The reemergence of monkeypox as a new potential health challenge: A critical review

Zeinab Mohseni Afshar[1], Hossein Nazari Rostami[2], Rezvan Hosseinzadeh[3], Alireza Janbakhsh[1], Ali Tavakoli Pirzaman[3], Arefeh Babazadeh[3], Zeinab Aryanian[4], Terence T. Sio[5], Mohammad Barary[2], and Soheil Ebrahimpour[3]

[1]Kermanshah University of Medical Sciences
[2]Shahid Beheshti University of Medical Sciences
[3]Babol University of Medical Science
[4]Tehran University of Medical Sciences
[5]Mayo Clinic Research in Arizona

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Abstract

Human monkeypox is a zoonotic Orthopoxvirus resembling smallpox in clinical course, making it difficult to distinguish it from smallpox and varicella. Laboratory diagnostics are critical components of illness identification and surveillance, and novel tests are required for more precise and quick diagnosis. The majority of human infections occur in Central Africa, where monitoring in remote regions with little infrastructure is challenging but may be performed using evidence-based methods and teaching materials that educate public health personnel on the fundamental principles of this infection. New medications and vaccinations showed promising results for the treatment and prevention of the disease, but more studies are required to show their efficacy in the actual endemic settings. Thus, more studies are needed on the virus's epidemiology, ecology, and biology in endemic locations to better understand and prevent human infections. This review discussed the etiology, epidemiology, and clinical course of the monkeypox and indicated diagnostic and treatment approaches for this disease.

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1. Clinical Research Development Center, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
2. Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Student Research Committee, Babol University of Medical Sciences, Babol, Iran
4. Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
5. Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran
6. Department of Radiation Oncology, Mayo Clinic, Phoenix, Arizona, USA
7. Student Research Committee, Virtual School of Medical Education and Management, Shahid Beheshti University of Medical Sciences, Tehran, Iran
8. Students' Scientific Research Center (SSRC), Tehran University of Medical Science, Tehran, Iran

Correspondence:

Soheil Ebrahimpour, Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran. Tel: +989111149309, Fax: +981132207918, Email:*drsoheil1503@yahoo.com*

Abstract

Human monkeypox is a zoonotic Orthopoxvirus resembling smallpox in clinical course, making it difficult to distinguish it from smallpox and varicella. Laboratory diagnostics are critical components of illness identification and surveillance, and novel tests are required for more precise and quick diagnosis. The majority of human infections occur in Central Africa, where monitoring in remote regions with little infrastructure is challenging but may be performed using evidence-based methods and teaching materials that educate public health personnel on the fundamental principles of this infection. New medications and vaccinations showed promising results for the treatment and prevention of the disease, but more studies are required to show their efficacy in the actual endemic settings. Thus, more studies are needed on the virus's epidemiology, ecology, and biology in endemic locations to better understand and prevent human infections. This review discussed the etiology, epidemiology, and clinical course of the monkeypox and indicated diagnostic and treatment approaches for this disease.

Keywords: Monkeypox; Orthopoxvirus; Smallpox; Outbreak; Infectious Disease

Introduction

Concerns about annual epidemics, such as influenza, had waned in the shadow of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, outbreaks of a reemerging virus have recently brought about concerns in many world regions (Leong, 2020). Monkeypox virus (MPXV) is a zoonotic infection with sporadic involvement in humans. The clinical manifestation of monkeypox infection resembles that of smallpox. Therefore, vaccination against smallpox could also protect against this virus. Routine smallpox vaccination, which was developed to prevent smallpox, ceased in 1980 along with global smallpox eradication. Therefore, outbreaks were expected with the waning cross-immunity (Reynolds & Damon, 2012). With new cases appearing in other parts of the world, concerns have arisen about the forthcoming pandemic. Thus, the Centers for Diseases Control and Prevention (CDC) has announced that any smallpox-like infection, manifesting as skin eruptions and fever, added to lymphadenopathy should be suspected of MPXV (Walensky, 2022). In the past, most people, especially in the endemic areas, had gotten vaccinated against smallpox. This vaccine is cross-protected against MPXV and other related orthopoxviruses, eradicating universal smallpox. With time passing and immunity waning, susceptibility to MPXV increased. Accordingly, viral mutations have also increased.

On the other hand, ecological changes have given more human exposure to animals. MPXV has a broad range of small animal hosts whose control is challenging. Climate change, deforestation, urbanization, transboundary migration, poverty, unsafe traditional practices, and civil wars are other causes of monkeypox reemergence. Underreporting and under-recognition of cases, insufficient access to healthcare facilities, inexperienced staff, and poor laboratory diagnosis would promote epidemic evolution (Edghill-Smith et al., 2005; Nguyen, Ajisegiri, Costantino, Chughtai, & MacIntyre, 2021; Reynolds, Carroll, & Karem, 2012; Simpson et al., 2020). Therefore, in this review, we aim to discuss the data on the monkeypox virus.

Etiology

Monkeypox virus (MPXV) is a double-stranded DNA virus and one of the most virulent members of the Orthopoxvirus genus, the Poxviridae family. Other members of this genus include vaccinia virus (the live virus component of orthopoxvirus vaccines), variola virus (the causative agent of smallpox), and cowpox, all pathogenic to humans. There are two clades of the MPXV species, the West African clade, and the Congo Basin clade. MPXV is a virus of various mammalian species, including squirrels, mice, monkeys, and dogs, with African rodents as the reservoirs, but it sporadically involved humans in regional outbreaks (Babkin, Babkina, & Tikunova, 2022; Mauldin et al., 2022).

Epidemiology

Monkeypox was first discovered in laboratory monkeys in 1958 after two outbreaks of a pox-like disease. Twelve years later, the first human case of monkeypox was identified as a human pathogen in the Democratic Republic of the Congo (DRC) in 1970. Since then, the disease has been endemic in Africa. Until the 2003 outbreak in the United States (US), nearly all cases were from Africa. Nevertheless, international travel or importing animals has led to monkeypox infection outbreaks outside Africa. The origin of the US 2003 outbreak was determined as a shipment of rodents, like squirrels, rats, and mice, from Ghana to Texas (Reed et al., 2004). Subsequently, outbreaks took place periodically due to travels across the world. The largest West monkeypox outbreak originating from some travelers from Nigeria began in 2017 (Bunge et al., 2022; Yinka-Ogunleye et al., 2019). This human-to-human transmission continued to be increasingly reported, especially in immunocompromised patients in different parts of the world, including Israel, Singapore, the United Kingdom (UK), and lastly, the US in November 2021 (Erez et al., 2019; Ng et al., 2019; Agam K Rao et al., 2022; Vaughan et al., 2018a; Vaughan et al., 2020; Yinka-Ogunleye et al., 2019). A summary of the reported cases of the monkeypox is indicated in Table 1.

Interestingly, no epidemiologic link to Nigeria was identified in more recent outbreaks as no correspondent case had been found there. Since then, no human case has been reported out of Africa until lately in May 2022, when one US resident was diagnosed with monkeypox after returning from Canada. Subsequently, several cases have been reported from Spain, Portugal, Canada, the UK, Italy, and others. Interestingly, many detected patients have had no travel history to Africa or no epidemiologic connection with confirmed cases (Mahase, 2022a, 2022b). The epidemiology of monkeypox infection has changed between different outbreaks as the number and the median age of the cases have increased. Younger individuals are expected to be the most susceptible population to monkeypox, as people born after 1980 had not received the smallpox vaccine. Therefore, it is expected to demonstrate more infection reports in individuals younger than 40 years (Bunge et al., 2022; E. Petersen et al., 2019).

Risk factors like a history of travel, gender, or sexual orientation should be considered in suspecting monkeypox infection. Other risk factors include living in rural or forested areas of central and western Africa, being involved in preparing bushmeat, recent exposure to an infected patient, and absence of smallpox vaccination (Nolen et al., 2015; Quiner et al., 2017; Reynolds et al., 2007). It has been rumored that men who have sex with men (MSM) comprise most monkeypox cases in the current outbreak, but the issue should be verified. Monkeypox is not a gay-related infection, but it was first identified in gay and bisexual men in the UK and in two raves held in Spain and Belgium. Moreover, the virus also transmits via close contact, including during sexual affairs. Therefore, this population should be warned to monitor for compatible symptoms. Nevertheless, it is important not to direct stigmas toward these people during this process (Mahase, 2022a, 2022b).

Another important issue is the mode of transmission. Human-to-human transmission usually occurs through exposure to body fluids, wounds, or respiratory particles of wild animals or infected patients, and sometimes infectious fomites (Walker, 2022). Patients are contagious from the beginning of the prodromal phase to the desquamation phase. However, the most significant phase would be the prodromal phase which might last up to 3 weeks without any cutaneous eruption, and the infected patient may unwantedly transmit the virus to several people during this prolonged prodromal period (Erez et al., 2019; Reynolds et al., 2006). It has been acknowledged in many articles and news that droplets are the main respiratory route of spread; therefore, it is emphasized that prolonged face-to-face contact is necessary for disease spread. However, some authorities and the literature point out the airborne route as a possible transmission route. Thus, considering appropriate precautions and isolation measures is vital (Brown & Leggat, 2016; Fleischauer et al., 2005; B. W. Petersen, Karem, & Damon, 2014).

Clinical manifestation

The period between being infected and the onset of manifestations ranges from 5 to 21 days. Then, mucocutaneous lesions arise after a short prodrome of fever, headache, myalgia, malaise, lymphadenopathy,

and sometimes cough, nasal congestion, and sore throat. Initially, enanthems appear in the oropharynx, and then skin eruptions become evident, beginning with macular lesions, evolving to papular, vesicular, and pustular (usually umbilicated) and ultimately crusted lesions within 3-4 weeks. Skin eruptions are usually well-circumscribed and might be generalized or localized, discrete or confluent. Lesions have a centrifugal distribution, beginning on the face and extremities and then involving the genitalia and the trunk. Unlike many infections with cutaneous involvement, monkeypox is among the rare ones that involve palms and soles. Each evolutional cutaneous phase takes 2-3 days to transform to the subsequent phase, except the pustular phase, which lasts 5-7 days before switching to scabs. The desquamation phase continues for about 1-2 weeks, and the total duration of eruptions is estimated to be 3-4 weeks. In brief, after an incubation period of 5-21 days, a 1-4-day febrile stage occurs, followed by the rash stage of 2-4 weeks duration, and lastly, the recovery takes days to weeks (Breman, 2000; D. Ogoina et al., 2020; Parker, Nuara, Buller, & Schultz, 2007; Weinstein, Nalca, Rimoin, Bavari, & Whitehouse, 2005). A summary of the clinical presentations of this infection is illustrated in Figure 1.

Differential diagnosis

The vesicular phase of monkeypox infection can readily be diagnosed as few infectious diseases manifest with vesiculopustular lesions. However, clinical diagnosis is more challenging in the early macule and papule phases. Monkeypox infection's most important differential diagnoses include smallpox, chickenpox, generalized vaccinia, disseminated zoster, disseminated herpes simplex, and eczema herpeticum. Nonetheless, syphilis, scabies, measles, and drug eruption should also be considered. The main distinguishing feature of monkeypox from smallpox includes the presence of lymphadenopathy in the former. Moreover, symptoms of monkeypox are milder than those of smallpox. However, the incubation and prodromal periods and the total length of the disease are of the same duration in both infections. In addition, the distribution pattern of skin lesions is centrifugal, and eruptions are homogenous in both conditions (Weinstein et al., 2005).

The common characteristics of both chickenpox and monkeypox include their airborne transmission and vesicle formation. However, chickenpox is well-known for its eruptions in various developmental stages (macules, papules, vesicles, and crusts) simultaneously, while monkeypox lesions change synchronously. Cutaneous eruptions of chickenpox are soft and superficial with irregular borders, while those of monkeypox are firm, deep-seated, well-circumscribed, and umbilicated. Every cutaneous eruptions stage of monkeypox takes 1-2 days, or even 5-7 days for the pustular phase, while rashes of chickenpox rapidly evolve from macules to crusts within one day. Therefore, the total duration of skin lesions is much longer in monkeypox than in chickenpox. Chickenpox is contagious until the last skin lesions become crusted, for a maximum of 3 weeks, while monkeypox might be transmittable for weeks or even months. Also, the incubation period of monkeypox is much longer than that of chickenpox, so the index patient can infect much more individuals before being identified as infected. Other distinguishing features of monkeypox from varicella include prodromal high-grade fever and the presence of lymphadenopathy in monkeypox.

Furthermore, palms and soles involvement is more common in monkeypox infection than chickenpox. Apart from the clinical differentiating criteria, epidemiological patterns can also help us distinguish the two infections; monkeypox is a zoonosis and has an animal reservoir with animal-to-human and human-to-human transmission capability, while chickenpox has only a human reservoir and is only spread among humans. In addition, the secondary attack rate is much higher for chickenpox than for monkeypox. Varicella predominantly involves younger pediatrics, while monkeypox is more common in adulthood (Macneil, Reynolds, Braden, et al., 2009; MacNeil, Reynolds, Carroll, et al., 2009; Seguin & Stoner Halpern, 2004; Wardiana, Rahmadewi, & Sawitri, 2021). Those with herpes and chancroid can mistake Monkeypox genital sores (D. Ogoina et al., 2020), and generalized eruption and palms and soles are mostly misdiagnosed as secondary syphilis or involvement rickettsia infections (Tabasi, 2018). It is important to consider that monkeypox co-infection with other pathogens is also likely, as reported for varicella, human immunodeficiency virus (HIV), or SARS-CoV-2 co-infections (Bhunu, Mushayabasa, & Hyman, 2012; Echekwube, Mbaave, Abidakun, Utoo, & Swende, 2020; Hoff et al., 2017; C. M. Hughes et al., 2021; Uwishema et al., 2021).

Diagnosis

Monkeypox infection should be suspected in any individual with compatible presentations, including fever, skin eruptions, new lymphadenopathy, perianal or genital lesions, and compatible epidemiology, including a recent travel history to endemic areas, exposure to wild animals, or contact with an infected animal or human. MSMs should be of particular attention as having a significant risk factor for this infection. Diagnostic assays should be done to detect and contain the infection early in any suspected case. Different diagnostic tests can diagnose different phases of monkeypox infection. Nasopharyngeal or oropharyngeal swab samples are the best ones for diagnosis in the febrile phase, while the infection can be best diagnosed by examining eruptions (fluid or crust) during the rash period. Both samples, best to be dry, can be sent for viral culture.

Nevertheless, molecular tests such as PCR are readily available and more rapid in giving the results (Damon, 2011). Serologic tests for antibody detection, if conclusive, only help in the near-to-recovery period and are merely used for epidemiological and research purposes. Anti-orthopoxvirus IgM indicates recent exposure, while its IgG counterpart is suggestive of prior exposure or vaccination. The radioimmunoassay absorption (RIAA) test is the gold standard serologic diagnostic test for monkeypox (Karem et al., 2005). Other diagnostic tests, including visualization on electron microscopy, and immunohistochemical staining, might rarely be utilized (Bayer-Garner, 2005).

Treatment

Since there has been no proven therapeutic for treating monkeypox, supportive and symptomatic therapy is the basis of management like many other viral infections (Durski et al., 2018). The US utilized antivirals, the smallpox vaccine, and vaccinia immune globulin (VIG) in the previous epidemics to control the outbreak. Since monkeypox virus and vaccinia virus are genetically related, medications effective on smallpox might also be beneficial in managing monkeypox. Antivirals suggested to defend against monkeypox include brincidofovir and tecovirimat (Jabeen & Umbreen, 2017).

Brincidofovir (CMX001), a lipophilic conjugate of cidofovir with less toxicity, is an oral DNA polymerase inhibitor with anti-poxvirus activity (Hutson et al., 2021). Tecovirimat (ST-246), an oral intracellular viral release inhibitor, is another antiviral agent with potential therapeutic effects on monkeypox (Berhanu et al., 2015). VIG is also proposed to treat monkeypox complications as it had been used for such circumstances in the smallpox outbreaks. Moreover, it can be considered a post-exposure prophylactic agent in exposed immunocompromised individuals who are contraindicated to receiving the smallpox vaccine as a post-exposure preventive measure (Baker, Bray, & Huggins, 2003; Sejvar et al., 2004; Xiao & Isaacs, 2010).

Complications and prognosis

Monkeypox infection usually lasts for 2-4 weeks. The severity of infection varies considerably. Nevertheless, complications may intervene, such as bacterial skin superinfection, skin discoloration or scarring, sepsis, and encephalitis (Kabuga & El Zowalaty, 2019). Despite not being lethal, cutaneous scars and the associated stigma may be physically and psychologically annoying, with a case of suicide had been reported in a patient affected by monkeypox in a 2017 outbreak (Dimie Ogoina, Mohammed, Yinka-Ogunleye, & Ihekweazu, 2022). Vision loss resulting from permanent corneal scarring is one of its most severe complications (C. Hughes et al., 2014). Mortality occurs in 1 to 10% of the affected patients, less in the West African and more in Central African clades. Unvaccinated individuals, younger children, and immunocompromised people are more likely to develop fatal infections (Anderson, Frenkel, Homann, & Guffey, 2003; Huhn et al., 2005).

Prevention

Early detection, management, and isolation of the infected individuals would be the main strategy to contain the epidemic. Educating healthcare workers and the public about the potential manifestations of this infection can help in early recognition and prevention of further transmission. All the population, particularly health care workers, media, travel airlines, and stakeholders, should be warned about the importance of reporting suspected cases to health officials (Silenou et al., 2020). The main barrier to restricting further spread among humans is monkeypox's relatively long incubation period, which leads to asymptomatic viral spread. Therefore, contacts of suspected patients should be monitored for developing symptoms (Grant,

Nguyen, & Breban, 2020). Standard preventive measures, including avoiding contact with suspected animals or humans, practicing proper hand hygiene after any potential exposure, and using personal protective equipment (PPE) when close to the patients, are the cornerstone of primary prevention. Due to the airborne transmission as the main spreading route, isolating the patient in a negative pressure room with full PPE is required besides taking standard, contact, and droplet precautions (Angelo, Petersen, Hamer, Schwartz, & Brunette, 2019; Vaughan et al., 2020).

Smallpox's eradication by vaccination turns back to the virus-host, as smallpox had only a human host and was transmitted from human to human. On the other hand, eradicating the monkeypox virus through human vaccination seems to be quite difficult as this virus has several various animal hosts that are hard to control and monitor (Reynolds & Damon, 2012). Nonetheless, vaccination has always been the best and cost-beneficial preventive measure to limit infection, especially for healthcare personnel who are more likely to have occupational exposure. Fortunately, other orthopoxvirus vaccines, such as the smallpox vaccine, have cross-protection against monkeypox. Currently, two live orthopoxvirus vaccines are available from CDC, which had been considered for high-risk occupational exposure: the JYNNEOS and the ACAM2000 vaccines. Although the former has been licensed for smallpox and monkeypox and the latter was intended only for smallpox, both can be utilized to prevent monkeypox (Keckler et al., 2020; B. W. Petersen, 2021).

Recommendations for post-exposure prophylaxis depend upon the exposure risk level. High-risk exposure is defined as 1) contact with damaged skin, mucous membranes, lesions, or body fluids of an infected patient; or 2) exposure to aerosol-generating procedures without PPE. Intermediate-risk exposure is defined as 1) contact with intact skin, lesions, or body fluids of an infected patient; 2) being less than 6 feet close to the patient for more than 3 hours; or 3) taking care of a patient without donning appropriate PPE. Low-risk exposure is defined as taking care of a patient with full PPE. Post-exposure prophylaxis is indicated in high-risk and often intermediate-risk exposures. Individuals with low-risk exposures should only be monitored for signs and symptoms of monkeypox, such as fever, new lymphadenopathy, and new eruptions, until 21 days after the exposure (Agam K Rao et al., 2022). Post-exposure prevention of monkeypox can sometimes be feasible by post-exposure smallpox vaccination, which should be done as soon as possible, ideally within 4 days up to 2 weeks of exposure, to prevent disease onset or decrease disease severity. This strategy can confer up to 85% protection against monkeypox. The only contraindications of smallpox vaccination include allergy to any of the vaccine components and its use in immunocompromised individuals and populations with a high prevalence of HIV infection because of potential complications (Heraud et al., 2006; Russo et al., 2020; Smith et al., 2009).

Conclusion

The spreading of monkeypox across West Africa over the last decade, as well as the current outbreaks in many nations, indicate that it is no longer an uncommon viral zoonotic disease found only in remote areas of Central and West Africa. Its potential for additional regional and worldwide spreading continues to be a major issue. The ecological, zoonotic, epidemiologic, clinical, and public health aspects of monkeypox are still poorly understood. The cessation of the smallpox vaccination program has produced an ecological gap in which an increasing proportion of the population has diminishing or nonexistent protection against the monkeypox virus. A global effort should be undertaken to develop better diagnostic and treatment options for this viral illness to avert new epidemics.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflict of interest disclosure

Terence T. Sio reports that he provides strategic and scientific recommendations as a member of the Advisory Board and speaker for Novocure, Inc. and also as a member of the Advisory Board to Galera Therapeutics, which are not in any way associated with the content or disease site as presented in this manuscript. All other authors have no conflict of interests to be declared.

Author contributions

Zeinab Mohseni Afshar: Conceptualization, Writing - Original Draft; **Hossein Nazari Rostami:** Investigation, Writing - Original Draft; **Rezvan Hosseinzadeh:** Visualization, Writing - Review & Editing; **Alireza Janbakhsh:** Writing - Review & Editing; **Ali Tavakoli Pirzaman** : Investigation, Writing - Original Draft; **Arefeh Babazadeh:** Investigation, Writing - Original Draft; **Zeinab Aryanian:** Investigation, Writing - Original Draft; **Terence T. Sio:** Writing - Review & Editing;**Mohammad Barary:** Investigation, Writing - Original Draft, Writing - Review & Editing; **Soheil Ebrahimpour:**Conceptualization, Writing - Original Draft, Supervision.

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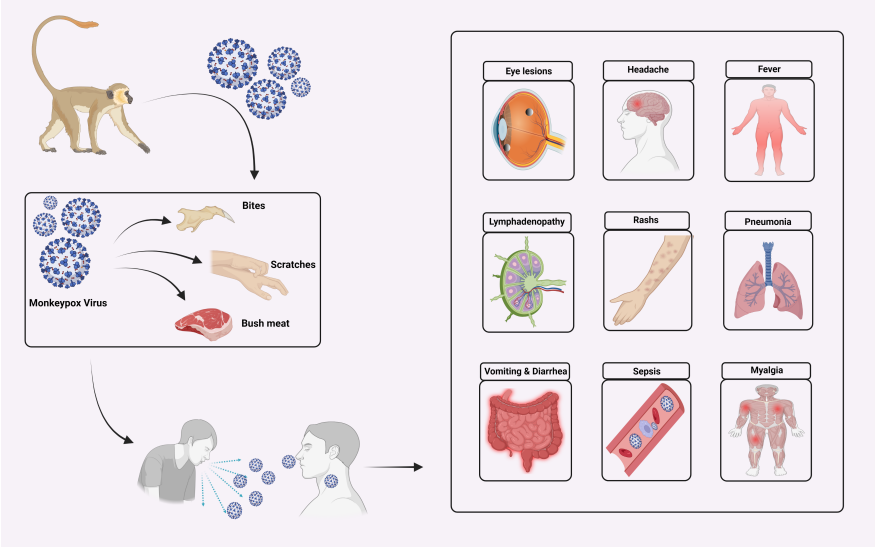
Figure legend

Figure 1. Monkeypox virus transmission and clinical manifestations in humans. The monkeypox virus can be transmitted directly from monkeys to humans. It can also be transmitted to humans through monkey bites or scratches or eating bush meat of infected animals. After transmitting the virus, an infected person can have manifestations, such as skin rashes, myalgia, sepsis, fever, eye lesions, vomiting and diarrhea, headache, lymphadenopathy, or pneumonia.



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