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## An updated review of human monkeypox disease: A new potential global hazard

S. Rehman<sup>1</sup>, M.H. Khan<sup>2</sup>, M. Bilal<sup>3</sup>, W.P. Lokapirnasari<sup>4</sup>, S. Ullah<sup>5</sup>, M.S. Khan<sup>5</sup>, M.K. Shah<sup>5</sup>, A. Tariq<sup>6</sup>

<sup>1</sup>Division of Veterinary Public Health, Faculty of Veterinary Medicine, University of Airlangga, Surabaya, Indonesia, <sup>2</sup>Department of Epidemiology and Public Health, Faculty of Veterinary Science, University of Veterinary and Animal Sciences, Lahore, Pakistan, <sup>3</sup>Faculty of Veterinary Medical Sciences, University of Calgary, Alberta, Canada, <sup>4</sup>Division of Animal Husbandry, Faculty of Veterinary Medicine, University of Airlangga, Surabaya, Indonesia, <sup>5</sup>Faculty of Veterinary and Animal Sciences, <sup>6</sup>Department of Livestock and Dairy Development, Gomal University Dera Ismail Khan, Khyber Pakhtunkhwa, Pakistan

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Correspondence: W.P. Lokapirnasari widya-p-l@fkh.unair.ac.id

#### **Abstract**

Monkeypox, a recently developed viral infectious disease, has become a concern for the general public. This predicament has emerged because of the increased incidence of human monkeypox infections. It was previously a serious zoonotic virus native to just sections of Central and Western Africa and was never recorded outside endemic areas. In this review, the author presented considerable data on this disease and offered a detailed summary of MPXV. More recently, as of October 27, 2022, Monkeypox cases spread quickly across the globe, infecting 76713 people globally, with the majority of cases from Europe, the United Kingdom, North and South America, Asia, and the Middle East. By October 27, 2022, the disease had spread to almost 109 countries. In the United States, there were 28244 (36.82%) cases of Monkeypox; in Brazil, 9045 (11.79%); in Spain, 7317 (9.53%); in the United Kingdom, 3698 (4.82%); in France, 4094 (5.34%); in Germany, 3662 (4.77%); in Colombia, 3298 (4.29%); in Peru, 3048 (3.92%); in Canada, 1436 (1.87%); in Belgium, 786 (1.02%) and Portugal, 944 (1.23%). In terms of the overall number of deaths, 36 deaths were reported, with the maximum eight deaths being from Brazil (22.22%), seven from Nigeria (19.44%), and six deaths from the United States (16.67%). However, human Monkeypox epidemiological trends are rapidly changing, leaving endemic areas and moving to nonendemic countries. Therefore, international health authorities must implement prioritybased preventive measures to prevent the spread of Monkeypox infection worldwide.

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#### Introduction

Globally, as of October 18, 2022, there have been 622,389,418 confirmed cases of COVID-19, with 6,548,492 deaths reported to the WHO (1). With the COVID-19 pandemic still active, the world is on high alert due to another public health concern: the global Monkeypox virus epidemic. More than 350 suspected and confirmed

incidences of the illness, a significantly milder relative of smallpox, have been documented as of May 26, 2022, in a dozen countries across America, Australia, the Middle East, North Africa, and Europe (2). Human Monkeypox is a severe but neglected viral zoonotic illness. Initially, the disease was found only in central and western Africa (3). However, changing epidemiology creates significant epidemics worldwide and is an individual's principal source of concern

(4). On July 23, 2022, the WHO recently labeled Monkeypox a public health emergency of global importance (5). The virus (MPXV) is not novel. It was initially recognized by Alexander von Magnus (1912-1973), a Danish virologist (6). He detected the virus among monkeys maintained in a research center to identify two nonfatal rash outbreaks among monkeys in Copenhagen in 1958 (7). However, the disease was prominent when the first documented case was reported in 1970 in the Republic of Congo in a nine-monthold boy suspected of being infected by smallpox (8). The viruses that cause smallpox and Monkeypox are both members of the orthopoxvirus family, meaning they are related but separate viruses. Smallpox, on the other hand, is a disease that only affects people, whereas Monkeypox can be passed from person to person and through intimate personal contact with infected animals, including monkeys, rats, and squirrels. Smallpox is more severe than Monkeypox. The illness is self-limiting and has symptoms that last between two and four weeks. These frequently include skin lesions, fever, rashes, headaches, bodily aches, and enlarged lymph nodes and can cause further issues (9). Smallpox was abolished in a particular region two years prior, in 1968 (10). The virus is an enclosed DNA virus with a double-stranded structure that belongs to the genus Orthopoxvirus of the family Poxviridae and subfamily Chordopoxvirinae, with symptoms similar to those of the pox virus (11). The size ranges from 200-400 nm with an oval or brick-like virus shape. There are two major genetic clades: the West African clade and the Congo clade (10). However, the epidemic in 2022 differs between the two clades (12). It has been reported that Monkeypox can spread from animals to humans or humans to humans (13). Transmission can also occur via nosocomial and congenital routes (14,15). People who live in forested areas, care for diseased animals, and are around affected people throughout the infectious period (21 days) are more likely to contract the disease. The risk of contracting MPXV infection is significantly higher in infants, pregnant women, and immunocompromised patients, including HIV-positive patients (16). The gold standard method for determining MPXV infection is PCR with or without sequencing and virus isolation (13). Most infections are initially detected clinically in remote settings and places with few resources. Monkeypox is distinguished from other OPVX infections primarily by lymphadenopathy (16). This review provides a comprehensive overview of the epidemiology of the Monkeypox virus (MPXV), including its spatial and temporal distribution, incubation period, transmission routes, pathogenesis, clinical manifestations, diagnosis, and therapeutic and prophylactic treatment interventions to combat this dreadful virus. It will also boost the knowledge of primary and secondary healthcare workers about this lethal virus and will produce awareness and emergency plan preparedness in the event of a pandemic.

#### **Epidemiology**

Initial epidemics were localized exclusively to the African continent (3). The Central African or Congo clade is the most lethal (17). It originated in Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, and Sudan. Ivory Coast, Liberia, Nigeria, Sierra Leone, and the United States are the origins of the West African clade (18). The prognosis is poor owing to a higher case fatality rate of 10.6% for the Central African clade (19), which is predominantly responsible for severe outbreaks in Africa.

The West African clade is less severe, with a case-fatality rate (CFR) of 3.6% (19) between 1970 and 1979. Six countries in Central Africa have reported 48 cases, with 38 cases reported in the Congo (12). There were 400 documented human MPXV cases in 1986, with routine outbreaks in Central and West Africa (20). The number grew to 500 in the Congo alone from 1991 to 1999 (21). However, the virus causes more than 1000 cases yearly in the Congo (12).

#### Re-emergence of the virus

In Early 2000, the virus resurfaced when cases of human Monkeypox were detected outside Africa. Almost 53 individuals in the Midwest of the United States acquired Monkeypox in 2003 due to importing Gambian rats from Ghana (22). Infections were also recorded in Israel and the United Kingdom among travelers from Nigeria in 2018. Similar circumstances have occurred in the United States in 2021 (10). However, the WHO has eradicated the disease since 1980 (10). Still, Sweden, Italy, and Belgium authenticated their index case on May 19, 2022. Australia also reported two such events on May 20. One was from Sydney, and the other was from Melbourne. Both patients returned home on a trip to Europe. Likewise, on May 20, the Netherlands, Germany, and France reported their initial cases. On May 20, the UK's Health Secretary also reported 11 MPXV cases, increasing the total to 71 (12). Multiplex real-time PCR was performed to detect these cases.

#### **Epidemiological metrics**

In 2022, the overall adequate reproductive number (Re) of 70 nations for Monkeypox virus infection was 1.29 during the early phase of the outbreak as of July 22, whereas it was 1.55 for the United States (23). While the net reproduction number was relatively high for males having sex with men, it was 2.43 even during the first week of June (24). Between the 1970s and 2019, the median age at presentation ranged from 4-year-old children to 21-year-old adults (8). Historically, for Monkeypox, the general population's case fatality rate (CFR) ranges from 0 to 11%, with children being more susceptible. The fatality rate recently fluctuated between 3% and 6% (10). In the Democratic Republic of Congo, the annual crude incidence is 5.53 per 10,000 people (25). In the United States, a comparable situation exists, with

a current incidence of 5.2 incidents per 100,000 population (26). Evidence suggests that the median age of MPX patients has risen from 4 years in the 1970s to 21 years in the 2010s and the 2020s (27). In 2018, the median age of patients infected in Nigeria was approximately 30. Furthermore, more men were affected than women. While the majority of cases in DRC were recorded from rural areas, in small villages surrounded by humid evergreen tropical forests, the majority of cases in Nigeria were reported from urban and peri-urban areas in the country's southern regions (13,28).

#### **Current Monkeypox cases**

More recently, as of October 27, 2022, Monkeypox infections have spread swiftly around the globe, infecting 76713 people globally, with the majority of cases from Europe, the United Kingdom, North and South America, Asia, and the Middle East. By October 27, 2022, the illness had spread to approximately 109 countries. Overall, there were maximum cases of Monkeypox in the United States 28244 (36.82%). In Brazil, 9045 (11.79%); Spain, 7317 (9.53%); the United Kingdom, 3698 (4.82%); France, 4094 (5.34%); Germany, 3662 (4.77%); Colombia, 3298 (4.29%); Peru, 3048 (3.92%); Canada, 1436 (1.87%); Belgium, 785 (1.02%); and Portugal, 944 (1.23%). In terms of the number of deaths, 36 were reported. The highest number of deaths was from Brazil, with eight deaths (22.22%), seven from Nigeria (19.44%), and six from the United States (16.67%) (29,30) (Figure 1).

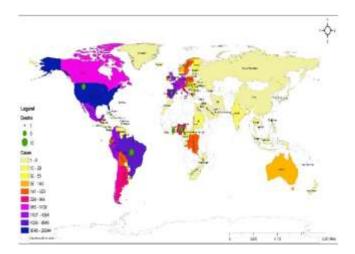


Figure 1: Depicting the current number of Monkeypox cases and deaths around the globe.

#### Reservoir of the virus

The MXPV virus is susceptible to several animal species. These include non-human primates, rope squirrels, pouched rats, dormice, and other species. However, there is still confusion regarding the natural history of the virus, and more detailed research is required to define the exact reservoir to understand the circulation of the virus in the wild (10).

#### Viral characteristics

The genus Orthopoxvirus of the Poxviridae family incorporates multiple viruses of zoonotic interest, including vaccinia, variola, cowpox, and Monkeypox viruses. The genus Orthopoxvirus of the Poxviridae family includes multiple zoonotic viruses, including vaccinia, variola, cowpox, and Monkeypox viruses. Orthopoxviruses have brick-like geometries surrounding their virions, which are approximately 200 nm wide and 250 nm long. The linear DNA genomes of the member viruses are-170-250 kb long. Viral replication occurs in the cytoplasm. Viral proteins connect to host glycosaminoglycans (GAGs), which facilitate cellular endocytosis of the virus, allowing entry into the host cell. The viral core is released into the host cytoplasm upon fusion of the viral envelope and plasma membrane. MPXV contains a linear DNA genome of approximately 197 kb and 190 nonoverlapping Open Reading Frames (ORFs) that are longer than 180 nt (31). Similar to all Orthopoxviruses, the central coding region sequence (CRS) is largely preserved at 56000–120000 virus nucleotide positions and is flanked by variable ends that feature inverted terminal repeats (ITRs). The terminal ends of the MPXV genome contain vaccinia virus (VACV) homologs to genes involved in immunomodulation, most of which affect pathogenicity and host range determination (32). In addition, the Monkeypox virus has at least four ORFs, unlike the variola virus (VARV), which lacks Open Reading Frames in the ITR region (31,32).

#### Incubation and transmission cycle

Infection with the Monkeypox virus occurs in three phases. The first stage is an incubation period that can run anywhere from 1-2 weeks with a maximum of 3 weeks. The second stage was the onset period. The main symptoms include high fever, severe weakness, and intense head, back, or muscle pain, accompanied by swollen lymph nodes (33). In contrast to other illnesses like smallpox, chickenpox, and measles, Monkeypox is characterized by swollen lymph nodes, specifically the swelling of cervical, maxillary, and inguinal lymph nodes (10,33,34). The third stage is the rash phase, during which a rash occurs on the face and limbs. Infected individuals develop papules, vesicles, pustules, umbilical pus, inflammatory lesions, and scabs ranging from a few to thousands in number (33).

#### Viral pathogenesis

MPXV infects a host through different routes, including the oropharynx, nasopharynx, and intradermal routes. It multiplies at the inoculation site and then spreads to adjacent lymph nodes. After a brief initial viremia, the virus moved to other internal organs. MPXV shares morphological properties with other recognized orthopoxviruses. The lipoprotein-based outer membrane surrounding MPXVs is oval or brick-shaped (35). Similarly, Double-stranded linear DNA comprises the MPXV genome (197 kb). Moreover, the

life cycle occurs in the cytoplasm, even though it is a DNA virus. In addition, viral DNA replication, transcription, and assembly of infected virions require many proteins. Like poxviruses, this virus also penetrates host cells through macropinocytosis, endocytosis, and fusion (36).

#### Transmission

In humans, Monkeypox is a zoonotic virus. The main transmission mechanisms include direct animal contact via bodily fluids, aerosols, blood, or infected lesions (37). Additionally, it can be spread by close human-to-human contact or respiratory secretions and is similar to smallpox in terms of its clinical characteristics and the formation of a serologically cross-reactive immune system. Interestingly, WHO revealed that intimate physical contact between males is the predominant mechanism of transmission, which is responsible for the most recent surge (37). However, this communication technique remains under investigation. Congenital Monkeypox can also be transmitted through the placenta. Transfer can also occur during and after delivery through close physical contact. However, intimate physical interactions are a known risk factor for transmission. However, it is unknown whether the virus is explicitly transmitted during sexual intercourse. Further studies are required better to understand this issue (10,33).

#### **Diagnosis**

To confirm Monkeypox infection, it is essential to correlate diagnostic tests with epidemiological and clinical data. Laboratory tests, history, and clinical symptoms were performed to confirm the infection. These tests included PCR, enzyme-linked immunosorbent assay (ELISA), immunohistochemistry, and western blotting. A more definitive diagnosis is essential to rule out other infectious diseases, such as smallpox (38). Exudate from the lesion or the crust was collected using a swab to detect viral nucleic acids. Next, real-time polymerase chain reaction (RT-PCR), specific to the viral genome, was performed using viral DNA. In contrast, viral proteins are also used to confirm Monkeypox virus infection through western blotting (39). However, during acute infection, the WHO recommends an RT-PCR test to diagnose the virus (10) rapidly.

#### **Prevention**

Some precautions should be taken to avoid MPXV infection. This includes avoiding direct contact with suspected animals, particularly in areas where the disease is common, isolating infected individuals in a room with negative pressure to stop the virus from person-to-person transmission, isolating and euthanizing animals suspected of being virus reservoirs, and avoiding contact with any objects that have come into contact with sick people or animals (39). Frontline staff caring for infected patients and other high-risk individuals should wear appropriate personal protective equipment (PPE) to avoid airborne infections. These include

masks, such as N-95, double-layered gloves, and fully protected water-resistant gowns (40). In addition, smallpox immunization is likely to offer resistance against MPXV infection owing to its shared genetic makeup. Furthermore, given the long incubation time of the virus, the United States CDC forecasts that if the vaccine is given within four days of exposure to the virus, protection from MPXV is possible. Therefore, it is believed that such immunization should confer complete immunity to the condition (41). Health officials have drafted regulations mandating frontline employees caring for infected patients in several countries to undergo smallpox vaccinations to curb the current MPXV outbreak. On May 24, 2022, the American CDC decided to release some of its live vaccinia vaccine JYNNEOS, which was initially authorized for the smallpox virus in 2019. This immunization is indicated for people at a high risk of coming into contact with MPXV (42). Another vaccine, ACAM2000®, is also available, a live-replicating competent vaccinia virus (43). However, it is not recommended that the general public utilize this vaccine. Correspondingly, the German government announced plans to purchase 40,000 doses of the Bavarian Nordic smallpox vaccine in a news release on May 25, 2022. Likewise, to challenge the surge of Monkeypox cases, the United Kingdom Health Security Agency stated on May 26, 2022, that they had already created 20,000 doses of the smallpox vaccine. Moreover, third-generation immunization for smallpox, termed Modified Vaccinia Virus Ankara (MVA), is available (44). This vaccine has also acquired permission against Monkeypox in the USA and Canada (45). Compared to the first- and second-generation smallpox vaccines, the modified Ankara vaccine comprises two injections four weeks apart. Giving the Ankara vaccine does not induce skin lesions or enhance the threat of local or broad transmission, similar to live vaccine formulations of the virus (46). In addition, clinical investigations have indicated that the Ankara vaccine is harmless and stimulates antibody production in individuals with compromised immune systems, which are recognized as contraindications to delivering live vaccinia vaccination (47).

#### **Treatment**

There are presently no known effective medicines for Monkeypox. The treatment is supportive only, as with most viral infections. However, there are actions you can take to avoid an outbreak. The infected individual should stay isolated and keep the infected lesion covered until all crusts naturally remove and new skin has developed. In extreme cases, drugs having a track record of efficacy against Orthopoxviruses in animal studies may be studied for experimental usage in outbreaks (48).

Most patients recover without therapy since the symptoms of Monkeypox sickness are often modest. According to CDC recommendations, infections with the Monkeypox virus do not currently have a specific therapy.

However, antiviral drugs licensed for smallpox treatment may also be used to treat Monkeypox. In vitro and preclinical experiments have revealed that the antiviral cidofovir (Vistide) is effective against poxviruses by inhibiting viral DNA polymerase (49).

According to the most recent CDC recommendations, this drug may be offered to Monkeypox patients in severe cases. However, the clinical effects are still questionable. The FDA-licensed antiviral Tecovirimat (ST-246) is also available to treat adult and pediatric patients with human smallpox infections. The European Medicines Agency EMA approves the drug for monkeypox virus (10). However, the FDA does not license this medicine to treat Monkeypox (50). Furthermore, to employ tecovirimat for treating Monkeypox in the United States, one must use an Expanded Access Investigational New Drug (EA-IND) mechanism supervised by the FDA (51).

Another medication, the medicine Vaccinia Immune Globulin Intravenous (VIGIV), is used to treat vaccinia vaccination-related adverse effects. These include dermatitis and infections brought on by the vaccinia virus. During an outbreak, it can be used to treat Monkeypox. An antiviral medicine named brincidofovir (Tembexa) has FDA approval to treat adult and pediatric patients with human smallpox infections. Moreover, to deploy brincidofovir as a treatment for Monkeypox, the CDC is currently creating an (EA-IND). Other antiviral drugs have also proven effective against some Orthopoxvirus species. These include the cidofovir drug version CMX-001. It has shown antiviral against Orthopoxvirus species, efficacy including Monkeypox, and it does not have the same amount of nephrotoxicity as cidofovir (38,51).

Regarding the antiviral medicine ST-246 (Tecovirimat, widely known as TPOXX), it stops the cell from releasing the intracellular virus. The tecovirimat drug is available in various formulation that is taken either orally (200 mg capsule) or intravenously (200 mg/20ml injection) (38,51). However, the use of these medications in endemic areas can be prescribed by doctors based on the status of affected people.

The lack of access to medical treatment, testing instruments, and infrastructure restricts their ability to make informed decisions on effectively managing this neglected tropical disease. However, more extensive data collection and feasibility analysis are needed to assess the prospective advantages and disadvantages of prophylactic Monkeypox immunization in endemic areas to manage the infection effectively.

#### **Conclusions**

The WHO 2022 has issued a warning that the world may face another massive challenge after overcoming the problems of the COVID-19 pandemic in the shape of the Monkeypox epidemic in the backdrop of the tragic Ukraine-

Russian war. 1,475 cases have been confirmed worldwide as of June 10, 2022. In the UK alone, 3698 incidences of Monkeypox have been reported. By October 27, 2022, the number of cases had increased dramatically in other countries, such as Spain (n=7317), Peru (n=3048), France (n=4094), Germany (n=3662), Canada (n=1436), and the USA (n=28244). Therefore, the global community is currently concerned about MPXV outbreaks. Scientists, epidemiologists, doctors, and decision-makers have been paying close attention to the Monkeypox outbreak.

Patients with Monkeypox are urged to isolate themselves according to international standards. Immunization, essential hygiene habits, and self-isolation or quarantine for patients and their contacts are practical approaches to control this illness. Men with intimate relationships with others are at a higher risk of developing MXPV infections. However, clinical virologists are still confused regarding whether MPXV is transmitted through sexual contact.

The urgent demand is to make prompt judgments, develop a thorough contract tracing program, segregate MPXV-exposed and-infected individuals, and deploy post-exposure vaccines that may stop the virus from spreading further. Moreover, because of the COVID-19 outbreak, the world is currently experiencing economic hardships. In addition, the prospects for economic advancement will be directly affected by the current spike in Monkeypox cases in the USA and worldwide. If Monkeypox disease is not swiftly controlled, economic issues become increasingly difficult.

Other issues people experience includes social isolation and stigma. In the past two years, people have dealt with this issue. Even among more affluent and more cultured segments of the population, the understanding of the mechanics of the disease remains relatively undeveloped. People refuse disease screening and ignore quarantines with impunity. There was no coughing hygiene. In developing countries, hand hygiene remains controversial. Better public health measures, such as controlled studies using animal models and other methods, are urgently needed to stop the spread of the virus. Children, the elderly, and pregnant women require extra care because they are more susceptible to disease.

Other sexually transmitted diseases (STDs), such as human immunodeficiency virus (HIV/AIDS), are equally important because of sexual transmission. Therefore, it is vital to collect information regarding these diseases. Consequently, it is necessary to monitor the pathophysiology of MPXV and HIV coinfection closely. Because of immune system damage induced by HIV infection, it is unknown how the immune system might respond to MPXV among individuals with HIV. Moreover, in the next few months, close surveillance will be needed for other comorbidities, such as MPXV coinfection, and other STDs, such as hepatitis B or C infection. However, this is a demanding task and poses considerable challenges.

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#### **Conflict of interest**

The authors declare that they have no conflicts of interest.

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## مراجعة محدثة لمرض جدري القرود البشري: خطر عالمي محتمل جديد

سيف الرحمن'، محمد حارس خان'، محمد بلال"، ويديا باراميتا لوكابيرناساري'، شكيب الله'، محمد شعيب خان'، محمد كمال شاه'، أميرينا طارق'

'قسم الصحة العامة البيطرية، كلية الطب البيطري، جامعة إير لانجا، سور ابايا، إندونيسيا، 'قسم علم الأوبئة والصحة العامة، كلية العلوم البيطرية، جامعة العلوم البيطرية، والحيوانية، لاهور، باكستان، "كلية العلوم الطبية البيطرية، جامعة كالجاري، ألبرتا، كندا، 'قسم تربية الحيوان، كلية الطب البيطري، جامعة أير لانجا، سور ابايا، إندونيسيا، "كلية العلوم البيطرية والحيوانية، 'قسم تنمية الثروة الحيوانية والألبان، جامعة جومال، دير السماعيل خان، خيير بختونخوا، باكستان جامعة جومال، دير السماعيل خان، خيير بختونخوا، باكستان

#### الخلاصة

أصبح جدرى القرود، وهو مرض معدٍ فيروسي تم تطويره مؤخرًا، مصدر قُلق لعامة الناس. وقد نشأ هذا التخوف بسبب زيادة حالات الإصابة بجدري القرود بين البشر. لقد كان في السابق فيروسًا حيوانيًا خطيرًا موطنه أجزاء فقط من وسط وغرب إفريقيا ولم يتم تسجيله مطلقًا خارج المناطق الموبوءة. في هذه المراجعة، قدم المؤلف بيانات كبيرة عن هذا المرض وقدم ملخصًا تفصيليًا لفيروس جدري القرود. في الأونة الأُخيرة، اعتبارًا من ٢٧ أكتوبر ٢٠٢٢، انتشرت حالات جدري القرود بسرعة في جميع أنحاء العالم، حيث أصابت ٧٦٧١٣ شخصًا على مستوى العالم، وكانت غالبية الحالات من أوروبا والمملكة المتحدة وأمريكا الشمالية والجنوبية وآسيا والشرق الأوسط وبحلول ٢٧ أكتوبر ٢٠٢٢، كان المرض قد انتشر إلى ما يقرب من ١٠٩ دول. في الولايات المتحدة، كان هذاك ٢٨٢٤٤ (٣٦,٨٢) حالة إصابة بجدري القرود؟ وفي البرازيل ٩٠٤٥ (١١,٧٩%)؛ وفي إسبانيا ٧٣١٧ (٩,٥٣%)؛ وفي المملكة المتحدة ٣٦٩٨ (٣٨,٤%)؛ وفي فرنسا ٤٠٩٤ (٣٤,٥%)؛ وفي ألمانيا ٣٦٦٢ (٤,٧٧)؛ وفي كولومبيا ٣٢٩٨ (٢٩,٤%)؛ وفي البيرو ٣٠٤٨ (٣,٩٢%)؛ وفي كندا ١٤٣٦ (١,٨٧)؛ وفي بلجيكا ٧٨٦ (١,٠٢) والبرتغال ٤٤٤ (٢٣,١%). ومن حيث العدد الإجمالي للوفيات، تم الإبلاغ عن ٣٦ حالة وفاة، وكان الحد الأقصى لثماني وفياتُ من البر ازيل (٢٢,٢٢%)، وسبع وفيات من نيجيريا (١٩,٤٤%)، وست وفيات من الولايات المتحدة (١٦,٦٧%). ومع ذلك، فإن الاتجاهات الوبائية لجدري القرود البشري تتغير بسرعة، مما يترك المناطق الموبوءة وينتقل إلى البلدان غير الموبوءة. ولذلك، يجب على السلطات الصحية الدولية تنفيذ التدابير الوقائية ذات الأولوية لمنع انتشار عدوى جدري القرود في جميع أنحاء العالم.