 million doses distributed annually and a recommendation that everyone over 6 months of age receive it each year.

The VSD study examined the incidence of subdeltoid bursitis following inactivated influenza vaccine during the 2016–2017 flu season in more than 2.9 million vaccinated people. The study included everyone aged 3 years and older, because children under the age of 3 typically receive injected vaccines in the thigh rather than the arm. Manual medical record review was used to confirm the diagnosis of bursitis and determine when the symptoms began in relation to when the vaccine was given. The study used a self-controlled risk interval analysis to compare the incidence of bursitis during the 3 days following vaccination to a control period 30-60 days following vaccination. A significant incidence rate ratio of 3.24 was found based on sixteen cases in the risk interval compared to 51 cases in the control interval. The attributable risk was estimated to be 7.78 excess cases of subdeltoid bursitis per one million people vaccinated during the 3 days following vaccination. The findings support an association between vaccination and subdeltoid bursitis but suggest that vaccine associated cases are uncommon.

Previous case reports have implicated poor injection technique as the cause of bursitis or other adverse events involving the shoulder joint. Some reports have attributed shoulder injuries to injections given too high on the arm or to injections given too deep through the deltoid muscle. The VSD study relied on retrospective assessment of documentation in the medical record and could not assess the role of injection technique, though among nine case patients who attributed their bursitis to vaccination, two stated specific concerns about incorrect injection technique. It is possible that some of these events could be the result of poor injection technique and are therefore preventable. To prevent possible vaccinations errors, vaccine providers should ensure all staff members who administer vaccines receive training on proper vaccine administration.

Political Epidemiology

Trump administration buries detailed CDC advice on reopening

Trump aides undercut Fauci as he speaks up on virus concerns

So it has come to this

CDC testing guidance was published against scientists' objections

WHO

Lawrence Gostin, JD writes about the WHO the world needs. Required are adequate funding and political independence. He also suggests moving WHO headquarters to Africa.

VSQ READERS

The spring VSQ was emailed to over 800 readers. An estimate from the returned reader survey shows 30% of readers are from the US followed by Canada and India. Occupations are varied from clinical research to statistics to fund raising. All readers are invited to submit comments and articles to the VSQ.

LITERATURE

There are over 23,000 citations in PubMed coded Vaccine Safety. This is increasing by about 150 per month. I have selected a few which may be of general interest.

1. Beliefs around childhood vaccines in the United States: A systematic review? Another survey of vaccine beliefs among the public

Vaccine. 2019 Oct 23;37(45):6793-6802. doi: 10.1016/j.vaccine.2019.08.068.

Corresponding Author: Courtney Gidengil (RAND Corporation; Boston Children's Hospital, Boston, MA, USA)

Background: While childhood vaccines are safe and effective, some parents remain hesitant to vaccinate their children, which has led to outbreaks of vaccine preventable diseases. The goal of this systematic review was to identify and summarize the range of beliefs around childhood vaccines elicited using open-ended questions, which are better suited for discovering beliefs compared to closed-ended questions.

Results: Of 1727 studies identified, 71 were included, focusing largely on parents (including in general, and those who were vaccine hesitant or at risk of hesitancy). Seven themes emerged: *Adverse effects* were most prominent, followed by *mistrust*, *perceived lack of necessity*, *pro-vaccine opinions*, *skepticism about effectiveness*, *desire for autonomy*, and *morality concerns*. The most commonly described beliefs included that vaccines can cause illnesses; a child's immune system can be overwhelmed if receiving too many vaccines at once; vaccines contain harmful ingredients; younger children are more susceptible to vaccine adverse events; the purpose of vaccines is profit-making; and naturally developed immunity is better than that acquired from vaccines. Nearly a third of the studies exclusively assessed minority populations, and more than half of the studies examined beliefs only regarding HPV vaccine.

Conclusions: Few studies used open-ended questions to elicit beliefs about vaccines. Many of the studies that did so focused on the HPV vaccine. Concerns about vaccine safety were the most commonly stated beliefs about childhood vaccines, likely because studies were designed to capture barriers and challenges to vaccination.

2. Determinants of vaccine hesitancy in Switzerland: study protocol of a mixed-methods national research programme. A review of vaccine hesitancy in another country, Switzerzerland

BMJ Open. 2019 Nov 2; 9(11):e032218. doi: 10.1136/bmjopen-2019-032218.

Corresponding Author: Philip E. Tarr (University of Basel, Basel, Switzerland)

Methods and analysis: Our transdisciplinary team employs a sequential exploratory mixed-methods study design. We have established a network of more than 150 medical providers across Switzerland, including more than 40 CAM practitioners. For the qualitative component, we conduct interviews with parents, youth, and biomedical and CAM providers and observations of vaccination consultations and school vaccination information sessions. For the quantitative component, a sample of 1350 parents of young children and 722 young adults (15–26 years) and their medical providers respond to questionnaires. We measure vaccine hesitancy with the Parent Attitudes about Childhood Vaccines 15-item survey and review vaccination certificates to assess vaccination status. We administer additional questions based on findings from qualitative research, addressing communication with medical providers, vaccine information sources and perceptions of risk control vis-à-vis vaccine-preventable diseases. The questionnaires capture sociodemographics, political views, religion and spirituality, and moral foundations.

3. The MMR Vaccine and Autism. The most recent rereview of this issue.

Annu Rev Virol. 2019 Sep 29;6(1):585-600. doi: 10.1146/annurev-virology-092818-015515. Epub 2019 Apr 15.

Corresponding Author: Frank DeStefano (Centers for Disease Control and Prevention, Atlanta, GA, USA)

A report published in 1998, but subsequently retracted by the journal, suggested that measles, mumps, and rubella (MMR) vaccine causes autism. However, autism is a neurodevelopmental condition that has a strong genetic component with genesis before one year of age, when MMR vaccine is typically administered. Several epidemiologic studies have not found an association between MMR vaccination and autism, including a study that found that MMR vaccine was not associated with an increased risk of autism even among high-risk children whose older siblings had autism. Despite strong evidence of its safety, some parents are still hesitant to accept MMR vaccination of their children. Decreasing acceptance of MMR vaccination has led to outbreaks or resurgence of measles. Health-care providers have a vital role in maintaining confidence in vaccination and preventing suffering, disability, and death from measles and other vaccine-preventable diseases.

4. Vaccine safety in infants and children: A report by and for a highly trusted group, nurses.

Nursing. 2019 Dec;49(12):42-49. doi: 10.1097/01.NURSE.0000604724.58449.ad.

Corresponding Author: Paula Barbel (College at Brockport, State University of New York)

Immunization is crucial to maintaining public health. This article addresses the benefits of childhood vaccinations and educates parents on the myths surrounding possible adverse reactions.

5. Vaccine hesitancy: Not a new phenomenon, but a new threat. A review of an old phenomenon to today

J Am Assoc Nurse Pract. 2019 Nov; 31(11):624-626. doi: 10.1097/JXX.0000000000000342.

Corresponding Author: Mary Koslap-Petraco (Stony Brook University School of Nursing, NY, USA)

Vaccines have been recognized as one of the top 10 public health achievements of the 20th century. In 1998, a study on the connection between measles, mumps, rubella vaccine and autism was published by the now discredited Andrew Wakefield. That study was retracted in 2010, but the damage was already done. The purpose of this article is to review the history of vaccine hesitancy and discuss a successful paradigm for speaking with vaccine-hesitant parents. Discussion of immunizations related to public health law and religious exemptions will also be reviewed.

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

NEW NEWS...

- Don't rush to deploy COVID-19 vaccines and drugs without sufficient safety guarantees
- Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomized, first-in-human trial
- The potential danger of suboptimal antibody responses in COVID-19
- COVID-19 vaccine research must involve Black and Latinx participants
- Study raises concerns for pregnant women with the coronavirus
- Mitochondrial respiratory states and rates (Gnaiger, E., Varrichio, F., et al, 2019)

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 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@taskforce.org