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Monkeypox and Transfusion Safety ☆

Roger Y. Dodd [a,*], Susan L. Stramer [b]

[a] American Red Cross, Holland Laboratory, Rockville, MD, USA
[b] American Red Cross, Scientific Affairs, Gaithersburg, MD, USA

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ABSTRACT

In May of 2022, a multinational outbreak of monkeypox was recognized. It expanded rapidly and over the following three-plus months, more than 50,000 cases were reported from 100 countries, largely among gay or bisexual men. The causative agent is a poxvirus, related to smallpox and vaccinia viruses. Available information implies that the virus might be transfusion-transmissible, although no cases had been reported by late August, 2022. Current data are reviewed, and the potential impacts of transfusion transmission are discussed, along with potential interventions.

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Introduction

Until May of 2022, monkeypox was a disease that attracted relatively little attention and human cases were mostly confined to the African continent. The disease is caused by the monkeypox virus (MPXV), which is transmitted by close contact, body fluids and potentially by contact with fomites. The virus primarily circulates among native rodents, with occasional transmission to humans [1]. It attracted interest in the United States in 2003, when an outbreak occurred through contact with prairie dogs, apparently infected in pet stores by contact with imported, Gambian pouched rats. Otherwise, in 2021 two cases were observed in travelers returning from affected areas. Since May 2022, an unexpected outbreak of monkeypox has been occurring in multiple countries and cases have been increasing rapidly and with generally little evidence of control [2]. MPXV has some characteristics that imply a potential for transmission by transfusion, although no cases had been reported at the time of writing (September, 2022). However, it is appropriate to consider this as a possibility.

Monkeypox

Monkeypox is a disease caused by MPXV, a virus belonging to the Orthopoxvirus genus in the family Poxviridae, which includes variola (smallpox) and vaccinia viruses. It is a large enveloped, double-stranded DNA virus. The virus routinely infects mammals (thought to be mainly rodents) in parts of Africa. Humans can be infected by contact with blood, body fluids, or cutaneous or mucosal lesions from infected animals. Subsequent human-to-human transmission is thought to occur through contact with lesions, skin, contaminated fomites (eg, clothing or linens) or prolonged close contact involving droplet exposure. There are two clades of the virus, currently identified as the central African (Congo Basin) and the West African clades. However, the World Health Organization (WHO) has proposed renaming the variants respectively as Clade I and Clade II. Clade II has two sub-clades, IIa and IIb; the latter designation is assigned to the virus of the 2022 outbreak [3]. Clade II appears to be associated with less severe disease and may be less transmissible than Clade I [1].

In humans, monkeypox disease has an incubation period of 6-13 days and a prodromal phase for about 2 days before the onset of rash with fever, malaise and lymphadenopathy, which occurs in about 90% of cases. The typical rash begins as macropapular lesions of 2-3.5 mm in diameter. The rash spreads in a centrifugal fashion. The skin lesions progress from macules to papules to vesicles followed by scabbing and desquamation over 14-21 days. Lesions may occur on mucous membranes and elsewhere (see below). The patient is thought to be contagious throughout the life of the lesions. The mortality rate has generally been 3%-10%, clade specific, with fatalities much less frequent during the 2022 outbreak (see below).

Treatment and vaccines

At least in the US, there is no approved treatment for monkeypox. However, tecovirimat (Tpoxx) is an antiviral that has been shown to be effective in treating Orthopoxvirus-related disease in animal models and from limited studies, there is some evidence of efficacy against MPXV in humans [4,5]. The drug is available through an expanded access Investigational New Drug program

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* Correspondence to: Roger Y. Dodd, PhD, American Red Cross, Holland Laboratory, 15601 Crabbs Branch Way, Rockville, Maryland 20855, USA.
E-mail address: roger.dodd@redcross.org (R.Y. Dodd).

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managed through the US Centers for Disease Control and Prevention (CDC). Other possible treatments, including the use of vaccinia immune globulin are noted by the CDC, but their efficacy is currently unknown.

There is no specific vaccine for monkeypox, but smallpox (vaccinia) vaccines appear to be effective if used pre-exposure or early after exposure. In the US, 2 such vaccines are available. JYNNEOS is the only vaccinia vaccine that is FDA-approved for the prevention of both monkeypox and smallpox disease. It contains a weakened, non-replicative live variant [Modified Vaccinia Ankara (MVA)] approved by the FDA for pre-and post-exposure prophylaxis in those 18 years or older. Two doses, given 4 weeks apart, are used and there are recommendations for subcutaneous and/or intradermal application. The other available smallpox vaccine, ACAM2000, is a live, replicating virus vaccine and is available for monkeypox prevention only under FDA's Expanded Access Investigational New Drug mechanism. A single dose is given by a multiple puncture technique, using a bifurcated needle. Since it is a live virus vaccine, an appropriate donation deferral period is required post-vaccination if used for pre-exposure prophylaxis (in contrast to JYNNEOS where no deferral period is necessary). ACAM2000 is associated with certain serious adverse reactions. While JYNNEOS is also a live virus vaccine, it is non-replicating; it is the approved and preferred vaccine for monkeypox, at least in part because it is less likely to have adverse effects [4,6].

The 2022 global outbreak

The 2022 outbreak was first reported in May, 2022, emerging essentially simultaneously in a number of countries outside the previously reported range for the disease in Africa and has expanded rapidly. In July, 2022, the WHO declared monkeypox to be a Public Health Emergency of International Concern, and in the United States, it was declared a public health emergency in early August, 2022. The outbreak was unexpected and unusual in a number of its characteristics. Notably, the disease was less severe than historical disease, particularly with respect to fatality rates. The disease appeared to be spreading through sexual networks of gay and bisexual men, likely via skin-to-skin contact, including sexual activities. Unusually, lesions were frequently found in the genital area and, in many cases, resulted in considerable pain. Many of the cases were in those who are HIV positive. MPXV DNA has been detected in the semen of individuals with monkeypox and, in at least one case, the virus was isolated from semen. However, the disease is not yet classified as sexually transmitted [7].

A recent study described key characteristics of 538 confirmed cases from 16 countries in five continents outside the endemic zone. Notably, all of the subjects were male, aged 18-68 (median 38) and 98% were gay or bisexual and 41% had HIV infection. Foreign travel in the month before diagnosis was reported by 28%. Sexual close contact was the likely route of infection among 504 (95.5%) of the 528 subjects, and 4 from non-sexual close contact, 3 from household contact, and 17 from unknown sources. Mucosal lesions were present in 41% of subjects, predominantly anogenital and/or oropharyngeal [8]. These demographic and disease characteristics appear to be stable over time.

By September 2, 2022 CDC reported 53,027 cases, with 15 deaths, from 100 countries of which only 7 had historically reported cases; these 7 countries account for only 511 (<1%) of the reported cases. The greatest number of cases were from the United States (19,962), followed by Spain (6543), France (3558), Germany (3493), and the United Kingdom (3413). (Current data may be found at https://www.cdc.gov/poxvirus/monkeypox/response/2022/index.html.) A report as of July 22, noted that 99% of cases in the US were in men, of whom 94% reported recent male-to-male sexual activity or close intimate contact [9]. In some countries, including the US and the UK, there are data suggesting that the rate of increase in cases may be showing signs of stabilizing potentially as the result of behavioral modification among those at greatest risk [10].

Blood safety

Clearly, an important question is whether the current outbreak of monkeypox impacts transfusion medicine. In order for a disease to be transfusion transmissible, the causative agent must be present in blood, must survive processing procedures, and, to be of concern, must cause detectable disease in the recipient. Further, the infectious agent would have to be present in the donor without detectable disease at the time of donation. Two issues have to be considered: first, whether the disease can be transmitted by transfusion, and second, whether the outbreak interferes with the collection and distribution of blood and its components. Experience with COVID-19 clearly shows that the latter issue may be very important, even in the absence of transfusion transmissibility.

The extent to which MPXV may be transmissible by transfusion is currently unknown and at the time of writing, no case has been reported. However, transmissibility by body fluids and fomites is suggestive, and limited animal studies have shown infectious virus in blood [11,12] making transfusion transmission theoretically possible. A number of studies from human cases have shown that viral DNA may be present in the blood during monkeypox disease. The data suggest that the presence or levels of such DNA are variable. In the small number of individuals followed, DNA was recovered intermittently from plasma in low concentrations after rash onset but for no longer than about 30 days [13]. There have been only very limited efforts to isolate replicative virus from blood and no such isolation has been reported [14]. The virus is thought to spread within the body via the blood and/or lymphatic systems. However, there is no information about circulating virus during the asymptomatic or incubation periods and it appears that the virus is likely transmissible mainly during symptomatic disease, mostly via contact with lesions. At least one report does demonstrate that asymptomatic infection with MPXV has occurred during the current outbreak, but again there is no evidence for or against infectivity from blood; viral DNA recovery occurred via stored samples from oropharyngeal and anorectal swabs [15]. Ideally, some of these open questions will be resolved by appropriate studies.

There are a number of measures that can be taken to reduce or eliminate the risk of transmitting a disease via blood transfusion. While it is relatively easy to describe approaches, it is not easy to decide which, if any, of the available methods should be implemented. This is particularly the case where it is not clear whether an intervention is needed, as decisions should ideally reflect a rational risk-to-benefit ratio.

Donor questioning and appropriate deferral is a logical approach. In the case of monkeypox, presenting donors could be asked about a recent or current history of the disease, and about recent exposure. In the case of active disease, it is appropriate to consider deferral until lesions have fully healed (about 21-28 days) and a similar deferral period might be appropriate for those exposed to infection. However, note that at the current stage of the outbreak, when 98% of cases are associated with gay or bisexual men, such questioning would not be necessary in countries that still use a time-based deferral for men who have had sex with other men (MSM) and their sexual contacts [16,17]. As noted above, deferral may be needed for donors who have received replication-competent vaccines.

Donation testing might be considered, but in the early phase of the outbreak, this approach, even if effective, would be costly, given the relatively small percentage of individuals at risk. Testing

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for nucleic acid by amplification methods is under development, but there is little experience in using such tests on blood samples, as diagnostic testing is usually performed on fluids from the lesions. As noted, the presence of DNA in blood samples appears, at least from the limited studies to date, to be sporadic [13]. Finally, pathogen reduction technology has been shown to be effective in eliminating infectivity and has been validated for vaccinia [18].

Future concerns

An important issue is the extent to which public health programs are able to control the outbreak. It is thought that, until recently, human infection may have been modulated by wide-scale smallpox vaccination – no longer necessary after the elimination of smallpox. Currently there does not appear to be an adequate amount of vaccine even to protect the segment of the population that is most at risk and it is not clear that suggestions for behavioral change will be adequate.

Currently the monkeypox outbreak is spreading rapidly, and at the time of this writing, is largely confined to sexual networks among gay men. This may be perceived as facilitating the management of blood safety, at least in countries such as the US, where there is still a 3 month deferral policy for gay men and their sexual contacts. This is likely a rationale for the current FDA position that further precautions for donor suitability may not be necessary [14]. However, this situation is unlikely to continue, as is clear from prior experience with HIV, although monkeypox does not have the lengthy infectious incubation period of HIV. It should be noted that MPXV is readily transmitted through skin-to-skin contact in the absence of sexual activity, thus potentially extending risk to all. Clearly, planning needs to consider the possibility of widespread transmission beyond gay men and their sexual contacts in the context of public health, including the need for testing, greatly expanded vaccination availability, appropriate treatment and advice for patients and their contacts. The extent to which this will impact blood safety is unclear, as it would depend on issues that are currently unknown. These issues include the extent to which the virus may be transmitted by blood transfusion, which has, in fact, been demonstrated in an animal model [12]. It will also be important to understand whether there is such infectivity during the incubation or prodromal periods and the extent to which asymptomatic infection occurs and whether such infection is also associated with blood-borne infectivity. Clearly, clinicians should also be alert to this possibility among transfused patients. Enhanced communication and collaboration between public health, blood providers and users will be essential to best manage the current level and any expansion of monkeypox.

In contrast to COVID 19, even widespread monkeypox is unlikely to impact the safety of donors and blood collection staff, as the virus does not appear to be readily transmitted without actual skin to skin contact and droplet infection (if it occurs) requiring close proximity and extended contact. Further, those with disease symptoms would not be expected to present to donate, or would be deferred at presentation.

In conclusion, the current outbreak of monkeypox is recognized to be a global health problem and the trajectory of the outbreak is alarming. The likelihood of spread outside the current high-risk population is likely, although currently with a lower rate of transmission and disease severity as compared to previous outbreaks. As of September 2022, there is no definitive evidence of transmission of the virus by blood transfusion, but the potential for that outcome cannot be ignored. Unfortunately, it will be difficult to establish optimal interventions in the absence of more information about pathology and epidemiology of the disease.

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