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# Defining the interval for monitoring potential adverse events following immunization (AEFIs) after receipt of live viral vectored vaccines

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ABSTRACT

Live viral vectors that express heterologous antigens of the target pathogen are being investigated in the development of novel vaccines against serious infectious agents like HIV and Ebola. As some live recombinant vectored vaccines may be replication-competent, a key challenge is defining the length of time for monitoring potential adverse events following immunization (AEFI) in clinical trials and epidemiologic studies. This time period must be chosen with care and based on considerations of pre-clinical and clinical trials data, biological plausibility and practical feasibility. The available options include: (1) adapting from the current relevant regulatory guidelines; (2) convening a panel of experts to review the evidence from a systematic literature search to narrow down a list of likely *potential or known* AEFI and establish the optimal risk window(s); and (3) conducting "near real-time" prospective monitoring for *unknown* clustering's of AEFI in validated large linked vaccine safety databases using Rapid Cycle Analysis for pre-specified adverse events of special interest (AESI) and Treescan to identify previously unsuspected outcomes. The risk window established by any of these options could be used along with (4) establishing a registry of clinically validated pre-specified AESI to include in case-control studies. Depending on the infrastructure, human resources and databases available in different countries, the appropriate option or combination of options can be determined by regulatory agencies and investigators.


## 1. Introduction

Immunization against vaccine-preventable diseases (VPD) is a highly cost-effective public health intervention [1,2]. Traditional methods of vaccine development against several major human pathogens may be less than optimal [3]. New biotechnology approaches are being explored [4] including the development of

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recombinant viral vector vaccines using an attenuated virus to carry and introduce viral DNA into antigen-presenting cells to induce both humoral and cell-mediated immune responses [5]. "Vector" refers to the virus used as the carrier [6]. Live viral vectors that express heterologous antigens of the target pathogen in vivo are being investigated in the development of vaccines against Human Immunodeficiency Virus type 1 (HIV-1) [7], Plasmodium falciparum [8], Influenza [9], severe acute respiratory syndrome coronavirus (SARS-CoV) [10], Ebola virus [11], Hepatitis C virus [12], Respiratory Syncytial Virus [13], Mycobacterium tuberculosis [14,15]. Middle East Respiratory Syndrome (MERS) [16,17] Lassa Fever, Nipah, [17], chikungunya and Zika viruses, etc. [18] (see Table 1).

Live recombinant viral vectored vaccines include replication-defective and replication-competent viruses with the possible association of two different heterologous vectors in prime-boost regimens. Replication-defective vectors may have a natural host-restriction such as the avipox vectors [21], or they may have been attenuated either by serial passage (e.g. yellow fever virus) so that they are less virulent with decreased replication competency in humans, e.g., Modified Vaccinia Ankara [22] or by genetic engineering that limits their replication to less than a single cycle (abortive replication), e.g., in the case of most adenovirus vectors [23]. The heterologous antigen gene may be of viral, bacterial, parasitic, oncologic, or gene therapy-based. The heterologous gene may comprise sequences coding for a portion of an antigen or an entire antigen, more than one antigen or heterologous antigen genes from more than one infectious agent [24,25]. In some cases protection against the wild-type virus from which the vector is derived, may also be sought [26].

The immune response induced by a live recombinant vectored-vaccine depends on the extent and duration of the replication of the vector, the immunogenicity of the expressed heterologous antigen and the antigens of the vector itself. The virulence of live recombinant viral vaccines cannot be predicted from that of the viral vector, even when the vector is already attenuated for humans [25], which emphasizes the need for extensive safety studies during clinical development before public health use. This will be even more critical where a vector of non-human virus origin is utilized. Information on the pathogenicity of the wild-type virus for humans may be limited or absent. The potential for reversion to virulence or for recombination or reassortment with circulating wild-type viruses also must be considered [25,26]. The same viral vector may not demonstrate an identical safety profile when expressing different foreign antigens [27] (see Table 2).

As noted earlier, the list of recombinant viral vectors in pre-clinical and clinical development has expanded and thousands of subjects have been enrolled in clinical development for the control of various infectious diseases with recombinant adenovirus and poxviruses being the most advanced platforms [25]. Given the large number of candidate vaccines now in clinical studies, the World Health Organization (WHO) [28,29], the US Food & Drug Administration (FDA) [30], and the European Medicines Agency (EMA) [24] have provided various guidance documents to identify appropriate regulatory pathways, development gaps and critical data sets to support the advancement of viral vector-based vaccines to licensure.

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 regard-

**Table 1**
Some viral vector vaccine candidates in different stages of development for use in humans [9,19,20].

| Non-recombinant viruses no-longer in use in humans | Non-recombinant viruses in use in humans | Viral vectors already tested in humans | Viral vectors in preclinical development | Viruses in preclinical development |
|---|---|---|---|---|
| Vaccinia | Ad4 (inactivated; live oral) | Vaccinia | hCMV | Reassortment of Lassa and Mopeia viruses |
| MVA | Ad7 (inactivated; live oral) | MVA | rLCMV | Live attenuated Zika |
| | Measles | NYVAC | rhCMV | Live attenuated Rift Valley Fever |
| | Mumps | ALVAC | Replicating Ad5 | |
| | Rubella | Fowlpox | Ad55 | |
| | MMR | Ad3 | ChimpAdY25 | |
| | YFV 17D, 17DD, 17D204, 17D 213 | Ad5 | YFV 17D | |
| | Live attenuated VZV | Ad35 | Chimeric Zika | |
| | Influenza virus (inactivated) | Ad26 | Rabies virus | |
| | | | Measles virus | |
| | Polio viruses (oral live attenuated; injectable inactivated) | ChimpAd63 | ChAdC7 | |
| | EV71 (inactivated) | ChimpAd3 | Kunjin virus | |
| | EV71 + CAV16 (inactivated) | ChimAdOx1 | | |
| | SA 14-14-2 JE live attenuated | Chimerivax (dengue, JE) | Canine distemper virus (CDV) | |
| | | Adeno Associated Virus | Rhesus rhadinovirus | |
| | | Sendai | Newcastle Disease Virus (NDV) | |
| | | VSV | Live attenuated Chinese equine infectious anemia virus (EIAV) | |

Ad – Adenovirus.
CMV – Cytomegalovirus.
MVA – Modified Vaccinia Ankara.
LCMV – Lymphocytic choriomeningitis.
NYVAC – Highly attenuated vaccinia virus strain.
hCMV – Human cytomegalovirus.
ALVAC – Canary pox virus.
MMR – Measles, Mumps, and Rubella.
YFV – Yellow Fever virus.
VZV – Varicella zoster virus.
EV – Enterovirus.
CAV – Chicken anaemia virus.
JE – Japanese encephalitis virus.

**Table 2**
Safety issues for consideration for candidate viral vector vaccines [24].

| |
|---|
| (1) Characteristics, pathogenesis, and known adverse events of the wild-type virus, viral vector (before incorporation of the foreign antigen) and final recombinant viral vector vaccine (data from completed Viral Vector Vaccines Safety Working Group (V3SWG) templates can help to determine this) [64] |
| (2) Potential for the generation of replication-competent virus from a replication-defective viral vector (measurement of the immune response to an antigen present in replication-competent viruses but absent in replication-defective viruses might help in identifying such a situation) |
| (3) Potential for reversion of the viral vector to virulence; this might also occur during manufacture of a batch of vaccine or in vaccine recipients |
| (4) Potential for recombination or reassortment with other infectious agents that might coincidentally occur in vaccinees around the time of dosing |
| (5) Incidence of viremia |
| (6) Assessment of the extent and duration of vaccine shedding and the potential for transmission of the live vectored vaccine to contacts |
| (7) Potential for vaccination to trigger autoimmune diseases |
| (8) Potential for integration of genes derived from the vector into the host genome |
| (9) Consideration of specific adverse events that might reflect the distribution of the vector to specific body sites |
| (10) Potential for certain adverse reactions to occur only in subsets, e.g. those with a particular genetic predisposition |
| (11) Potential for increased susceptibility to infection by the agent against which protection is being sought due to high levels of immunity to the vector virus |
| (12) Potential for nucleotide mutations resulting in changes in the immunogen affecting vaccine effectiveness [65] |
| (13) Potential of the viral vector to induce tolerance as evidenced by poor vaccine efficacy in clinical trials or epidemiological studies [66] |

ing viral vector vaccines in pre- and post-licensure settings [31]. The V3SWG hopes that by improving our ability to anticipate safety issues and meaningfully assess and interpret safety data from clinical trials of new viral vectored-vaccines, this will enhance safety knowledge as well as public confidence and vaccine uptake once licensed.

One way to enhance our understanding of vectored-vaccine safety is to improve surveillance for Adverse Events Following Immunization (AEFI). Vaccine Associated Adverse Events (VAERS), sponsored by CDC and the FDA, has been in use since the 1990s (see below). Robust vaccine safety monitoring has many advantages including the discovery of potentially novel and unanticipated adverse events associated with vectored vaccines, the development and use of safer vaccines and minimization of the risk of Adverse Events (AE) after vaccination by providing specific recommendations, including contraindications and precautions for use [31–35].

As some live recombinant vectored-vaccines may integrate, one key challenge is defining the length of time for monitoring potentially related AEFI after receipt of viral vectored-vaccines. This time period must be chosen with care and based on considerations of clinical trials data and biological plausibility [36]. The follow-up time must be long enough to include (a) the plausible period of increased risk (also called "risk window" or "risk interval"), and (b) the comparison control "non-risk" time period for study designs where this period occurs post- (vs. pre-) risk window. In some studies of vaccine-associated Guillain Barré syndrome (GBS), the risk interval included days 1–42 after vaccination during which vaccine-associated GBS was considered to be biologically plausible and the control interval was days 43–84 after vaccination. The number of events of each type was tabulated each week and the number of AE in the post-vaccination window was compared with the number in the pre-vaccination window. This case-only self-controlled method (also referred to as self-controlled case series or SCCS) is commonly used in influenza vaccine safety studies to eliminate between-person biases [37]. SCCS is a preferred study design to avoid the "healthy vaccinee" effect (HVE) commonly associated with pre-risk control windows. HVE refers to the fact that if an individual has been ill, recently hospitalized, or otherwise unwell, vaccination may be deferred by the health care provider, patient or primary caregiver until the health of the individual improves. This consideration is especially true for vaccinations in early infancy. Therefore, a vaccinated individual is more likely to be in a healthy state immediately before and after their vaccination. Consequently, HVE reduces AE rates in the immediate pre- and post-vaccination periods, reducing the power to detect AE [38]. Selecting a surveillance duration that is too short or too long could cause a true increase in risk to be missed or obscured by random noise. Ideally, this duration should be based on statistical power considerations (e.g., continued until 90% power is achieved to detect the minimum absolute excess risk that is important for public health) and continued until any important risk can be ruled out. Due to the differences in background rates of specific AESI, the length of planned surveillance may differ by outcome for the same vaccine under study [39]. AESI may take time to manifest and be detected (e.g., the VSV Ebola vaccine that was found in synovial fluid causing arthritis) [11].

A long duration of monitoring is often challenging in low- and middle-income countries (LMIC) with limited health infrastructure, in countries with evolving AEFI monitoring systems with multiple priorities and even in countries with excellent infrastructure which are challenged with new diseases and new vaccines [40,41].

## 2. Options for defining the length of follow-up

Some of the available options for defining the optimal length of follow-up for use in clinical trials and epidemiological studies of new pharmaceutical products, including viral vectored-vaccine candidates, are mentioned below.

(1) Adapt from current relevant existing guidelines

The Risk Interval Working Group of the Clinical Immunization Safety Assessment Network (CISA) was formed in September 2010 due to the critical role that correct specification of risk and control intervals for AEFI play in observational studies of vaccine safety, and the relative paucity of work done to formally assess and determine biologically plausible and evidence-based risk intervals [36]. The group used febrile seizure and acute disseminated encephalomyelitis as models to provide an in-depth review of methodological issues related to the selection of risk and control intervals for consideration in future studies of immunization safety. As knowledge of the risk profile relative to the time since immunization for many AEFI is often incomplete, choosing more than one (e.g., a short and long) biologically plausible risk interval to evaluate in an active surveillance study may be appropriate.

The 2006 FDA guidance on Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events [42] currently explicitly states it does not apply to "Vaccines used to prevent infectious diseases even if you use products analogous to those used for gene therapy." Nevertheless, its guidance may provide a starting upper bound of a plausible risk interval(s), which may be adjusted downwards for a shorter interval(s) with an appropriate scientific rationale. For example, this guidance recommends a minimum 15-year follow-up, with a possibly shorter risk period(s) if

supporting evidence is available (e.g., duration of in vivo vector persistence, transgene expression, feasibility etc.).

The 2015 FDA guidance on Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy (CGT) Products [43], states that a **year or more** of follow-up is appropriate for subjects in early-phase trials.

One source of relevant guidance more suited for resource-limited settings comes from maternal immunization trials [44]. The minimum recommended follow-up period for women is 6 months post-delivery or following the early termination of pregnancy. The minimum recommended follow-up period for infants is until 1 year of age.

Guidance [44] also allows for both shorter and longer follow-up periods with adequate scientific justification. The appropriate duration of follow-up depends on the results of preclinical studies, experience with related products, knowledge of the disease process, biological characteristics of the vaccine, the vaccine-targeted disease or an AESI, including outcomes identified in previous trials, or the characteristics of the vaccine recipient (e.g., nutritional state, underlying diseases such as immune-compromising condition and other associated co-morbidity conditions), or the intention to assess early childhood development (in the case of vaccines for pregnant women) and late-onset outcomes as part of the Risk Management Plan (which may require follow-up periods of **5 years** or more). These guidelines acknowledge there are significant logistical challenges with extended follow-up periods, especially in resource-limited settings [40,44].

In general, long-term monitoring focuses on subject survival, on serious adverse events and AESI (that could include hematologic, immunologic, neurologic, or oncologic AESI). For some purposes, a telephone call to the subject, rather than a clinic visit, may be sufficient to obtain the necessary follow-up information. In addition, completion of long-term monitoring usually is not necessary prior to initiating subsequent trials or submitting a marketing application [43]. Nevertheless, long-term monitoring in LMIC utilizing modern data collection methodology and recipient tracking to detect AEFI will be needed when a new viral vector vaccine is first introduced in these LMIC countries. Otherwise, the new vaccine's large-scale use may be delayed until such data has been gathered in other countries/settings with appropriate infrastructure.

(2) Convening a panel of experts to review the evidence from a systematic literature search to narrow down a list of likely *or known* AEFI and establish the optimal risk window(s)

The Delphi technique is well suited for consensus-building and may be considered for the panel. It utilizes a series of questionnaires delivered using multiple iterations to collect data from a panel of selected subjects. It provides anonymity to respondents, a controlled feedback process, and the suitability of a variety of statistical analysis techniques to interpret the data. Subject selection, time frames for conducting and completing a study, the possibility of low response rates, and unintentionally guiding feedback from the respondent group are areas which should be considered when designing and implementing a Delphi study [45].

For new viral vectored-vaccine candidates, it would involve convening a panel of experts with an appropriate understanding of the biological mechanism of action of the new viral vectored-vaccine and which AESI it may plausibly cause and the likely onset time frame for their occurrence. Such an expert panel was recently convened and was instrumental in developing the Vaccine Safety Datalink's (VSD) white paper to prioritize studies of the safety of routine childhood immunization schedule [46]. Once the specific AESI(s) and likely risk interval(s) have been pre-specified as hypothesis, the existing pharmacovigilance and pharmacoepidemiological infrastructure designed for pre- and post-marketing can be marshaled to detect and if needed, validate these safety signals.

While this expert-based approach has been widely used historically, the list of previously unsuspected AE once a pharmaceutical product is widely used is long [47]. Unlike efficacy and effectiveness, vaccine safety cannot be measured directly. Human clinical trials typically are conducted using healthy non-pregnant volunteers and the safety assessment is focused on common short-term pre-specified local and systemic AE (e.g., pain at injection site, fever). Rare but serious adverse events associated with vaccines or drugs are often nearly impossible to detect on account of the selected enrollment and limited follow-up of subjects in pre-licensure studies and their detection requires conducting post-marketing monitoring (also called pharmacovigilance) after the introduction in the general population. The FDA also requires more diversity in the population studied because the incidence of AEFI might vary in different populations [48]. Safety of these products can only be inferred by the relative absence of AESI when the population exposed to the new pharmaceutical product of interest is sufficiently large, diverse and monitored adequately. Absolute safety, while understandably desired as a goal, is difficult to assess, let alone guarantee, especially early in the lifecycle of any new product.

(3) "Real-time" prospective monitoring for *unknown* clusters of AEFIs in settings with validated large linked vaccine safety databases

Traditionally, passive surveillance (also called spontaneous reporting) systems have served as a relatively affordable first line source of signals of previously unknown AEFI. The practice of conducting manual individual case reviews is now usually augmented by implementing computerized data mining algorithms on the entire MedDRA coded adverse event database to detect patterns of disproportionate reporting of adverse events [49]. The US FDA and EMA have mandatory requirements for passive reporting of AEFI to the Vaccine Adverse Event Reporting System (VAERS) [47] and EudraVigilance systems [50], respectively. The World Health Organization (WHO) is helping many LMICs improve their capacity to monitor AEFI [51], and these efforts could help to upgrade the capacity to monitor AEFIs over longer follow up periods (including coding AEFI for ICD (International Classification of Diseases), MedDRA (Medical Dictionary for Regulatory Activities) etc. beyond the short follow-up periods currently used.

To help overcome the many methodological limitations of passive surveillance for AEFI (e.g., under-reporting, biased reporting, lack of control groups) [52], several high-income countries have developed active surveillance systems for AEFI for analyses of the association between a vaccine and one or more pre-specified adverse health outcomes. For example, the CDC created the Vaccine Safety Datalink [53] (VSD) project in 1990 in collaboration with several managed care organizations. The VSD uses a distributed data model and de-identified International Classification of Diseases (ICD) coded data downloaded from the individual's electronic health record to track the use of health services by the members of each participating site. This includes information on vaccinations (e.g., vaccine type, date of vaccination, and other vaccinations given on the same day) and the specific medical illnesses that have been diagnosed at doctors' offices, urgent care visits, emergency department visits, and hospital stays. AEFI need to be coded accurately to be able to be found in the database. The US FDA oversees a complementary active safety surveillance system for vaccines called the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program [54]. This consists mostly of insurance claims. The program is attempting to move to healthcare records and this brings with it new challenges.

Traditionally, the VSD and the PRISM systems conduct rigorous vaccine safety studies (e.g., comparing rates of AEFI within risk intervals to rates in control intervals) to test the hypothesized questions or concerns raised from the medical literature and reports to the VAERS. Such VSD studies usually take several years from inception to completion, however. VSD and PRISM studies, while population-based and rigorously conducted, have generally not addressed identification of previously unsuspected possible adverse reactions [55].

The Rapid Cycle Analysis (RCA) method of the VSD was created to allow more timely (e.g., weekly) analysis of *pre-specified* AESI with *pre-specified* risk intervals so the public can be informed quickly of possible risks of newly licensed vaccines or new immunization schedules [56]. The RCA uses dynamic data files, aggregation of data, and sequential analysis methods (a new signal detection method that supports continuous or time-period analysis of data as they are collected, adjusting for the multiple statistical testing). PRISM now is developing RCA capabilities. There are also reliable registries in countries like Denmark and Sweden that can do such studies [57].

Excitingly, prospectively scanning for *unknown* clusters of new AESI in both clinical trial participants, and if licensed, in vaccines in routine use in the general population has become a reality. In the era of "large data", the dream has been to develop methods that allow for ongoing scanning of administrative health records of pharmaceutical product exposures and medical outcomes for new safety signals, especially those not previously specified. Given the large number of statistical tests done, adjustments for multiple testing are needed to minimize the number of false positive signals that would otherwise waste valuable time and resources needed for assessment of true signals. This hope is coming closer to fruition with the development of the just described RCA for *pre-specified* AESI [58,59] and TreeScan [60] (https://www.treescan.org/) for *previously unspecified* outcomes.

TreeScan is a novel scan statistical method by which the surveillance can be conducted with a minimum of prior assumptions about the group of vaccines that increase risk, and which adjusts for the multiple testing inherent in the many potential combinations [61]. TreeScan is free data mining software that implements the tree-based scan statistic, a data mining method that simultaneously looks for excess risk in any of a large number of individual cells in a database as well as in groups of closely related cells, adjusting for the multiple testing inherent in the large number of overlapping groups evaluated. It has been developed for disease surveillance. For pharmacovigilance, it can be used to simultaneously evaluate thousands of potential adverse events and groups of adverse events, to determine if any one of them occur with higher probability among people exposed to a particular vaccine. For a particular disease outcome (e.g. kidney failure), it can be used to simultaneously evaluate if it occurs with increased risk among people exposed any of hundreds of pharmaceutical drugs or vaccines, or groups of related drugs or vaccines (https://www.treescan.org/). The TreeScan method allows a wide range of unsuspected but potentially adverse reactions to be simultaneously evaluated and otherwise unknown adverse reactions may be found. The main disadvantage is that it is not possible to adjust for all possible confounders. Indeed, no conclusion about causality should be based on TreeScan analyses alone. In effect, the TreeScan method serves as a tool for identifying AE that may merit a further careful pharmaco-epidemiologic investigation [55]. Treescan is only beginning to be used more widely, so more time is needed to assess its effectiveness (e.g., AESI with insidious onset have traditionally been challenging to study in traditional large-linked databases using methods requiring a prior definition of risk intervals). The use of Treescan will also likely to be limited to settings with high-quality administrative health (including immunization) records initially. For LMICs, this requirement may be more likely to be met in some urban centers and INDEPTH Network sites.

The risk-interval established by one or more of the above-mentioned methods can be used with the following option.

(4) AESI registry and case-control studies

In the cancer field, specific cancer disease registries have been very effective research tools [62]. Case-control studies are particularly suitable for the study of relatively rare diseases with a long induction period, such as cancer and possible AESI. Since cases in a case-control are by definition subjects who have already developed the condition of interest, there is no need to wait for time to elapse. A similar approach can be taken for safety monitoring of viral vector vaccine candidates with the establishment of a registry of cases identified with clinically valid pre-specified AESI and matched controls found from the hospital or neighborhood to compare for vaccine exposure history. These studies can be multinational under a similar protocol. Given the rarity of these AESI, this is likely feasible only with post-marketing surveillance after substantial vaccine use has occurred. For settings where high-quality administrative health records are unlikely to be a reality in near future, this may be one possible alternative.

## 3. Conclusion

Live viral vectors that express heterologous antigens of the target pathogen in vivo are being investigated in the development of vaccines for numerous infectious diseases, making use of a variety of viral vectors. Live viral vectored vaccines may be based on replication-defective as well as replication-competent viruses. As some live recombinant vectored vaccine may replicate, one key challenge is defining the length of time for monitoring AEFI after administration of vectored vaccines in clinical trials and epidemiological studies. This time period must be chosen with care and based on considerations of clinical trial data and biological plausibility. A long duration of monitoring is often challenging in countries with poor health infrastructure, in countries with evolving AEFI monitoring systems with multiple priorities and even in countries with excellent infrastructure which are challenged with new diseases and new vaccines [36,40]. Some of the available options for defining the length of follow-up to be used in studies of new viral vector vaccine candidates include adapting from current relevant regulatory guidelines; convening a panel of experts to review the evidence from a systematic literature search to narrow down a list of likely *or known* AEFI and optimal biologically plausible risk window(s); conducting "near-real-time" prospective monitoring for *unknown* clustering's of AEFI in validated large linked vaccine safety databases (e.g., Vaccine Safety Datalink (VSD), PRISM, etc.). This includes Rapid Cycle Analysis (RCA) for pre-specified AESI and TreeScan for previously unsuspected outcomes. The risk interval established by one of the above-mentioned methods can be used along with establishing a registry of cases identified with clinically validated pre-specified AESI to include in case-control studies. The available infrastructure, human and financial resources, coded databases in countries and regulatory guidelines will determine which (one or a combination) of these methods would be practically feasible. These options might be broadly applicable to the duration of surveillance for other new pharmaceutical products. The risk intervals selected for clinical trials or epidemiologic studies may not be of the appropriate length to rule out associations in individual cases. Since our knowledge of the pathophysiology of many AEFI is incomplete; a longer risk interval may be required when evaluating an AEFI in an individual. Rare individuals may have genetic immune defects that result in

increased susceptibility to vaccine viruses. Mortality rates in vaccine recipients with such defects may be high. However, because of their rarity, they are likely to be discovered only in post-marketing analyses [63].

## 4. Disclaimer

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 any participant's organization (e.g., government, university, or corporations) and should not be construed to represent any Agency determination or policy.

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## Conflict of interest

Dr Marc Gurwith is employed by PaxVax, Inc which markets and develops vaccines, including developing an adenovirus vector vaccine. He also consults for several other biotech companies, but none develop vector vaccines currently.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.08.085.

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