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Progressive vaccinia as an adverse event following exposure to vaccinia virus: Case definition and guidelines of data collection, analysis, and presentation of immunization safety data☆

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1. Preamble

1.1. Need for developing case definitions and guidelines for adverse events following exposure to vaccinia virus

Following a declaration by The World Health Assembly in 1980 on the worldwide eradication of smallpox [1], comprehensive smallpox vaccination programs around the world were stopped. Today, >50% of the world's population is potentially unprotected against smallpox disease [2]. Recent warnings about the possible threat of using smallpox virus as a biologic weapon [3,4] prompted a resurgence of public health vaccination programs against smallpox.

In this context, and in the broader context of a need for data comparability, as discussed in the overview paper in this volume, establishing criteria for assessing adverse events following smallpox (vaccinia) vaccination is important for clinicians administering the smallpox vaccine and appropriately treating patients with adverse events following immunization (AEFI), and also for scientists collecting, analyzing, and communicating data on AEFI. Understanding the normal changes and progression of a successful vaccine take is crucial for early recognition of complications. Frey et al. [5,6] completed two double-blind studies, using differ-

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ent dilutions of smallpox vaccine in previously unimmunized adults, and [6] noted the following descriptions about the vaccination sites (p. 1266):

"Success was defined by the presence of a primary vesicle at the inoculation site seven to nine days after scarification. Other signs and symptoms of the replication of vaccinia virus include edema, tenderness, and erythema at the site of vaccination and regional lymphadenopathy. Subsequently, the vesicle evolves into a small ulcer over which a scab forms [2nd week post vaccination], ultimately leaving a small scar [3rd week post vaccination]".

Successful vaccination correlates with the laboratory demonstration of the development of a cytotoxic T-cell response, lymphocyte proliferation, neutralizing antibodies, and vaccinia virus-specific interferon-γ production. This combination of clinical and laboratory response to smallpox vaccination provides long-term, and perhaps life-long immunity [7].

This paper lists, in Sections 2 and 3, respectively, the case definition and guidelines for data collection, analysis, and presentation that the Brighton Collaboration *Vaccinia Virus Adverse Events Working Group* has developed for the standardized collection and assessment of progressive vaccinia (PV) following exposure to vaccinia virus, with applicability in study settings with different availability of resources and access to health care. Widespread use of this definition with its guidelines will enable data comparability and lead to a better understanding of the adverse event.

1.2. Methods for the development of the case definition and guidelines for PV following exposure to vaccinia virus

Following the process described in the overview paper in this volume [8], a Brighton Collaboration *Vaccinia Virus Vaccine Adverse Events Working Group* was formed in January 2003 with 32 members. Members volunteered for at least one of five different subgroups for one adverse event following exposure to vaccinia virus The PV subgroup included 10 members with a clinical or public health background. The member composition and results of the web-based survey completed by the reference group (discussed in the overview paper in this volume) with subsequent discussions in the working group can be viewed at: http://www.brightoncollaboration.org/internet/en/index/working_groups.html.

To guide decision-making for the case definition and guidelines, a literature search was performed by the coordinators of the five subgroups, with substantial input from the respective team leads and additional working group participants with focus for this document on progressive or persistent vaccinia following smallpox vaccination, using as search terms progressive vaccinia, vaccinia necrosum, vaccinia gangrenosum, smallpox vaccination, and vaccinia within Medline and PubMed databases from 1966 to 2002. Additionally, multiple general medical, pediatric and infectious disease text books were searched as were case definitions from the Centers for Disease Control and Prevention (CDC) (http://www.bt.cdc.gov/agent/smallpox/vaccination/clinicians.asp#ae) [9], the Advisory Committee on Immunization Practices [10], and reviews [11–14] and references employed to develop these working definitions. References predating 1966 identified by working group participants were also included. A decision was made to limit the articles to those in the English language when few foreign publications were found. We did not initiate additional literature searches through our usual contact at the Cochrane Collaboration, because it was felt that the extensive search conducted by CDC and by this working group, in conjunction with the substantial input of scientists who generated much of the data from the 1960s and 1970s, was sufficiently comprehensive for our task. Articles describing medical conditions of immunologic impairment as a pre-existing condition for the potential development of PV were also reviewed. All articles were reviewed in detail to identify information on demographics of the vaccinee, previous vaccination status, a clinical description of PV including the time course post immunization, and immunologic impairment. Because of limitations of published literature addressing vaccinia virus AEFI case definitions and guidelines, and because the more recent smallpox vaccination experience did not result in a case of PV for further study, this working group relied particularly heavily on consultations with experts from previous vaccination programs for selected criteria during the development of the document and for an overall review of the final draft as well as on expert immunologists for the identification of current immunocompromising conditions.

1.3. Rationale for selected decisions about the case definition for PV following exposure to vaccinia virus

PV is a rare, albeit frequently fatal adverse event following vaccination with vaccinia virus that can occur in patients with an underlying cell-mediated immunodeficiency. During the 1960s vaccination program in the United States, the incidence of progressive vaccinia ranged between 0.7 and 3.0/million vaccinees [15,16]. The degree and kind of immunodeficiency seem to determine the likelihood of developing PV and the severity of the disease [17].

PV should be suspected when there is no evidence of onset of normal resolution of the lesion at the vaccination site within 14 days. The time line of 14 days is a somewhat arbitrary, but conservative estimate given the severity of this adverse event. The 'reoccurrence' of a seemingly healed lesion with subsequent failure to heal [17] should also raise suspicion. In PV, the vaccination site fails to heal and/or continues to progress with evidence of central necrosis, and formation of thick, dark eschars. There is little or no