REVIEW

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Smallpox and monkeypox: Looking back and looking ahead

ABSTRACT

The monkeypox (mpox) epidemic was declared a global health emergency in July 2022. The mpox virus belongs to the same virus family as the smallpox, or variola virus, but the infection is a less lethal threat than smallpox. Nevertheless, its relationship to smallpox is a worldwide concern, as is the discontinuation of universal smallpox vaccinations since the 1980s. Newer therapies and vaccines are available for both infections, including 2 antiviral drugs that can be used under certain conditions. Two vaccines have been developed for mpox prevention, but clarity is needed on when and how to use them. Preventive public health measures and prioritization of resources for managing infectious disease are concerns.

KEY POINTS

- Smallpox, with a case-fatality rate that at one time ranged from 30% to 50%, was declared eradicated in 1980, and worldwide vaccination ceased shortly thereafter.
- In North and South America in 2022, there were 57,338 reported cases of mpox and 58 deaths.
- Newer therapies and vaccines are available under certain conditions, but when and how to use them is not always clear.

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Few clinicians today have seen and treated a patient with smallpox, a disease the World Health Organization (WHO) declared eradicated in 1980.[1] Yet as recently as July 23, 2022, WHO declared monkeypox (mpox), whose causative virus is in the same family as the smallpox virus, a global health emergency.[2]

The smallpox or variola virus is a member of the genus *Orthopoxvirus*, belonging to the *Poxviridae* family.[3] The *Poxviridae* family includes the vaccinia virus (cowpox), mpox, and molluscum contagiosum, although the molluscum contagiosum genus differs from that of the other viruses in the family. All of these diseases are characterized by papulopustular skin lesions. The symptoms of smallpox and mpox are similar, but illness with mpox is milder and rarely fatal.

SMALLPOX: ERADICATED BUT STILL RELEVANT

The world's population has been subjected repeatedly since 100 AD to waves of smallpox. Naples, a city of 400,000 in 1768, lost 60,000 people to smallpox over a period of a few weeks.[4] Some 30 years later, in 1796, Edward Jenner inoculated a child with pustular material from a woman infected with the vaccinia virus, and the child did not contract smallpox.[4] Before Jenner's discovery, which was the first modern vaccine of any kind, the variolization method was used to prevent infectious disease. Pustular material was aspirated with consequences that included the onset of smallpox.

Since 1984, WHO has authorized only 2 sites for smallpox retention: the US Centers for

Disease Control and Prevention (CDC) in Atlanta, GA, and the Research Institute of Viral Preparations in Moscow. In 1994, viral preparations were transferred from the Moscow Research Institute to the State Research Center of Virology and Biotechnology in Novosibirsk, Russia.[5] There is concern that the fall of the Soviet Union on December 26, 1991, led to the illegal transfer of certain smallpox containers to organizations and countries other than those initially authorized by WHO.[3]

TRANSMISSION AND CLINICAL PICTURE

Smallpox is transmitted from human to human. After an incubation period of 10 to 14 days, the patient develops fever, headache, and vomiting. Transmission is predominantly by airborne droplets and lesions of the mucous membranes and skin. Unlike chickenpox skin lesions, which coexist in all stages of the disease, smallpox skin lesions are all in the same evolutionary stage. They have a centrifugal progression, starting on the face.

If smallpox is suspected, polymerase chain reaction testing of variola DNA is needed to confirm the diagnosis. However, the presence of antibodies is not specific to smallpox, but rather to orthopoxvirus.

Before the eradication of smallpox, the death rate in unvaccinated individuals with smallpox ranged from 30% to 50%. Causes of death were coagulopathy and multiple organ failure with sepsis from bacterial superinfection.

ANTIVIRAL TREATMENT

The US Food and Drug Administration (FDA) has approved 2 oral antiviral therapies for use in patients with orthopoxvirus infections under the FDA's Animal Rule, which allows findings from well-controlled animal efficacy studies to support approved use when efficacy trials in humans are unfeasible or unethical. Under these limitations, tecovirimat was approved in 2018 and brincidofovir in 2021. Tecovirimat is a potent inhibitor of an orthopoxvirus protein required for the formation of an infectious virus protein. Brincidofovir is a prodrug of cidofovir that inhibits viral DNA synthesis. Although not commercially available, both drugs can be used in patients with orthopoxvirus infections, including smallpox and mpox.[6]

Vaccine cessation

Since smallpox eradication in 1980, vaccination rates worldwide have decreased from 80% to less than 30%.[6] Population-based surveys suggested that in West and Central Africa before 1986, orthopoxvirus antibodies were present in 12% to 15% of children (mean age 4.4 years).[7]

MONKEYPOX

Mpox, a zoonotic disease whose reservoirs include rodents, rats, and dogs from the grasslands of Central and Western Africa, is spreading worldwide. The mpox virus was first isolated in 1958 in monkeys and in 1970 in a 9-month-old boy in the Democratic Republic of Congo (formerly Zaire).[8] Monkeys are the principal infected animals with a risk of transmission.

Until the 1970s and 1980s, the case-fatality rate associated with mpox was 15% to 20% in Africa.[9] Currently in Africa, where the disease is endemic, the case-fatality rate is 5% to 10%.[9] This lower rate is probably a consequence of improved health conditions in Africa.[9]

Two mpox clades, ie, viruses with a common ancestry, have been identified in Africa. Clade 1 from the Congo basin has a case-fatality rate of at least 10% and clade 2 from Western Africa has a case-fatality rate of about 3.6%.[10] In 2022, when WHO declared a health emergency during a new European and North American outbreak, a new clade (variant) was identified and designated as 2b.[11]

The main risk factors for transmission of mpox in endemic areas include slaughtering or handling infected animals such as monkeys and rodents. Household contact is also a risk factor. Human-to-human transmission occurs through close contact with lesions, bodily fluids, respiratory droplets, and contaminated materials.

The 2022 outbreak

The first mpox outbreak in the Western Hemisphere occurred in the United States in 2003 with 81 cases and no deaths. Those who were infected had close contact with pet mammals. The 2022 mpox outbreak was a worldwide epidemic attributable not to direct contact with reservoir animals but to transmission between humans in the same manner as smallpox—ie, close contact and transmission of respiratory secretions. As of January 2023, the recorded and confirmed cases and deaths were as follows[12]:

- North and South America: 57,338 cases, 58 deaths
- Europe: 25,743 cases, 5 deaths
- Africa: 1,214 cases, 15 deaths.[12]

Individuals affected are predominantly young, sometimes with homosexual contacts or immunodeficiency, or both.

Disease manifestations

Mpox presents similarly to smallpox, with systemic symptoms and cutaneous and oral mucosal manifestations. The incubation period varies from 5 to 20 days. The clinical signs appear in 2 stages—a prodrome stage and an eruptive stage. The prodrome stage lasts about 5 days and is characterized by fever, swelling of lymph nodes, myalgia, back pain, and severe fatigue. The eruptive stage appears about 3 days after the prodrome stage, with skin rashes that consist of papules, vesicles, and pustules, which last 2 to 3 weeks and evolve into scabs. The rash develops initially on the face and then on the palms of the hands and the soles of the feet. The skin lesions share the same evolutionary stages as those caused by smallpox. Papules, vesicles, and pustules can be found in the oral mucosa, on external genitalia, and in the conjunctiva, as well as on the skin.

Systemic complications can include bronchopneumonia, septicemia, and encephalitis. The duration of the disease is approximately 3 to 4 weeks, during which transmissibility is high. Treatment is supportive, although in severe cases antivirals are used, including tecovirimat and brincidofovir.

Prevention

Previous vaccination against smallpox can reduce the severity of mpox symptoms. The 2 vaccines for mpox prevention, both of which are live vaccines, are as follows:

Modified Vaccinia-Ankara–Bavarian Nordic vaccine (MVA-BN, JYNNEOS) is approved for the prevention of smallpox, and it received emergency use authorization from the FDA for individuals at high risk of mpox infection.[13] Administration requires 2 subcutaneous doses.[13]

ACAM2000 was approved for smallpox prevention in 2007. In the United States, it is only available under the FDA Expanded Access program for investigational new drugs and is administered in 1 percutaneous dose.[12] However, ACAM2000 is associated with serious adverse effects including myocarditis, pericarditis, and cerebral edema—effects that have not been observed with MVA-BN.[13] ACAM2000 is not available commercially.

Because of safety considerations, only MVA-BN is approved for emergency use in patients at high risk of mpox infection. Definitive data are lacking on the clinical efficacy of these vaccines.[14] In addition to preventive use, they may be administered to a sick patient after exposure, but preferably within 4 days of exposure. The CDC considers vaccination to be practical until the 14th day after exposure.[15]

ADDITIONAL CONSIDERATIONS

Vaccination strategies, preventive measures, and resource utilization are relevant considerations in addressing the mpox epidemic.

Vaccination

It may be time to consider a smallpox vaccination campaign targeting several vulnerable populations. These include adolescents and young adults who have not been vaccinated against smallpox; individuals who are immunodeficient because of neoplasia, transplants, or autoimmune disease; and healthcare personnel at risk of infection who are not already vaccinated against smallpox. The objective of a vaccine strategy in these groups would be to reduce the disease burden on healthcare facilities.

The negative effects from a reduction in the overall workforce caused by an mpox outbreak must also be considered. WHO advised against mass vaccinations in its report of June 14, 2022, but it continues to advise vaccination coverage for those who have been in close contact with infected individuals (post-prophylaxis exposure) and for healthcare personnel or others at risk because of their work (pre-exposure prophylaxis).[15] The vaccines recommended by WHO are second-generation (ACAM2000) or third-generation (MVA-BN, LC16) vaccines, which have fewer reported adverse events than vaccines used before 1980.

CURRENT TRENDS, FUTURE NEEDS

The mpox epidemic is taking place during the COVID-19 pandemic with all of its variants, as well as during the Ukrainian-Russian war. Wars are excellent amplifiers of infectious disease.[16] It is significant that the preventive measures for mpox are the same as those for COVID-19, ie, distancing and masking. The relaxation of COVID-19 preventive measures now occurring will likely result in a higher disease burden of COVID-19 and mpox than if we remained more vigilant to transmission.

In recent decades, great importance has been placed on the diagnosis and treatment of chronic diseases such as cardiovascular and respiratory illnesses. This shift in priorities is contributing to the dismantling of facilities dedicated to infectious diseases, and the misperception that many infectious diseases have been eradicated is contributing to the shift. Tuberculosis dispensaries, infectious disease clinics, and laboratories with dedicated sections of microbiology and virology are no longer standard.

We believe it is time for an organizational review and implementation of training for specialists in the infectious disease sector.

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DISCLOSURES

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