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Review

The effects of post-exposure smallpox vaccination on clinical disease presentation: Addressing the data gaps between historical epidemiology and modern surrogate model data

M. Shannon Keckler*, Mary G. Reynolds, Inger K. Damon, Kevin L. Karem

Centers for Disease Control and Prevention, Division of High-Consequence Pathogens and Pathology, Poxvirus and Rabies Branch, United States

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ABSTRACT

Decades after public health interventions – including pre- and post-exposure vaccination – were used to eradicate smallpox, zoonotic orthopoxvirus outbreaks and the potential threat of a release of variola virus remain public health concerns. Routine prophylactic smallpox vaccination of the public ceased worldwide in 1980, and the adverse event rate associated with the currently licensed live vaccinia virus vaccine makes reinstatement of policies recommending routine pre-exposure vaccination unlikely in the absence of an orthopoxvirus outbreak. Consequently, licensing of safer vaccines and therapeutics that can be used post-orthopoxvirus exposure is necessary to protect the global population from these threats. Variola virus is a solely human pathogen that does not naturally infect any other known animal species. Therefore, the use of surrogate viruses in animal models of orthopoxvirus infection is important for the development of novel vaccines and therapeutics. Major complications involved with the use of surrogate models include both the absence of a model that accurately mimics all aspects of human smallpox disease and a lack of reproducibility across model species. These complications limit our ability to model post-exposure vaccination with newer vaccines for application to human orthopoxvirus outbreaks. This review seeks to (1) summarize conclusions about the efficacy of post-exposure smallpox vaccination from historic epidemiological reports and modern animal studies; (2) identify data gaps in these studies; and (3) summarize the clinical features of orthopoxvirus-associated infections in various animal models to identify those models that are most useful for post-exposure vaccination studies. The ultimate purpose of this review is to provide observations and comments regarding available model systems and data gaps for use in improving post-exposure medical countermeasures against orthopoxviruses.

Contents

* Corresponding author at: Centers for Disease Control and Prevention, Division of High-Consequence Pathogens and Pathology, Poxvirus and Rabies Branch, 1600 Clifton Road, Mailstop G-06, Atlanta, GA 30333, United States. Tel.: +1 404 639 4179; fax: +1 404 639 1061.
E-mail addresses: hbq0@cdc.gov, shaoK@aol.com (M.S. Keckler).

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1. Introduction

1.1. Overview

This review has three major goals: (1) to summarize conclusions about the efficacy of post-exposure smallpox vaccination against clinical disease presentation from historic epidemiological reports and modern animal studies; (2) to identify data gaps in these studies; and (3) to summarize the clinical features of orthopoxvirus-associated infections in various animal models in order to identify those models that are most useful for post-exposure vaccination studies.

1.2. The origins of modern smallpox vaccines

Smallpox vaccination using a heterologous species of orthopoxvirus (OPXV) became common practice after Edward Jenner's famous experiment in which he inoculated a young James Phipps with material from a cowpox (CPXV) lesion in 1796 [1]. Early reports on the effectiveness of pre-exposure vaccination were confirmed by well-documented studies performed throughout the 19th century which demonstrated significantly lower rates of smallpox mortality in geographic areas with mandatory vaccination as opposed to areas where vaccination was not required [2].

1.3. The role of vaccination in the eradication of smallpox

One major contribution to the eradication of smallpox was the availability of an effective live vaccinia virus (VACV) vaccine. Vaccination was utilized pre-exposure to prevent smallpox infection and post-exposure during smallpox outbreaks to vaccinate potentially exposed contacts of infected patients. This methodology coupled with the strict isolation of patients was successful in protecting those contacts from severe disease and producing a "ring" of protection that halted disease transmission. Other factors, including the lack of a reservoir for variola virus (VARV), the development of a heat-stable vaccine, the introduction of the bifurcated needle, and a disease course which allowed time for post-exposure vaccination to elicit a protective immune response, all contributed to the development and implementation of the smallpox eradication effort [3]. Because of widespread pre-exposure vaccination, serious adverse events (SAEs) of smallpox vaccination were well known by the early 20th century but the more significant threat of endemic smallpox ensured that mass vaccination campaigns remained an important defense against outbreaks [4,5]. As eradication efforts progressed, it became apparent that eradication goals could not be met until surveillance systems, systematic investigation of outbreaks, and post-exposure isolation and vaccination were all successfully implemented [6,7]. As cases of smallpox declined, the relative risk of SAEs associated with 1st generation vaccines (vaccines utilizing live VACV propagated on livestock) rose, which led to the recommendation that mandatory vaccination be halted. This was done in the United States in 1971 and worldwide by 1980, when smallpox was officially declared eradicated by the World Health Organization (WHO) [8]. The efficacy of pre-exposure vaccination using these 1st generation vaccines in preventing smallpox disease was well documented during the eradication era. However, post-exposure vaccination with 1st generation vaccines, while generally believed to be at least partially protective, remains less defined, which makes the evaluation of the efficacy of newer and future vaccines more complicated.

1.4. Post-exposure vaccination as a medical countermeasure

The cessation of mandatory prophylactic vaccination has resulted in over half of the global population being potentially naïve to OPXV threats. Despite decades of continuous research to increase vaccine safety without a loss in efficacy, and the creation of 2nd generation vaccines (live VACV propagated in cell lines), 3rd generation vaccines (attenuated VACV) [9] and subunit vaccines [10,11]; only one vaccine (Acambis 2000) has been licensed for use at this time [12]. However, the use of Acambis 2000 continues to be limited due to its adverse event profile [13]. Recommendations to vaccinate U.S. health care workers and laboratorians have previously met with low compliance rates, largely due to the known risk of SAE's following vaccination [14]. In addition, a sizable proportion of the global population is contraindicated for vaccination with Acambis 2000 due to various health conditions [15]. The development of medical countermeasures and safer vaccines that are efficacious against OPXV is an ongoing effort – one which requires an understanding of 1st, 2nd, 3rd and subunit vaccine efficacy in both pre- and post-exposure scenarios [11].

1.5. Assessment of the threat of OPXV-related diseases

Medical countermeasures to OPXVs are important because smallpox re-emergence through a release of VARV would be a high-consequence event (although the risk of this happening is perceived to be low), and because emerging and re-emerging zoonotic OPXV-associated diseases continue to be a public health issue. The WHO Commission to Certify Smallpox Eradication instituted an international surveillance program for smallpox-like diseases in 1971 [16], which ultimately resulted in an increased awareness of human monkeypox virus (MPXV) infection [17]. Today, MPXV infections are on the rise in the Democratic Republic of the Congo (DRC) [18], and outbreaks in Sudan and the United States indicate the potential for MPXV to spread [19]. Other OPXV infection outbreaks are routinely observed and include VACV in Brazil [20], CPXV in Europe [21], and buffalopox in India [22]. Current research also indicates that OPXV in wildlife reservoirs is more prevalent than previously thought [23–25]. Lastly, long-held concerns regarding the threat of smallpox as a weapon of bioterrorism increased after the events of September 11, 2001 and the subsequent anthrax releases [26]. Combined, these conditions make the development of medical countermeasures against OPXV-associated disease an ongoing and current research effort.

1.6. Future vaccine research

During the global eradication of smallpox, a wealth of epidemiologic data was collected. These data have subsequently informed public health practices regarding response strategies to outbreaks of OPXV-associated diseases. However, in the absence of smallpox disease, evaluating the efficacy of newer medical countermeasures – to include 2nd and 3rd generation as well as subunit