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## The Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG)\*

Robert T Chen, MD MA<sup>a,1</sup>, Baevin Carbery, MPH<sup>a,b</sup>, Lisa Mac<sup>a</sup>, Louisa Chapman<sup>a</sup>, Richard C. Condit<sup>c</sup>, Jean-Louis Excler<sup>d,e</sup>, Marc Gurwith<sup>f</sup>, Michael Hendry<sup>a</sup>, Arifa S. Khan<sup>g</sup>, Najwa Khuri-Bulos<sup>h</sup>, Bettina Klug<sup>i</sup>, Jim S Robertson<sup>j,2</sup>, Stephen J. Seligman<sup>k</sup>, Rebecca Sheets<sup>l,2</sup>, and Anna-Lise Williamson<sup>m</sup> for the V3SWG<sup>3</sup>

<sup>a</sup>DHAP, NCHHSTP, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333

<sup>b</sup>Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA

<sup>c</sup>Department of Molecular Genetics and Microbiology, University of Florida College of Medicine, P.O. Box 100266, Gainesville, Florida 32610, USA

<sup>d</sup>International AIDS Vaccine Initiative, New York, NY, USA

<sup>e</sup>U.S. Military HIV Research Program (MHRP), Bethesda, MD 20817, USA

<sup>f</sup>PaxVax, San Diego, CA, 92121, USA

<sup>g</sup>Laboratory of Retroviruses, Division of Viral Products, Center for Biologics Evaluation and Research, US Food and Drug Administration, Bethesda, MD 20892, USA

<sup>h</sup>Division of Infectious Disease, Jordan University Hospital, Amman, Jordan

<sup>i</sup>Paul-Ehrlich-Institut, 63225 Langen, Germany

<sup>j</sup>National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Potters Bar, UK (retired)

<sup>k</sup>Department of Microbiology and Immunology, New York Medical College, Valhalla, NY 10595

<sup>l</sup>Division of AIDS, National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health, Bethesda, MD 20892

<sup>m</sup>Institute of Infectious Disease and Molecular Medicine, University of Cape Town and National Health Laboratory Service, Cape Town, South Africa

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The Brighton Collaboration was launched in 2000 to improve the science of vaccine safety (1) - an issue that had become increasingly controversial and prominent worldwide,

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\*The findings, opinions, conclusions, and assertions contained in this consensus document are those of the individual members of the Working Group. They do not necessarily represent the official positions of each participant's organization (e.g., government, university, or corporations) and should not be construed to represent any Agency determination or policy.

<sup>1</sup>Corresponding author: brightoncollaborationv3swg@gmail.com.

<sup>2</sup>Retired

<sup>3</sup>See Acknowledgement for other V3SWG members

particularly in countries with mature immunization programs which had nearly eliminated targeted vaccine-preventable diseases.(2–4) To provide a common vocabulary for vaccine safety researchers, the Brighton Collaboration focused its initial efforts on developing standardized case definitions for adverse events following immunizations (AEFI), including guidelines for data collection, analysis, and presentation (5). To date, over 30 AEFI case definitions have been developed by voluntary Brighton working groups, endorsed by normative bodies such as the Council of International Organizations of Medical Science (CIOMS) (6), the U.S., Food and Drug Administration (FDA) (7), and the European Medicines Agency (EMA)(8) and are freely available for public use at [www.brightoncollaboration.org](http://www.brightoncollaboration.org). These Brighton AEFI case definitions are increasingly being used and recognized as “common currency”, allowing greater ease in comparing vaccine safety studies. This was evidenced in recent international studies of intussusception after rotavirus vaccination, (9) Guillain-Barre/Fisher syndrome, (10) and narcolepsy after influenza vaccination.(11)

While vaccine safety issues are frequently most prominent in the post-licensure setting when administered to larger and heterogeneous populations, they should be viewed as a continuum with a product life cycle that begins pre-licensure(12–14). Consistent with this, each Brighton Collaboration case definition is designed for use in pre-and post-licensure setting, and are associated with guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies (15), including a template protocol (16).

Since traditional methods of vaccine development have failed for several major human pathogens (e.g., human immunodeficiency virus (HIV), tuberculosis, and malaria), new approaches emerging from the biotechnology revolution are being explored (17). Amongst these new approaches, recombinant viral vectors provide an efficient means for heterologous antigen expression in vivo and thus provide a promising platform for developing novel vaccines against diseases that have posed a challenge to vaccine development(18–26). Some veterinary viral vector vaccines have been licensed(24) but there is as yet limited clinical experience of the efficacy and safety of such vectors in humans. A 2003 World Health Organization (WHO) informal consultation on the characterization and quality aspects of vaccines based on live viral vectors (27) and the EMA’s guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines (28) identified several issues of critical importance which warrant further investigation. These include recombination with wild-type pathogenic strains and exploration of public acceptance (see items 1–7 in Table 1).

With increasing numbers of viral vectors now entering human clinical trials, there is an urgent need to establish appropriate regulatory measures to ensure their quality, safety and efficacy. This need was highlighted by recent developments such as:

1. planned expedited human trials of two Ebola vaccine candidates; one using chimp adenovirus 3 (ChAd3) and the other recombinant vesicular stomatitis virus (rVSV) viral vector(29),

2. the higher rates of HIV acquisition among participants of the STEP(30, 31) and Phambili(32) trials who had received a replication-defective Ad5 vector vaccine candidate,
3. the first HIV vaccine candidate to show (modest) protection in large human trials consisted of a recombinant canarypox virus vector vaccine (ALVAC-HIV [vCP1521]) and a recombinant glycoprotein 120 subunit vaccine(33), and
4. the development of a recombinant rhesus cytomegalovirus (CMV) vaccine vector engineered to express simian immunodeficiency virus (SIV) proteins that resulted in progressive clearance of a pathogenic SIV infection in rhesus macaques(34).

Specific to the Brighton Collaboration, improving our ability to anticipate safety issues and meaningfully assess and interpret safety data from trials of new viral vector vaccines will enhance public confidence for their safety and efficacy. With encouragement of the WHO's Initiative for Vaccine Research, the Brighton Collaboration formed the Viral Vector Vaccines Safety Working Group (V3SWG) in October 2008 to help standardize the collection, analysis and dissemination of safety data regarding viral vector vaccines in pre- and post-licensure settings. As with other Brighton Collaboration working groups, the V3SWG was formed by identifying a critical mass (N~15 from initial >300 interested individuals) of academic, government, and industry volunteers with the appropriate expertise and interest in vaccine safety and virology. Through email exchanges and monthly conference calls coordinated by a secretariat at the CDC Division of HIV/AIDS Prevention, the V3SWG has focused on two main sets of activities.

First, the V3SWG adopted the list of seven issues of critical importance needing further investigation as identified by the 2003 WHO consultation on live viral vectors (see the first seven issues listed in Table 1) and added four additional issues (see last four issues listed in Table 1). By addressing several issues simultaneously, the V3SWG hopes to develop harmonized guidelines which will enhance comparability and interpretation of data.

Second, recognizing the value of Brighton Collaboration standardized case definitions for AEFI, the V3SWG is working to develop a standardized template describing the key characteristics of a novel vaccine vector to facilitate the scientific discourse among key stakeholders and increase the transparency and comparability of information. Fortunately, the International AIDS Vaccine Initiative (IAVI) had developed an internal template tool to assess the risk/benefit of different viral vectors. This tool aimed at flagging issues that may either be showstoppers or need to be carefully addressed, helping to prioritize vector development activities. The template gathers information on the characteristics of the wild type virus from which the vector was derived; it also aids in the ascertainment of known effects of the proposed vaccine vector in animals and humans, manufacturing details, toxicology and potency, pre-clinical studies, and human use with an overall adverse effect and risk assessment. The IAVI kindly shared this tool with the V3SWG for adaptation and broader use as a standardized template for collection of key information for risk/benefit assessment on any viral vector vaccines.

In this issue of *Vaccine*, Monath et al publishes the first completed Brighton Collaboration V3SWG template on Risk/Benefit Assessment for Live Virus Vaccines Based on a Yellow

Fever Vaccine Backbone (35). The V3SWG hopes that eventually, all developers/researchers of viral vector vaccines, especially those likely to be used in humans, will complete this template and submit it to the V3SWG and Brighton Collaboration for peer review, and eventual publication in *Vaccine*. We recognize that while desirable, the information needed to complete the entire template, especially from peer reviewed scientific publications or systematic reviews, may currently be unavailable for a new candidate vector vaccine. Nevertheless, the existence of such gaps in current knowledge should not deter researchers from initiating completion of the template to the best of their ability; any gaps may provide a constructive signal for prioritizing areas of future research. We also recognize that some researchers and sponsors may wish to delay sharing some information for proprietary or intellectual property reasons. Hopefully, such a stance will evolve as the development of a viral vector vaccine candidate “matures” from evaluation in human trials and the need for information sharing and transparency grows to maximize public acceptance. Furthermore, it is likely that the pace of accumulation of new scientific knowledge during vaccine development may be more rapid than changes in clinical diagnosis relevant to AEFI case definitions. Therefore, the Brighton Collaboration V3SWG hopes to maintain these templates in a dynamic “wiki” style (i.e., online collaborative editing) with the help of each vector vaccine research “community.” We seek your assistance to identify and encourage researchers of new viral vector vaccine candidates to complete a template and join in the subsequent vector-specific wiki community in this exciting new era of vaccine development during this as well as in future decades (36).

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**Table 1**

Issues of critical importance to be investigated by Brighton Collaboration Viral Vector Vaccine Safety Working Group (V3SWG).\*

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- 1 Potential of recombination of the viral vector vaccine with wild type pathogenic strains.
    - a. Vector – circulating virus could create a more pathogenic strain.
    - b. This issue should be addressed in vitro or in animal studies.
  - 2 Implications of prior infections on the immunogenicity of vectored vaccines.
    - a. Prior infection with related viruses may reduce vaccine immunogenicity (e.g., adenoviruses, poxviruses (smallpox vaccine))
    - b. Immunogenicity of subsequent doses, especially with different gene in same vector (e.g., modified poxviruses, adenoviruses): should be addressed if relevant.
  - 3 Genetic stability of replicating *recombinant* viruses in vivo should be studied focusing on:
    - a. The sequence insert, and known areas of attenuation
    - b. Known epitopes
  - 4 *The impact of the addition of foreign genes on the pathogenicity of the viral vaccine vector when compared to the parent virus.*\*\*
  - 5 Tests for absence of reversion to virulence should be performed when an attenuated vector is used.
  - 6 The absence of replication competent virus when replication incompetent vectors are used should be demonstrated.
  - 7 Public acceptance of vectored vaccines with specific safety concerns could be an issue. A need for a forum to discuss concerns, and how best to communicate the risks and benefits of the new approach to general public was identified and WHO was requested to take a lead on it.
  - 8 Assessing vectored vaccine effects on innate immunity and on the possible induction of an immunosuppressive window or *alternatively* immune activation.
  - 9 Defining the length of time for monitoring AEFIs after receipt of vectored vaccines.
  - 10 Developing guidelines for archiving samples of vectored vaccine samples to enable potential future testing to assess inadvertent contamination by adventitious agents.
  - 11 Assessing possible secondary transmission of vectored vaccine virus.
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\* Items 1–7 identified by WHO informal consultation on characterization and quality aspect of vaccines based on live viral vectors, December 2003. (27)]; items 8–11 added by V3SWG.

\*\* originally: Potential changes of tropism may lead to know properties of replicating viruses and should be carefully evaluated.