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Whither Monkeypox Vaccination

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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.

Keywords

Orthopoxvirus; vaccine; biodefense; smallpox; variola

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 forest¹.

The discovery of human MPX raised the concern that the disease might evolve to occupy the niche being vacated by smallpox². 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 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

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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 increased⁸. 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 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.

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 population⁸. 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 protective efficacy of >80% was achieved for >30 years⁸. 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 – 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.

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 humans¹⁵. American ground squirrels are also highly susceptible to the virus, suggesting that the host range of New World species may be large¹⁶. 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.

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 concerns¹⁹. 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.

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 to be reliance on expertise and judgment from outside consultants and regulatory authorities from more developed countries.

There have been many natural history and epidemiology studies performed in DRC, and Congolese investigators have distinguished themselves particularly in the area of HIV/AIDS and filovirus research. The body of work produced by Projet SIDA in the 1980s was a singular contribution to the clinical understanding of AIDS. However, there have been few interventional studies performed; these have greater requirements for maintenance of clinical records and safety monitoring, and require significantly more resources and staff to accomplish. Establishing systems and training to assure Good Clinical Practice (GCP) would require investment prior to initiating clinical trials, but is achievable.

Although T cell-mediated immunity is known to be important for clearing poxvirus infections, protection is strongly associated with antibody responses. This is noted because the complexity and cost of a Phase I vaccine trial is significantly higher if cryopreservation of peripheral blood mononuclear cells (PBMCs) is required. For Phase I testing of candidate poxvirus vaccines, serum collection for vaccine-induced antibody would be sufficient. Phase I trials on many of the new candidate vaccines have been performed in the countries where the products were developed and manufactured. Additional Phase I testing should also be performed in countries where advanced testing is planned. The laboratory infrastructure for performing the necessary clinical safety testing is available in Kinshasa associated with the national blood bank and Mama Yemo hospital. The equipment needed for isolation and storage of serum is also available in Kinshasa, and the DRC National Institute for Biomedical Research (INRB) has successfully performed PBMC cryopreservation on field samples in other studies.

Advancing from Phase I safety and immunogenicity testing to a Phase IIb or Phase III efficacy trial would add a new level of complexity not only because of the size, but because the study location would shift from Kinshasa to the Sankuru District in the central part of DRC where there are few health care facilities and few roads making access difficult and creating logistical challenges for managing the delivery of biological products and clinical samples. Performance of epidemiological studies required an elaborate system of vehicles, motorcycles, bicycles, and foot travel to access populations and transport diagnostic samples. Even with an annual incidence approaching 0.2% (in 5–19 year old children), a placebo-controlled efficacy trial with one year of follow-up would require about 20,000

subjects to detect a vaccine efficacy of 80% with 80% power. Fewer subjects would be needed if the follow-up period could be extended, provided immunity was expected to be maintained.

Benefits of vaccine clinical trials in areas endemic for MPX

Performing clinical trials in the DRC would have a number of benefits for distinct constituencies. First, the people of the Congo River Basin who are primarily affected by the disease would benefit. Clinical studies would call attention to the problem of MPX, improve general knowledge about MPX prevention, and potentially improve knowledge about other health conditions by strengthening the public health infrastructure. There would also be intangible benefits that accompany clinical trial activities including stimulation of local economies. Secondly, Congolese people in general and the Congolese health system would benefit because an interventional vaccine trial would require investment in the regulatory infrastructure. In addition, it would expand research capacity by increasing the number of active investigators and staff. With an efficacy of 85% at the current incidence rate, approximately one MPX infection could be prevented for every 600 persons vaccinated.

Vaccine developers of alternative smallpox vaccines and stakeholders in the area of biodefense and emerging infectious diseases would derive benefit from the opportunity to evaluate candidate smallpox vaccines in the field against a virulent orthopoxvirus. This benefit should not be underestimated because live vaccinia inoculation is the only smallpox vaccination that has proven efficacy in humans. All other candidate vaccines will be provisionally approved by applying The Animal Rule²⁰. Having human efficacy data would provide a significant selection advantage for one candidate vaccine over another.

Risks and concerns associated with vaccinating for MPX

The greatest safety concern for immunizing against MPX is the potential for live vaccinia vaccines to cause untoward side effects. Although live vaccinia inoculation successfully eradicated smallpox, and it is generally well tolerated, it reliably creates a pustular lesion at the site of inoculation, regional lymphadenopathy, and malaise. The malaise is typically short-lived, but the pustular lesions take 2–3 weeks for total resolution. More severe side effects like myocarditis (~1:10,000) or encephalopathy (~1:1,000,000) can also occasionally occur in normal hosts. In hosts with pre-existing atopic dermatitis or systemic immunodeficiency (e.g. late stage AIDS) there are concerns about vaccine virus dissemination that can be fatal. LC16M8 is highly attenuated live vaccinia and does not have significant safety concerns in healthy children²¹, and has advantages because replication-competence improves immunogenicity. However, LC16m8 has not been tested in atopic or HIV-infected persons and would require exclusionary screening for those conditions or additional safety testing in those risks groups before widespread implementation. Replication-defective poxviruses (MVA or NYVAC), replication-defective vectors and protein-based subunit approaches would be expected to have a large safety margin even in these potential risk groups.

Another major consideration for testing and/or deploying MPX vaccines involves opportunity cost. Prioritization of resources will be viewed differently by the various constituencies and stakeholders and will therefore require extensive discussions and consensus building. For example, if a vaccination program displaced the development of therapeutic approaches for MPX, an analysis would be needed to determine cost effectiveness of each approach before proceeding. Likewise, if MPX vaccination programs interfered or competed with the implementation of routine childhood vaccination programs, which have proven safety and efficacy, then the MPX program should be reconsidered.

Investment in education, development of alternative food sources, or control of MPX in the intermediate hosts may provide benefit and should be considered in the analysis.

MPX vaccination as a public health intervention in endemic regions

Targeted vaccination in at-risk populations such as health care workers who treat monkeypox patients and individuals who are highly exposed to animal reservoir species in endemic regions could be considered with alternative vaccines mentioned above which have the potential to circumvent problems associated with the current smallpox vaccine.

Alternatives to smallpox vaccination

Given the risks of adverse events, cost and logistical considerations associated with smallpox vaccination, alternate strategies should also be considered for control of human MPX. An alternative to vaccination could be treatment of incident cases with antiviral therapy to reduce the morbidity and transmission, and by providing access to antibiotics for treatment of secondary bacterial infections. Clinical diagnosis of MPX is relatively easy, thus effective antivirals and supportive clinical care may be more practical options than vaccination at this time.

Reducing the frequency of human MPX infection could be also be accomplished through health education on handling potential animal reservoir species to prevent animal-to-human transmission and by quarantine or contact isolation to prevent human-to-human spread. Defining the factors underlying increased incidence, and their impact on primary versus secondary transmission, is thus a crucial direction for on-going research. Additionally, a better understanding of the mortality and complications associated with monkeypox infection should be assessed. Continued active disease surveillance in endemic regions coupled with household and contact studies with long term follow up would address these important questions.

Further studies are also needed to identify intermediate hosts and animal reservoirs. Smallpox vaccination will not modify the reservoir nor the amount of MPX virus found in amplification species. Introduction of MPX into human populations is dependent upon contact with infected species, thus vaccination alone will not be effective in controlling the geographic spread of MPX as it is determined by the movement of animals and driven largely by the loss of natural habitat.

Factors that may influence the risk/cost: benefit analysis

There are a number of issues that should receive significant discussion and achieve consensus among stakeholders before clinical trials are initiated. The first is an ethical question. Should clinical trials be performed in endemic regions if there is no plan or mechanism to deploy a successful product to the general population of that area? Affordability, sustainability, and logistics would have to be considered, and metrics for safety and efficacy would need to be clearly defined to determine whether a product would advance towards licensure and clinical use. The factors that will influence the analysis are dynamic and could change incrementally or abruptly. Changes in incidence, MPX genetic evolution, frequency of person-to-person spread, and geographic distribution could be followed prospectively and decisions to act could be made based on predetermined thresholds. Other factors like new bioterrorism threats, sudden emergence of MPX in an entirely new geographic area or in new intermediate hosts, emergence of new co-existing conditions in local populations that would change safety considerations or change relative priorities for resource expenditures, or changes in political or social stability would be more difficult to anticipate²².

Conclusions

MPX is endemic in some regions of Central Africa, particularly where people have a direct interface with remote forested areas. It causes disease with significant morbidity and mortality, and the incidence has been increasing since routine smallpox vaccination ended. There are a number of vaccine concepts that have been developed as alternative smallpox vaccines beyond live vaccinia inoculation that have demonstrated efficacy against MPX in preclinical testing. Here we discussed factors that would influence a cost:benefit or risk:benefit analysis of whether candidate smallpox vaccines should be evaluated in regions endemic for MPX to determine whether they can prevent virulent orthopoxvirus infection in the field. In addition, we considered factors that may influence decisions to implement vaccination as a public health measure to control the spread of MPX. There are benefits to field-testing candidate smallpox vaccines, and in addition there would be immediate public health benefits from implementing MPX vaccination in endemic regions. This dynamic subject merits ongoing discussion among scientists, ethicists, public health officials, industry representatives, and political leaders to track the factors that would alter the tipping point in favor of or against implementing vaccination programs for MPX.

Recommendations

The questions of whether or not to conduct field trials for vaccines and implement vaccination to control MPX in endemic regions will need to be answered periodically by the appropriate stakeholders for each affected region. The authors suggest that the current actions should be taken to inform these decisions:

1. Maintain surveillance in endemic regions to monitor incidence, disease severity and frequency of person-to-person spread, and change in geographic range.
2. Selectively sequence MPX isolates to define genetic changes associated with transmissibility or virulence.
3. Define intermediate hosts and animal reservoirs. Immunization of people will not modify the reservoir or the amount of MPX found in amplification vectors, and therefore may not be effective in controlling the geographic spread of MPX if it is determined by the movement of animals.
4. Explore MPX treatment options and other prevention measures. Because clinical diagnosis is relatively easy, an effective treatment option may be a more practical intervention than vaccination.
5. If immunization studies in developing countries are contemplated to support the licensure of orthopoxvirus vaccines for industrialized countries or for military purposes, then provisions from those countries or organizations should be secured to distribute successful products in endemic regions where the products were tested.

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1. Monkeypox (MPX) incidence in Democratic Republic of Congo is rising.
2. Traditional smallpox vaccines can provide immunity against MPX infection.
3. Decision to evaluate vaccines is complex and will require risk:benefit analysis.
4. Ongoing epidemiological and virological surveillance will be needed.
5. Dynamic conditions will call for periodic reassessment by relevant stakeholders.