

# Monkeypoxvirus infections

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## Summary

During and after the smallpox eradication campaign, human cases of monkeypox appeared in West and Central Africa, as isolated cases or as small epidemics. Since inter-human transmission has never or only very exceptionally been documented, monkeypox does not represent a serious threat to humans. The virus reservoir is among tree squirrels living in the tropical rain forests of Africa and humans are infected by hunting, killing and skinning these animals. However, the modernisation of society lessens human contact with the virus reservoir. Since the eradication of smallpox, stocks of variola virus have been maintained; whether these stocks should now be destroyed is a political question, which is seriously compromised by mistrust between countries.

## Keywords

Monkeypox – Orthopoxviruses – Public health – Smallpox – Variola – Virus reservoirs – Virus stocks – Zoonoses.

## Introduction

The principal interest of monkeypox, besides the ecology of the virus, which remained an enigma for many years, lies in the relation of the disease with human smallpox and smallpox eradication.

After the last case of smallpox had been documented on 26 October 1977 in Somalia, the Global Commission for the Certification of Smallpox Eradication certified global eradication in 1980 and advised the discontinuation of smallpox vaccination. This encountered a great deal of scepticism and even disbelief in medical circles. Many people found it difficult to admit that a dreadful disease, present since time immemorial, had been eradicated, especially since the last cases had been notified in regions which were difficult to access and were not devoid of political turmoil. Moreover, many feared that smallpox eradication and the absence of smallpox vaccination would create a form of immunological void, ready to be occupied by any new threat, as though a biological rule existed that mankind should be plagued by dreadful infections. In this view, monkeypoxvirus, which had caused sporadic human infections in Africa since 1970, was the main suspect. The virus was seen as potentially still more dangerous when, in the Netherlands and in the Union of Socialist Soviet Republics, viruses indistinguishable from smallpox were obtained through manipulations of monkeypoxvirus in the laboratory (11). However, the latter

threat was removed relatively rapidly when these monkeypox-derived smallpox strains were shown to be laboratory contaminations.

Careful epidemiological studies conducted between 1970 and 1986 confirmed the 1979 thesis of the Global Commission for the Certification of Smallpox Eradication that monkeypox did not constitute a new threat for humans. With the hindsight of another twenty years, this thesis has been amply confirmed, although as late as 1996-1997, monkeypox was active once again. In the meantime, the virus reservoir of monkeypox was discovered, and knowledge concerning the virus has broadened, confirming beyond doubt that monkeypox is not an emerging disease.

## Importance for animal and public health

Monkeypox occurs sporadically among monkeys and non-human primates in captivity in Europe and North America. The virus gives rise to a benign eruption, and is more a nuisance than a disease. Humans may also be infected sporadically, mainly in Central Africa, from the reservoir in the wild. With the increasing urbanisation of the human population and the decline of traditional ways of life, monkeypox is probably a disappearing disease. However, political unrest in the tropical rain forests of Africa may create

conditions favourable for an outbreak of the disease, as was the case in 1996 and 1997.

## Aetiological agent: classification and characterisation

Poxviruses are the largest vertebrate viruses known. The virions contain a linear double-stranded deoxyribonucleic acid (DNA) genome and enzymes that synthesise messenger ribonucleic acid (RNA). The viruses multiply in the cytoplasm of the host cells. The poxvirus family consists of two subfamilies, namely: the *Chordopoxvirinae* and the *Entomopoxvirinae*, with the *Chordopoxvirinae* consisting of eight genera. Members of a genus are genetically and antigenetically related. The genus *Orthopoxvirus* comprises camelpox, cowpox, ectromelia, monkeypox, racoonpox, skunkpox, taterapox, Uasin Gishu, vaccinia, variola and volepox. African swine fever viruses share some properties of the poxviruses. Many poxviruses are associated with a specific vertebrate species, which indicates that the transmission of these viruses occurs preferentially among one particular vertebrate species. Accidental transmission to another vertebrate species can occur, but without production of the necessary clinico-pathological conditions to be maintained in this 'aberrant' species (7).

The orthopoxviruses able to infect humans are variola, vaccinia, cowpox and monkeypox. Variola virus is a virus which only infects humans; two remaining virus stocks are maintained: one in the United States of America (USA) and the other in the Russian Federation. Vaccinia virus, the smallpox vaccine virus, does not exist in nature, the virus originated in the 18th Century from an unknown vertebrate species. Cowpox is a rodent virus that may infect cats, cows and zoo animals and through these, humans. Monkeypox is also a rodent virus, and occurs only in West and Central Africa.

The identification of monkeypoxvirus is based on biological characteristics and endonuclease patterns of viral DNA. In contrast to smallpox, monkeypoxvirus can infect rabbit skin and can be transmitted serially by intracerebral inoculation of mice. The four orthopoxviruses that may infect man produce macroscopically characteristic lesions on the inoculated chorioallantoic membrane of an embryonated chicken egg (4, 11). The maximum, or 'ceiling' temperature at which the viruses can proliferate in the chorioallantoic membrane differs for monkeypox and smallpox. These viruses differ also in the ability to multiply in different tissue culture cells. However, at present the clearest results are obtained by the endonuclease restriction patterns of the virus DNA (6). Some genetic variation has been found between monkeypoxviruses from West and Central Africa. On the basis of genome studies, there is also strong evidence that monkeypox is not ancestral to variola virus. This may be important in view of the fear

expressed by some that variola might evolve from monkeypox. In the pre-molecular era, great efforts were made to distinguish the four viruses by serological reactions. These were delicate studies since the viruses share most antigens (8). Some results were obtained through the use of absorbed sera in agar gel diffusion tests, but these were rapidly superseded by the study of the biological characteristics and DNA restriction patterns, the latter being used exclusively at present. The development of relatively specific antigens has been extremely useful for serological surveys in man and animals.

In the field, rapid presumptive diagnosis of orthopoxvirus infection is necessary, as is differentiation from chickenpox, as confusion is possible on clinical grounds. For this purpose, scabs of the lesions are sent, without transport medium, to the diagnostic laboratory. Electron microscopic examination of this material allows the differentiation of orthopox- and herpesviruses. The poxviruses can be detected in more than 95% of the scabs, whereas varicella-zoster virus is detected in only half of the material from cases of chickenpox, meaning that electron microscopy negative specimens are very unlikely to be monkeypox (11).

## Epidemiology

Monkeypox was discovered in a monkey in Copenhagen Zoo in 1959 (14), and was later observed sporadically in captive primate colonies in the industrialised world. In 1970, the first cases of human monkeypox were diagnosed in Central and West Africa, in areas where cases of smallpox had not been reported for over a year as a result of the smallpox eradication campaign. The reaction was fear that monkeypox would replace smallpox. Smallpox eradication surveillance was maintained in Zaire (formerly the Congo) until 1976. Detailed epidemiological studies were performed between 1976 and 1986 on 300 of the 400 documented cases of human monkeypox. All cases occurred in remote villages in the tropical rain forest, where children trap small rodents and have contact with carcasses of monkeys brought home by hunters. In Zaire, 72% of the cases were primary cases (i.e. possibly infected through contact with small rodents or monkeys), or were co-primary cases (i.e. infected at the same time by the same source). Only 28% were suspected to have been secondary cases, contracted through person-to-person contact. A small number of third, fourth and fifth generation cases were documented, but the incidence diminished at each generation.

Serological surveys were carried out in Zaire (formerly the Congo) on people without a vaccination scar. Among 50,000 people spread over 400 localities in the region of Kole, only 15% of the population did not have a vaccination scar. An annual crude incidence rate of human monkeypox of 0.63/10,000 population was inferred. Those at high risk were young unvaccinated children (especially boys) and adult

women. Approximately one third of the infections were estimated to be sub-clinical. Vaccination provided 85% protection. Since vaccination ceased in 1980, the proportion of unvaccinated individuals in the population was increasing. Nevertheless, calculations and computer simulations showed that since the basic case reproduction rate of monkeypox in human populations was below one, the virus could not persist in humans (1). All outbreaks would be self-limiting, even in the absence of special sanitary interventions. Between 1987 and 1992, thirteen cases of human monkeypox were documented; no case was reported between 1990 and 1995. In 1996, monkeypox became active once again. Between February 1996 and October 1997, 419 cases were reported from the Katako Kombe and Lodja zones in the Sankuru region of the Democratic Republic of the Congo (5). An epidemiological investigation revealed 301 probable, and 115 possible cases. The patients were mainly 4 to 8 years old and presented a moderate rash. The fatality rate of 1.5% compared favourably to that recorded in the 1980s (10%). The secondary outbreak rate was 8%, similar to that reported in the 1980s. The increase in cases was ascribed to the effect of the civil war which had led to increased hunting for forest animals that carry monkeypox, particularly squirrels. By the end of 1997, the number of cases of monkeypox had diminished rapidly. Vaccinia vaccination was not considered because of the possible high prevalence of human immunodeficiency virus (HIV) infection in the population. The control measures recommended were to limit contact with patients to those who had been vaccinated against smallpox in the past, or who had been affected by monkeypox, and to avoid handling dead or diseased animals.

With changes in lifestyle due to increasing urbanisation, and intensified agricultural activities replacing hunting and trapping, the chances of contracting monkeypox, either from the primary reservoir or intermediate hosts, will decrease and monkeypox will become a disappearing disease.

## Biology

The search for the virus reservoir of monkeypox was conducted in different stages. Initially, serum surveys were performed among primates in West and Central Africa, revealing prevalence of antibodies in monkeys (9). However, since all monkeys live in small troops and no evidence exists for either persistent infections or transmission by flying arthropods, it was unlikely that this kind of population could constitute the virus reservoir. The reservoir was most likely to be found among animals with high population numbers and rapid turnover rates. These factors led to the production of immunologically naïve subjects on a regular basis, thereby enabling enzootic transmission. Monkeypox-specific antibodies were found in monkey and squirrel sera. Hundreds of kidneys and spleens from animals were screened for the presence of monkeypoxvirus without success. Finally, a diseased squirrel, *Funisciurus anerythrus*, was found showing

superficial skin lesions, and virus was isolated from its organs. More directed serum surveys revealed monkeypox antibodies in two species, *F. anerythrus* and *F. rufobrachium* and, in addition, in some species of *Heliosciurus*. The present understanding of the ecology of monkeypoxvirus is that the reservoir of the virus is in arboreal squirrels, *Funisciurus* spp. and, to a lesser degree, *Heliosciurus* spp., living in the secondary forest surrounding human settlements and fields. These animals may infect humans directly or occasionally through monkeys. Contact with wild animals through trapping, hunting, skinning and manipulation of carcasses may transmit the virus to humans.

## Pathogenesis

Transmission of smallpox is aerogenic, whereas transmission of the other orthopoxviruses that can infect man is through the skin (3). Monkeypox is therefore also likely to be transmitted through the skin, through handling of infected animals. The virus is thought to multiply locally in the abraded skin, and to be rapidly transported to the regional lymph node where it multiplies and then invades the bloodstream to localise in the skin, producing the characteristic nodules, papules and pustules.

## Diagnosis and surveillance

The skin lesions caused by human monkeypox are indistinguishable from variola, except for a greater enlargement of the lymph nodes. No haemorrhagic type of monkeypox disease has ever been reported, and mortality is extremely low.

The geographic location of the patient is important in the diagnosis of monkeypox, as the disease usually occurs in remote villages in the tropical African rain forests. Differentiation from chickenpox is important; the latter appears in successive crops so that lesions at various stages of development are visible at any time. In contrast with smallpox, the distribution of chickenpox is 'centripetal' with more lesions on the trunk than on the face and extremities. For definitive diagnosis, scabs can be forwarded to a reference laboratory where electron microscopy may confirm the presence of an orthopoxvirus and differentiate this virus from varicella virus. The virus can be cultured in tissue culture and identified by DNA restriction analysis.

## Prophylaxis and treatment

As human monkeypox is a rare disease, with a vanishing incidence, no benefit would be derived from vaccination with vaccinia. Furthermore, smallpox vaccination cannot be undertaken in populations with high prevalence of HIV infection because of the risk of serious complications.

Antiviral chemotherapeutic treatment is not a viable option in those remote places where the disease is likely to appear. The treatment would have to be administered in the very early stages of the disease and it is unlikely that the treatment could be made available in time. In addition, the treatment is not devoid of side effects.

## Destruction of variola virus stocks

When smallpox eradication was certified in 1980, the Global Commission for the Certification of Smallpox Eradication proposed that all laboratory-maintained smallpoxvirus stocks be destroyed to achieve deliberate world-wide elimination of a biological species. The World Health Organization (WHO) made repeated efforts in the same direction (in December 1990, September 1994 and January 1999). At present, two virus stocks subsist, one at the Centers for Disease Control in Atlanta, USA, and the other at the Russian State Research Centre of Virology and Biotechnology in Koltsovo, Novosibirsk Region, Russian Federation. The complete destruction was originally scheduled for 1993, after the genome had been completely sequenced in 1991, but did not take place. In September 1994, the date was set at 30 June 1995, but destruction was again postponed. In 1996, the World Health Assembly adopted a resolution recommending smallpoxvirus destruction on 30 June 1999. The period from 1996 to 1999 was to be used to achieve a broader consensus. In 1998, the WHO Secretariat conducted a survey on the position of 191 member states. Seventy-nine responded, seventy-four were in favour, one was against and four (the United Kingdom, France, Italy and the USA) were undecided (2, 10, 12, 13, 15).

In January 1999, the Ad Hoc Committee members were not unanimous: five were in favour of destruction, two thought destruction might be possible after a review five years later and two were in favour of retention for scientific reasons, although the other members expressed greater concern at the risk of the virus being released. The following proposals were also made:

- a) gamma-irradiated killed variola virus should be kept for use as an essential antigen in diagnostic tests;
- b) amplification of variola virus DNA by polymerase chain reaction, followed by expression in other orthopoxvirus vectors, should be prohibited in addition to chemical synthesis of viable virus DNA;
- c) work should be accepted in only two laboratories;
- d) the WHO should appoint a new group to establish the type of research, if any, to be carried out in order to reach a global consensus on the timing of the destruction of viable virus stocks.

## Arguments for and against destruction

### Pro destruction

The arguments in favour of destruction of smallpoxvirus stocks include the following:

- to eliminate the most devastating of human pathogens
- to prevent accidental release and use by terrorists
- the virus is too dangerous to be allowed to live
- the study of a virus of a disease that no longer exists is pointless
- the genome has now been sequenced and cloned
- no research was performed using the virus during the last fifteen years (the virus has been grown only twice, to make more copies for sequencing studies)
- some information will be lost by destroying the virus, but the value of such information is unknown
- the biosecurity level 4 (BL4) facilities necessary for the handling of variola virus are limited and should be used for more realistic priorities
- emergency development of new drugs or a novel vaccine in response to the unexpected reintroduction of the virus into the community is unrealistic
- a supply of between 60 and 70 million doses of vaccine is available (this has to be properly stored and tested regularly for potency)
- it is hoped that other infectious agents will be eradicated in the not too distant future (this leads to the question of whether these agents should also be maintained; examples are poliovirus and *Dracunculus medinensis*, the latter can only be maintained as a living parasite in humans).

### Pro maintenance

Maintenance of the variola virus stock is supported by the following arguments:

- the virus is indispensable for the development of new antiviral medicines and novel vaccines to protect the population in the event of accidental or terrorist release of virus
- officials of the Russian Federation claim that valuable research remains to be performed (without any specifications)
- there is pressure from the Defence Department in the USA
- it is impossible to anticipate the questions which may be posed about the virus in the next ten to twenty years, in areas such as human immunology
- the unique specificity of smallpox is justification for preservation of the virus
- the virulence segment of the genome has not been identified
- destruction is pointless since the virus can be synthesised
- use by terrorists is unlikely and vaccine remains available

- destruction is illusory because the virus may subsist in cadavers in permafrost
- a wealth of scientific information is to be gleaned from the live virus concerning virulence, pathogenic mechanisms and potential for screening drugs.

### Conclusion on destruction

Although from a purely biological point of view, destruction of the remaining smallpoxvirus would indeed signify some loss of biological diversity, the scientific reasons for non-destruction are not very pertinent. The main reason for

not destroying the smallpoxvirus stocks is the profound political mistrust between certain countries. If this distrust could be removed, the only remaining question would be whether the cost of keeping the virus in a single high-security environment, with strict rules for its use, would outweigh the utility of the virus.

## Infections dues au virus de la variole du singe

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### Résumé

Au cours de la campagne d'éradication de la variole et dans la période qui suivit, des cas humains de variole du singe sont apparus en Afrique de l'Ouest et en Afrique centrale, sous forme de foyers isolés ou de petites épidémies. Comme la transmission interhumaine n'a été observée que très exceptionnellement, la variole du singe ne représente pas une menace sérieuse pour l'homme. Le réservoir du virus est un écureuil arboricole, qui vit dans les forêts ombrophiles tropicales d'Afrique. C'est en chassant, tuant et dépouillant cet animal que l'homme contracte l'infection. Cependant, avec la modernisation de la société, les contacts avec ce réservoir du virus seront moins fréquents. Depuis l'éradication de la variole, des stocks de virus de la variole ont été conservés. La question de savoir s'ils doivent être détruits relève d'une décision politique, sérieusement compromise par la méfiance qui règne entre les pays.

### Mots-clés

Orthopoxvirus – Réservoirs du virus – Santé publique – Stocks de virus – Variole – Variole du singe – Virus de la variole – Zoonoses.

## Infecciones por monkeypoxvirus

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### Resumen

Durante la campaña de erradicación de la viruela, y también después de ella, se declararon en el África Central y Occidental casos aislados o pequeñas epidemias de viruela símica (*monkeypox*) en el ser humano. Considerando que nunca o muy rara vez se ha documentado la transmisión de esta enfermedad de un ser humano a otro, cabe decir que la viruela de los monos no representa una grave amenaza para el hombre. Las ardillas arbóreas de la pluviselva tropical africana constituyen el reservorio natural del virus, y el ser humano se infecta al cazarlas, sacrificarlas y despellejarlas. No obstante, la modernización de la sociedad está reduciendo el contacto del hombre con este reservorio. Aunque la

viruela ha quedado definitivamente erradicada del medio natural, se conservan en laboratorio muestras del virus variólico. La decisión de destruir o no esa reserva es una cuestión política, cuya resolución se ve comprometida por la desconfianza existente entre países.

**Palabras clave**

Orthopoxvirus – Reservas de virus – Reservorios víricos – Salud pública – Viruela – Viruela símica – Zoonosis.

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