Vaccine 29S (2011) D60–D64

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Whither monkeypox vaccination

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ARTICLE INFO

Article history:
Received 30 April 2011
Received in revised form 26 August 2011
Accepted 1 September 2011
Available online 19 December 2011

Keywords:
Orthopoxvirus
Vaccine
Biodefense
Smallpox
Variola

ABSTRACT

Monkeypox (MPX) is a virulent orthopoxvirus that is endemic in some regions of Central Africa. MPX incidence has been rising since the cessation of routine smallpox immunization. While it causes significant disease, there is limited person-to-person spread, the incidence is still relatively low, and cases are generally restricted to remote areas that are difficult to access. Therefore, initiating vaccine trials or implementing vaccination programs would be challenging. This paper considers the factors that may influence future decisions on whether MPX vaccination should be pursued.

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1. Introduction

The eradication of smallpox was one of the greatest achievements in the history of public health. One of the tragic ironies of this success is the emergence of monkeypox (MPX), a zoonotic orthopoxvirus that can produce a smallpox-like illness in humans with significant morbidity and mortality. MPX has presumably circulated in central Africa for millennia, but was only recognized as a distinct human disease in 1970 when smallpox elimination from the Democratic Republic of the Congo (DRC, formerly Zaire) revealed the sporadic occurrence of a smallpox-like illness among rural villagers living in close proximity to the rain forest [1].

The discovery of human MPX raised the concern that the disease might evolve to occupy the niche being vacated by smallpox [2]. After smallpox was officially declared eradicated from the planet in 1980, epidemiologic and ecologic studies were conducted in DRC to assess the risk of MPX emergence [3,4]. These studies suggested that the majority of cases were acquired through direct exposure to wild animals (particularly certain rodent and squirrel species) that were commonly found in agricultural areas adjacent to rain forest villages, but the virus itself was not sufficiently transmissible from person-to-person to spread and become self-sustaining [5–7]. For these reasons, even though smallpox (vaccinia) vaccination provided good protection against MPX, public health authorities including the World Health Organization (WHO) decided that the risks were not sufficient to warrant continued immunization.

Thirty years later, the incidence of human MPX in the same region appears to have markedly increased [8]. In addition to diminished vaccine-induced orthopoxvirus immunity, there have been profound social and demographic changes that have increased human MPX exposures and the likelihood of severe disease. Recurrent civil war and subsequent economic decline have forced rural residents to flee deep into the rain forests for extended periods of time, disrupted traditional village life and increased dependence on hunting for sustenance, thus increasing exposure to animal reservoirs of MPX. Additionally, extensive malnutrition and the high burden of traditional and emerging infectious diseases including human immunodeficiency virus (HIV) have made the population more vulnerable. Although orthopoxviruses are relatively genetically stable MPX has diverged into two clades with different levels of virulence [9,10]. As incidence rises, each new MPX infection provides an opportunity for viral evolution or adaptation that may result in a more virulent or contagious variant capable of sustained person-to-person transmission. These new circumstances merit a re-evaluation of the need for immunizing against MPX.

The second great irony is that the eradication of smallpox, the cessation of routine poxvirus immunization, and the maintenance of variola virus in archival storage has created the potential for an intentional release and the use of variola or modified variola virus as a bioweapon. The perception of this threat has driven a significant research enterprise reviving the study of poxvirus biology and the development of new vaccines and

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0264-410X/$ – see front matter. Published by Elsevier Ltd.
doi:10.1016/j.vaccine.2011.09.004

treatment options. This effort has produced candidate vaccines that are safer than live vaccinia virus vaccination whose side effects were considered acceptable when compared to the risks associated with smallpox infection. However, in an era where the threat of smallpox is not imminent and there are conditions such as AIDS, tissue transplantation, and therapies for cancer and autoimmunity that cause immunodeficiency, the adverse events associated with live vaccinia are no longer considered acceptable for the general population. New candidate vaccines have been evaluated in humans for immunogenicity, but since smallpox is eradicated, all efficacy testing has been conducted in animal models. Therefore, none of the products recently developed for the prevention and treatment of variola virus infection have been field-tested in humans, and have been manufactured and deposited into the biodefense stockpile based on animal studies and the presumption they will work in humans in the event of a crisis.

In this short commentary we will address two questions. First, we consider a test-of-concept research question: What are the risks and benefits of conducting field trials of candidate poxvirus vaccines in the Congo River basin to determine their efficacy against MPX infection? Second, we will address the public health question: Does the risk of human MPX infection warrant re-instituting orthopoxvirus vaccination in at-risk populations? These two questions have different constituencies and stakeholders, but there are a number of shared interests where incentives may be aligned. We will confine our analysis primarily to conditions that exist in the Sankuru District of the Democratic Republic of Congo (DRC) where we have the most experience and data, but will attempt to make the considerations generalizable when possible. The answers to these questions will change over time, and there are many constituencies that will need to reach consensus on the answers at a given point in time. Therefore, our primary goal in this commentary is not to provide answers for these questions, but to develop an analytical framework in which to make these important public health decisions in the future.

2. Current understanding of the epidemiology of MPX infection in DRC

A recent analysis of health zones with surveillance efforts, demographics and ecology comparable to those surveyed in the 1980s has shown that the two-year cumulative incidence of MPX in the DRC Sankuru District has increased from 0.48 to 11.25 per 10,000 population [8]. MPX infections were most common in males between the ages of 5–14 and individuals who live in densely forested regions, and risk of human MPX was inversely associated with previous smallpox vaccination. In individuals who were born before the cessation of official vaccination campaigns in 1980, vaccinated persons had a 5.21-fold lower risk of MPX compared with unvaccinated persons indicating that protective efficacy of >80% was achieved for >30 years [8]. Estimates of case fatality and person-to-person transmission have not been documented since the 1980s due to the difficulty of repeated visits to remote locations where cases most commonly occur, however previous studies and anecdotal reports have suggested that fatality rates fall between 1 and 10% [11,12] and that sustained chains of human-to-human transmission occur, but at a significantly lower rate than zoonotic infections [6,13,14]. Given the declining immunity and increased opportunities for exposure and spread, it seems reasonable to assume that the incidence of human MPX will continue to rise in regions where populations are in close contact with host species that harbor MPX.

3. Public health importance of MPX

The emergence of human MPX has serious public health consequences for populations in the DRC but is also a global health concern. The 2003 MPX outbreak in the U.S. demonstrated that the virus can easily spread to new animal reservoirs outside central Africa. In this case, American prairie dogs were infected by rodents imported from Ghana and served as amplification vectors, ultimately transmitting disease to humans [15]. American ground squirrels are also highly susceptible to the virus, suggesting that the host range of New World species may be large [16]. If MPX were to become established in a wildlife reservoir outside Africa, the public health consequences may be impossible to reverse. The possibility that rising incidence may reflect increased human-to-human transmission raises concerns because of the possibility for geographic spread by travelers and sustained transmission in urban areas. Increased prevalence in humans, particularly immunocompromised hosts, may also provide more opportunity for MPX virus to acquire mutations that increase its fitness in human hosts, possibly leading to increased transmissibility and virulence.

4. Vaccine candidates to consider for MPX

There are a variety of orthopoxvirus vaccine approaches that have been advanced [17,18]. Live vaccinia vaccines (e.g. Dryvax®, ACAM2000) have proven efficacy in the field and could potentially be implemented without additional Phase III testing. However, even though the risks are well documented and may be acceptable in the setting of an outbreak, currently available products are not formulated in exactly the same way as the original product and may need additional safety and stability testing. The live attenuated LC16m8 and replication-defective vaccinia (MVA, NYVAC) have large safety databases, and have been shown to protect nonhuman primates (NHP) from MPX challenge. Regulatory authorities may require additional efficacy testing in the field for these platforms to be used on a widespread basis, and additional work on formulations may be needed to improve their stability for areas with an uncertain cold chain. LC16m8 may receive additional scrutiny because it is replication competent and there has been concern about its use in an area that may be endemic for HIV. However, recent studies including the national Demographics and Health Survey (DHS) conducted throughout the DRC in 2007 indicate that national HIV seroprevalence is extremely low (1.3%), particularly in rural regions where it has been estimated to be 0.8% which may lessen those concerns [19]. A number of novel protein or gene-based subunit approaches, including DNA, replication-competent and replication-defective vectors are being developed and some have shown efficacy against MPX in NHP. These products will all face a relatively long clinical development process including an assessment of durability of protection and will require a full safety evaluation and formulation considerations to optimize stability.

5. Feasibility of clinical trials to assess MPX vaccine safety, immunogenicity, and efficacy

Clinical trials would be needed to assess whether a product could be used in vaccination campaigns. Clinical trials require regulatory, clinical, and laboratory infrastructure. While the biomedical infrastructure of DRC has suffered over the last 2 decades, there is a National Institutional Review Board administered through the Kinshasa School of Public Health to provide ethical and volunteer safety oversight for clinical studies. The Ministries of Health and Science and Technology have mechanisms in place to approve the use of investigational products and permits for importing and exporting biologicals including clinical samples. However, there would have