Official journal of the Spanish Society of Chemotherapy

ISSN: 0214-3429 / ©The Author 2022. Published by Sociedad Española de Quimioterapia. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0)(https://creativecommons.org/licenses/by-nc/4.0/).

Review

Revista Española de Quimioterapia
doi:10.37201/req/059.2022

Monkeypox in humans: a new outbreak

Mari Cruz Martín-Delgado[1]
Francisco Javier Martín Sánchez[2]
Manuel Martínez-Sellés[3]
José María Molero García[4]
Santiago Moreno Guillén[5]
Fernando Rodríguez-Artalejo[6]
Julián Ruiz-Galiana[7]
Rafael Cantón[8]
Pilar De Lucas Ramos[9]
Alejandra García-Botella[10]
Alberto García-Lledó[11]
Teresa Hernández-Sampelayo[12]
Javier Gómez-Pavón[13]
Juan González del Castillo[14]
Patricia Muñoz[15]
Maricela Valerio[15]
Pilar Catalán[15]
Almudena Burillo[15]
Alejandro Cobo[15]
Antonio Alcamí[16]
Emilio Bouza[17]

[1]Intensive Medicine Service. Torrejón University Hospital. Francisco de Vitoria University. Madrid.
[2]Geriatrics Service. San Carlos University Clinical Hospital. Complutense University. Madrid
[3]Cardiology Service. Gregorio Marañón General University Hospital, European University. Madrid.
[4]Family Medicine. Infectious diseases. Madrid.
[5]Infectious Diseases Service. Ramón y Cajal Hospital. University of Alcalá de Henares. Madrid.
[6]Department of Public Health. Autonomous University. Madrid
[7]Internal Medicine Service. Ruber International Hospital. Madrid.
[8]Microbiology Service. Ramón y Cajal Hospital and Ramón y Cajal Institute for Health Research (IRYCIS). Spanish Network for Research in Infectious Pathology (REIPI). Madrid.
[9]Emeritus. Pneumology Service. Gregorio Marañón General University Hospital, Complutense University. Madrid
[10]General Surgery Service. San Carlos University Clinical Hospital. Complutense University. Madrid.
[11]Cardiology Service. Prince of Asturias Hospital. University of Alcalá. Madrid.
[12]Pediatrics and ACES Service. Gregorio Marañón General University Hospital, Complutense University. Madrid.
[13]Geriatrics Service. Central Hospital of the Red-Cross. Alfonso X el Sabio University. Madrid
[14]Emergency Service. San Carlos University Clinical Hospital. Complutense University. Madrid.
[15]Clinical Microbiology and Infectious Diseases Service of the Gregorio Marañón General University Hospital, Complutense University. CIBERES. Cyber of Respiratory Diseases. Madrid.
[16]Center for Molecular Biology Severo Ochoa. Consejo Superior de Investigaciones Científicas. Madrid.
[17]Clinical Emeritus, Community of Madrid. Clinical Microbiology and Infectious Diseases Service of the Gregorio Marañón General University Hospital, Complutense University. CIBERES. Cyber of Respiratory Diseases. Madrid.

Article history
Received: 27 June 2022; Accepted: 1 July 2022; Published: 6 July2022

ABSTRACT

Infection caused by Monkeypox Virus (MPVX) has small rodents as its natural reservoir and both monkeys and humans are occasional hosts. The causative agent is an Orthopoxvirus (MPVX) that was isolated in monkeys in 1958 and proved capable of passing to humans in 1970. It remained contained in Africa, causing isolated episodes of infection, until 2003 when an outbreak occurred in the United States following importation of animals from that continent. Since then, anecdotal cases have continued to be reported outside Africa, usually very clearly linked to travelers to those countries, but in May 2022, a broad outbreak of this disease has begun, now affecting several continents, with the emergence of human cases of MPVX (H-MPVX) infection mainly among Men that have Sex with Men (MSM). The disease has an incubation time ranging from 5 to 15 days and is characterized by the presence of pustules, fever, malaise and headache. The presence of significant regional lymphadenopathy is a differential feature with episodes of classical smallpox. Proctitis and pharyngitis, with minimal skin lesions, may be another form of presentation. Diagnosis can be confirmed by PCR testing of lesions or by demonstration of MPVX in other body fluids or tissues, although in the appropriate epidemiologic setting the clinical picture is highly suggestive of the disease. Effective drug treatment has been developed as part of programs to protect against potential bioterrorist agents and smallpox vaccinees are known to have high protection against monkeypox. New vaccines are available, but neither the drugs nor the vaccines are yet freely available on the market. The prognosis of the disease appears, at least in adults in developed countries, to be good, with very low mortality figures and much less aggressive behavior than that described in classical smallpox. Isolation measures, essential for the control of the outbreak, have been published by the health authorities.

Keywords: Monkeypox, MPVX, Poxvirus, outbreaks, vaccines, smallpox, outbreak, sexually transmitted infections

Monkeypox (Viruela del mono) en humanos: un nuevo brote

RESUMEN

La infección causada por el Virus de la Viruela del Mono o Monkeypox (MPVX) tiene como reservorio natural los pequeños roedores y tanto el mono como el hombre son huéspedes ocasionales. El agente causal es un Orthopoxvirus (MPVX) que fue aislado en monos en 1958 y se demostró capaz de pasar a humanos en 1970. Se mantuvo contenido en África, causando episodios aislados de infección, hasta el año 2003 en que se produjo un brote en los Estados Unidos tras la importación de animales desde dicho continente. Desde entonces, han seguido

Correspondence:
Emilio Bouza Servicio de Microbiología Clínica y Enfermedades Infecciosas del Hospital General Universitario Gregorio Marañón, Universidad Complutense. CIBERES. Ciber de Enfermedades Respiratorias. Madrid
E-mail: emilio.bouza@gmail.com

All authors belong to the Scientific Committee on COVID-19 of the Madrid College of Physicians (ICOMEM) and Emerging Pathogens

comunicándose casos fuera de África, por lo general muy claramente vinculados a viajeros a dichos países, pero en mayo de 2022 se ha iniciado un brote amplio de esta enfermedad que afecta ya a varios continentes, con la aparición de casos humanos de infección por MPVX (H-MPVX) principalmente vinculados a fiestas en las que hay relaciones sexuales de hombres con hombres (HSH). La enfermedad tiene un tiempo de incubación que puede oscilar entre 5 y 15 días y se caracteriza por la presencia de pústulas, fiebre, malestar general y cefalea. La presencia de importantes adenopatías regionales es una característica diferencial con los episodios de viruela clásica. La proctitis y la faringitis, con mínimas lesiones cutáneas, pueden ser otras formas de presentación. El diagnóstico puede confirmarse con una prueba de PCR en las lesiones o con la demostración de MPVX en otros fluidos o tejidos corporales, aunque en el contexto epidemiológico oportuno el cuadro clínico es altamente sugerente de la enfermedad. Hay tratamiento medicamentoso eficaz que ha sido desarrollado como parte de los programas de protección frente a potenciales agentes bioterroristas y se sabe que los vacunados de viruela tienen una protección elevada frente a H-MPVX. Se dispone de nuevas vacunas, pero ni los medicamentos ni las vacunas están todavía libremente disponibles en el mercado. El pronóstico de la enfermedad parece bueno, al menos en países desarrollados y en adultos, con cifras de mortalidad muy bajas y un comportamiento mucho menos agresivo que el descrito en la viruela clásica. Las medidas de aislamiento, imprescindibles para el control del brote, han sido publicadas por las autoridades sanitarias

Palabras clave: Monkeypox, MPVX, Viruela del mono, Poxvirus, brotes, vacunas, viruela

INTRODUCTION

Monkeypox (MP) is a zoonotic viral infection (transmitted to humans from animals) caused by a member of the genus Orthopoxvirus of the family Poxviridae.

Monkeypox virus (MPVX) was discovered in a Danish laboratory in 1958 [1] when it was identified as the causative agent of a disease in Cynomolgus monkeys similar to human smallpox.

Initially, man was considered to have little susceptibility to this new virus [2], but in 1970 its zoonotic nature was demonstrated by its confirmed transmission to a 9-month-old child (Human Monkeypox) in the Democratic Republic of Congo [3].

The disease in humans has remained endemic in Central African countries [4-9] and, outside Africa, a multistate outbreak of cases occurred in the United States of America [10] in 2003, among people who had contact with imported animals.

The disease has just jumped into the media with an outbreak in humans residing outside Africa starting in May 2022, with more than 3.000 cases reported from more than 50 countries in the first month after the beginning of the outbreak. The outbreak is, at present, linked primarily, but not exclusively, to groups of men who have sex with men (MSM).

The COVID and Transmissible Pathogens Committee of the Illustrious College of Physicians of Madrid (ICOMEM) has tried to bring together existing and rapidly changing information on this topic that could be of interest to members of ICOMEM and anyone else. Trying to stratify the data, we have formulated some questions that the members of the Committee have considered relevant. We have invited physicians from Madrid who are not usually part of the Standing Committee of the College to participate in the writing of this paper because of their experience in the diagnostic and therapeutic management of these cases [11] and from the Center for Molecular Biology Severo Ochoa of the Spanish National Research Council.

We will now discuss some of the questions raised.

WHAT IS A POXVIRUS AND WHAT CHARACTERIZES IT?

The Poxvirus family (Poxviridae) consists of a group of large, complex, double-stranded deoxyribonucleic acid (DNA) viruses that replicate in human cells and are defined by their genomic, structural, and antigenic characteristics.

The 8 vertebrate Poxvirus genera are: Orthopoxvirus, Parapoxvirus, Avipoxvirus, Capripoxvirus, Leporipoxvirus, Suipoxvirus, Molluscipoxvirus and Yatapoxvirus. They all share a similar DNA sequence with very similar antigens that have cross-reactivity [12].

Poxviruses include human smallpox virus (Variola), which was declared eradicated by the World Health Organization (WHO) in 1980. Other poxviruses that can affect humans include cowpox virus (Cowpox), the virus used in the smallpox vaccine (Vaccinia), Akhmeta virus and monkeypox virus (MPVX), as well as other zoonotic species with epidemic potential. Of these, MPVX is the most prevalent in humans.

Bovine smallpox is another zoonotic disease, with a wide reservoir in the animal kingdom, which can produce papulo-vesicular disease in humans, in a clear relationship of contact with cattle, of variable dissemination and severity, generally with very low mortality and weeks of evolution.

Another viral genus of the Poxvirus family are the Parapoxviruses, which include species of wide dissemination in sheep, goats, cattle, camelids and cervids. They are Orf viruses that produce different clinical manifestations in animals, in general with oral or pharyngeal affection (papular stomatitis) or cutaneous (papular dermatosis) that by contact affect humans (milker's nodule) and that induce nodular or macrovesicular lesions with granulomatous reaction, of medium duration. This genus induces less immunity than Orthopoxviruses and therefore reinfections are more frequent.

Molluscum Contagiosum is a frequent disease of humans, children and adults, produced by species of the genus Molluscipoxvirus, with special epidermal tropism and inducing papules that mimic soft tumors, generally small, of variable number depending on the sites of inoculation, preferentially distributed on the trunk and root of the extremities, self-lim-

ited in the immunocompetent. Molluscum Contagiosum is transmitted by direct contact, facilitated by sexual intercourse with genital proximity lesions and also transmitted by fomites.

Finally, the genus Yatapoxvirus, which includes the Tana River pox virus (Kenya), induces in humans a vesicular-papular disease in areas of exposed skin, with adenopathic reaction and systemic symptoms of up to 6 weeks of evolution.

Equivalent in African and Asian apes is the disease produced by the Yaba virus, which produces lesions that mimic histiocytomas and can be transmitted to humans by bites or direct inoculation.

Unlike other viruses, the ability of Poxviruses to mutate is much lower than that exhibited by RNA viruses, such as influenza virus or SARS-CoV-2. Nevertheless, these viruses have a large genetic endowment responsible for their virulence and ability to invade and evade the immune system [13,14].

Interest in these viruses has been sustained, among other reasons, because of the potential use of some of these agents, particularly Variola virus, as a biological weapon since Orthopoxviruses and Poxviruses can be created and modified in laboratories using molecular biology tools [15,16].

Two distinct genetic clades of MPVX have been identified, Congo Basin and West African. The former is more virulent and transmissible than the latter. The geographical division between the two clades is believed to be in Cameroon, as it is the only country where both clades of the virus have been detected simultaneously. The cases currently affecting Spain are caused by the less virulent West African clade [17].

WHAT DID SMALLPOX MEAN IN THE HISTORY OF MANKIND?

Smallpox was a disease with very high mortality, which fortunately was eradicated in 1980 thanks to vaccination and the fact that its reservoir was only human [18,19]. Smallpox lesions have already been identified in Egyptian mummies from 300 BC, and it has subsequently affected humanity periodically through large epidemic outbreaks [20-22]. Recent studies have sequenced complete smallpox virus genomes in human remains from the Viking era (9th-12th centuries), a Lithuanian mummy (18th century) and specimens from a 19th century Czech museum [23]. Human smallpox, after infection, is followed by an incubation period ranging from 7 to 14 days, after which skin lesions appear abruptly and intensely. A rash usually appears, either diffuse (scarlatiniform) or macular (macular or measles) and with variable involvement of the skin surface, mainly on the face, extremities, hands and feet and later on the trunk, evolving into papules.

Between the fifth and sixth day after their appearance, the papules become round vesicles, with a central umblication and on the eighth day they become clear pustules with a grayish and turgid content. It is very characteristic, from the semiological point of view, that all the cutaneous elements are in the same morphological stage, a fact that differentiates it from other vesicular-eruptive diseases, mainly with chickenpox.

In the crust formation phase, these may remain adhered to the skin for a long time and their fall will leave a scar.

Smallpox was, for centuries, one of the first causes of blindness in mankind and its mortality has ranged from 10-75%, It is estimated that in the 20th century approximately 300 million people worldwide still died from smallpox before its eradication [20-22,24-28].

Smallpox was the first disease against which a vaccine was available, and Spain played a key role in spreading smallpox vaccination throughout its extensive empire, by means of the famous Royal Philanthropic Vaccine Expedition, led by Francisco Javier Balmis [29-32].

WHAT ANIMALS ARE INFECTED BY MPVX?

There are multiple animals that are susceptible to infection by MPVX including non-human primates, rodents, squirrels and dormice. Some of these animals have been used as models on poxvirus acquisition and transmission and for testing vaccines and protective drugs after it was learned that the former Soviet Union had turned these viruses into potential biological weapons [33].

In non-human primates, MPVX usually produces a short-lived rash. Initial clinical signs are fever and cutaneous papules of 1-4 mm, which develop into pustules and then crust over. A typical lesion has a red, necrotic, depressed center surrounded by epidermal hyperplasia. These "smallpox pustules" can be located all over the body, but preferentially on the face and extremities. Most infected animals recover quickly; however, fatal cases can occur, especially in neonatal monkeys.

The disease caused by MPVX has also been observed naturally in some rodents, such as prairie dogs, and after inoculation in dormice and squirrels. In all of these cases, clinical manifestations are varied, but fever, weight loss, nasal discharge, sneezing and/or coughing, respiratory involvement, and nodular skin rash or mouth ulcers may occur [33-37].

WHAT CASES OF MPVX INFECTION HAVE BEEN DESCRIBED IN HUMANS?

Until recently, MPVX was an occasional, endemic disease in humans in contact with animals that spread mainly in rainforest areas of Central and West Africa, causing isolated cases or small outbreaks in 11 African countries: Benin, Cameroon, Central African Republic, Democratic Republic of Congo, Gabon, Ivory Coast, Liberia, Nigeria, Republic of Congo, Sierra Leone and South Sudan.

In 1996-1997, a large outbreak of MPVX in humans was described in the Democratic Republic of Congo with a low case fatality rate, but with a higher than usual attack rate [38-42]. In 2017 Nigeria experienced the largest documented outbreak, 40 years after the last confirmed case [43].

As of 2018, occasional cases have been reported in Israel [44] in September 2018, in the United Kingdom in December

2019 [45,46] and in Singapore in May 2019 [47] in travelers from Nigeria who became ill with monkeypox after arrival. One health care worker was infected and became ill.

WHEN AND HOW DOES THE CURRENT OUTBREAK BEGIN?

On May 7, 2022, a case of H-MPVX is confirmed in the United Kingdom in a patient with recent travel to Nigeria [48]. On May 14, 2022, two additional cases of H-MPVX were identified in London in two unrelated cohabitants of the previous case and new cases have been confirmed in the United Kingdom, in and outside of London. The current outbreak is multinational and includes more than 50 countries as far afield as Australia, North America and Europe [49-51].

The majority of cases have occurred in young men, many of whom were identified as MSM, with genital lesions suggesting that transmission likely occurred through close physical contact [52-58].

In Spain, the number of confirmed cases as of June 10 exceeds 200, mostly related to MSM parties.

WHAT ARE THE CLINICAL MANIFESTATIONS OF MONKEYPOX IN HUMANS?

A publication presents the clinical features and evolution of 282 patients with H-MPVX in the Congo during 1980-1985. The ages of the patients ranged from one month to 69 years; 90% were younger than 15 years. The clinical picture was similar to that of the ordinary and modified forms of smallpox. Lymphadenopathy, appearing early in the disease, was the most important sign differentiating monkeypox from smallpox and chickenpox in humans. Symptoms, signs, and disease course in patients who had been vaccinated against smallpox differed significantly from those of unvaccinated subjects. Varicella-like pleomorphism and cropping occurred in 31% of vaccinated and 18% of unvaccinated patients. Prognosis was largely dependent on the presence of severe complications, and no deaths occurred among vaccinated patients. In unvaccinated patients, the crude mortality rate was 11%, but was higher among younger children (15%) [59].

Clinical manifestations of human infection usually appear after incubation periods of 5 to 21 days. It usually presents clinically with fever, rash and swollen lymph nodes. It is usually a self-limiting disease with symptoms lasting 2 to 4 weeks. Severe cases are more frequent in children and are related to the degree of exposure to the virus, the patient's state of health and the nature of the complications.

Skin lesions are more frequent on the face and extremities than on the trunk. The lesions do not affect the palms of the hands and soles of the feet (in 75% of cases) or the oral, genital or rectal mucous membranes. The conjunctiva and cornea may be affected.

Complications of monkeypox may include deep abscesses and secondary infections.

Some patients, in this outbreak, manifest preferentially with proctitis or pharyngitis with minimal or absent skin lesions.

WHAT IS THE EPIDEMIOLOGY OF HUMAN MPVX DISEASE?

In 1980 the WHO [60] reported that since 1970 there have been 47 human cases of monkeypox in 5 countries in Central and West Africa; 38 of which have been reported in the Congo. Human MPVX disease had at that time a mortality rate of approximately 17% and children under 10 years of age accounted for 83% of the cases. All cases had occurred in tropical rainforest areas and clustering of cases had been observed in certain areas within countries and within families. Although the low rate of transmission and the low frequency of disease indicated that monkeypox was not then a public health problem, authorities cautioned that more data on this disease were needed.

Many animals near human cases of MPVX were shown to have antibodies to Orthopoxvirus, but the natural reservoirs and vectors of MPVX were unknown [61]. Even so, the disease was beginning to be accepted as a probable zoonosis [60,62-64].

Human-to-human transmission was progressively well demonstrated [65] by small family outbreaks after acquisition of the index case from a monkey [65].

A study of 2,510 contacts of 214 patients with H-MPVX was conducted in Zaire between 1980 and 1984 [66]. Among the contacts of 130 primary cases, an additional 22 co-primary and 62 secondary cases were detected, and fourteen other persons who had no evidence of clinical disease had positive serological results. Most of those clinical and subclinical cases of monkeypox occurred in children under 10 years of age. The overall attack rate of contacts without smallpox vaccination scar (7.2%) was significantly different from those with vaccination scar (0.9%) [66].

Secondary or person-to-person transmission would occur by close contact with infected respiratory tract secretions or skin lesions of an infected person, or with objects recently contaminated with the patient's fluids or lesion materials. Transmission occurred mainly by respiratory droplets, usually after prolonged face-to-face contact with the patient, exposing family members of active cases to an increased risk of infection [67].

Infection of index cases results from direct contact with blood, body fluids, or skin or mucosal lesions of infected animals.

In recently reported cases outside the African continent, the virus is transmitted from person to person by contact with skin lesions, body fluids, respiratory droplets, and contaminated materials such as bedding. This form of transmission is what is occurring in the present outbreak. Transmission via respiratory droplet particles usually requires prolonged face-to-face contact, which poses a greater risk to unprotected health care

workers and specially to close household members of active cases. Transmission can also occur through the placenta from mother to fetus (congenital monkeypox).

WHAT SHOULD BE DONE AT THIS TIME IN SPAIN IN THE EVENT OF A SUSPECTED CASE? HOW IS THE DIAGNOSIS CONFIRMED?

If H-MPVX is suspected, healthcare personnel should:

1) Attend patients with appropriate PPE: waterproof gown, gloves, FP2 mask and closed goggles.

2) Inform the Microbiology laboratory of the existence of a suspected case.

3) Prior to sampling, make sure to have a swab for sample collection, which should be sent in a dry sterile tube or in virus transport medium and kept cold. The sample should be accompanied by sufficient clinical information so that the microbiologist can fill in all the sections requested by the reference laboratory. At a minimum: age, sex, risk factors, date of onset of symptoms, date of onset of rash.

4) So far, a blood sample for serology and another in an EDTA tube can also be obtained, as well as a urine sample to be sent in the urine culture bottle.

5) It should be noted that the optimal samples for MPVX diagnosis come from skin lesions: the roof or fluid of vesicles and pustules, and dry crusts.

6) Once ready, the on-call microbiologist will be notified of their shipment, correctly identified.

7) The Microbiology laboratory staff will arrange for the samples to be sent to the corresponding reference laboratory where the polymerase chain reaction (PCR) will be performed, this being the laboratory test of choice due to its accuracy and sensitivity.

8) Clinical samples are considered category B samples. Similar precautions to those used for COVID with three successive containers are sufficient for specimen transport.

Mucosal specimens showing lesions, including respiratory, vaginal or rectal mucosa, may also be used. In cases of proctitis, it is recommended to send rectal specimens as well, since in current cases there is a strong association with sexual transmission.

In biopsy specimens, the histopathological lesions of MPVX are indistinguishable from those of human smallpox [68] and consist of necrosis affecting the stratum basale of the skin and adjacent areas of the dermal papillae. The necrosis also affects the stratum spinosum above the destroyed stratum basale. There are occasional multinuclear giant cells and some bodies resembling Guarnieri bodies.

Electron microscopy shows abundant orthopoxvirus particles in the cytoplasm of infected epidermal cells. In general, the features are indistinguishable from the papulonecrotic phase of smallpox [68].

Viral strains of MPVX isolated initially were readily differentiated from Variola and Vaccinia viruses. The isolated strains produced small necrotic hemorrhagic spots, grew well at 39.0 degrees, formed large plaques in Vero cell cultures and showed markedly greater virulence to chick embryos and mice than the Variola strains [6,7,69,70].

ARE THERE DRUGS EFFECTIVE AGAINST MPVX IN HUMANS?

Tecovirimat (ST-246) is a drug first reported in 2005. It is a low molecular weight compound with potent activity against multiple Orthopoxviruses, including smallpox, vaccinia, MPVX, camelpox, cowpox and mousepox viruses. It acts against the Orthopoxvirus V061 gene that encodes an important envelope protein (p37) required for extracellular virus production. In cell culture. ST-246 inhibited plaque formation and virus-induced cytopathic effects [71-76). Oral administration of ST-246 protected BALB/c mice from lethal infection following intranasal inoculation of the vaccinia virus strain. ST-246-treated mice that survived infection acquired protective immunity and were resistant to subsequent challenge with a new lethal dose (10x LD(50)) of vaccinia virus [71,76].

Tecovirimat is an antiviral drug tested in several animal species in which it has demonstrated efficacy against Orthopoxvirus infections. The drug has undergone clinical trials in non-human primates and human volunteers demonstrating good tolerance for up to 14 days of oral administration [77-80]. Also in the treatment of cases of bovine smallpox in accidentally infected or vaccinated immunodeficient patients [81, 82]. A British patient who received the drug in 2021 experienced very short duration of symptoms and viral excretion from the respiratory tract [83]

The approval of tecovirimat to treat smallpox represents a major milestone in biosafety preparedness. Incorporation of the drug into the CDC smallpox response plan, development of pediatric liquid and intravenous formulations, and approval for post-exposure prophylaxis would be an additional health security benefit. Although currently stockpiled by the U.S. Strategic National Stockpile, use of ST-246 may be administered under special circumstances (IND) [84-90].

Tecovirimat's efficacy is maintained even when administration is delayed a few days after inoculation in animal models of Poxvirus infection [73,75]. Its activity is synergistic with other drugs such as cidofovir or CMX001 [74].

No data are available on the efficacy of cidofovir and brincidofovir in the treatment of human cases of MPVX. However, both have demonstrated activity against poxviruses in in vitro and animal studies [91,92].

WHAT VACCINES ARE AVAILABLE AGAINST THIS DISEASE?

The first vaccines, without even knowing the viral nature of smallpox, were made from the material of bovine smallpox pustules. Subsequently, the vaccine virus replaced attenuated strains of smallpox for mass immunization of

populations prior to the eradication of smallpox. It was administered by scarification with a bifurcated needle, inducing a suffusion in the skin on which a papule appeared between the following two and five days, evolving into a vesicle and pustule from the eighth to the tenth day. The vaccinal pustule reached up to 1 cm in diameter, which finally dried and left a scab, which after falling off, between the 14th and 21st day, left a scar. The development of regional adenopathy was frequent.

The efficacy of these vaccines against smallpox is estimated to be complete in the first years, very important in the following twenty years and with protection against severe disease, of longer duration, probably for life.

These vaccines, however, had their complications. One of them was the local extension of the vaccine inoculation lesion to a necrotizing or gangrenous lesion, sometimes with little inflammatory component, with high mortality, and which has been described even in immunocompetent patients. Another more frequent complication (4.6 cases per million vaccinees) was the so-called Eczema Vaccinatum, or extension by inoculation on atopic skin or skin with other skin diseases, of the vaccinee himself or of accidental contacts. As in the previous complication, it was treated with hyperimmune serum.

The generalized extension of the vaccine lesion was another complication, difficult to justify. It was usually self-limited and generally did not require treatment and its incidence was estimated in large vaccination series at 242 cases per million vaccinated. Finally, encephalomyelitis could appear between day 11 to 15 of the first vaccination and was not described in the revaccinations. Its incidence was between 2.9 to 12.3 cases per million vaccinated. Focal lesions with aphasia or hemiplegia presenting closer to vaccination could occur in children under two years of age.

A vaccine produced with an attenuated, non-replicating strain approved for Smallpox and Monkeypox (AVA/ANKARA) could be considered in the immunocompromised and is licensed for use in emergency situations. It has different names in different regions (Invanex; Jynneos; Imvamune). It was approved by the EMA in 2013 for the prevention of human smallpox in adults aged 18 years and older (data sheet updated in April 2022 in Spanish). In the U.S., it received approval for the prevention of human and monkeypox in 2019.

The vast majority of H-MPVX, both in Africa and worldwide, have occurred in people who were not vaccinated against human smallpox [4,34,93-102]. Furthermore, in a study of confirmed and suspected cases of monkeypox in Central Africa, the disease attack rate was much lower in subjects with variola vaccination than among unvaccinated subjects (0.95/1000 versus 3.6/1000) [103].

The smallpox vaccine has so far not been available to the general public and was part of a strategic stockpile.

WHAT SHOULD BE THE PREVENTION MEASURES IN CONTACTS OF PATIENTS WITH H-MPVX?

In any case of H-MPVX under investigation or confirmed, the search for and identification of close contacts will be initiated both among healthcare personnel and among work or social cohabitants. The search for contacts will be interrupted if the case is ruled out after laboratory results.

Contacts of cases will be classified as close, direct or low-risk contacts.

Close contact (less than 1 meter in the same room is defined as contact with an investigational or confirmed case of monkeypox virus in its infectious period, without PPE (or with incidences in its use). Cohabitants, contacts at work, social activities and health personnel who have cared for the patient should be assessed.

Direct contact is defined as contact with clothing, bedding or fomites used by an investigational or confirmed case of monkeypox virus during the infectious period, without the appropriate PPE (or with incidences in its use).

Low-risk contacts are those that do not meet the above criteria.

All contacts will be informed of the symptoms of monkeypox and will be instructed to self-monitor their temperature twice daily for 21 days after exposure. Close contacts will not be quarantined, but should exercise extreme caution and reduce social interactions as much as possible by wearing a facemask at all times.

The responsible person/institution will contact high-risk contacts at least once daily to record temperature and inquire about the presence of any symptoms related to the disease. Contacts should be reachable throughout the follow-up period.

In any of the cases, if any of the contacts presents fever or any other symptom compatible with the clinical signs of the disease, they should immediately self-isolate at home, and urgently contact the person in charge of the follow-up. In this case, the contact will be considered as a case under investigation until laboratory results are available.

The recommended environmental control measures are as follows:

Bed linens, towels, etc., should be washed in a standard washing machine with hot water (60 degrees) and detergent. Bleach may be added, but is not necessary. Care should be taken when handling soiled linen to avoid direct contact with contaminated material. Soiled linen should not be shaken or handled in a manner that could disperse infectious particles.

Dishes and other eating utensils should not be shared with those of cases. Dirty dishes and eating utensils should be washed in a dishwasher or by hand with soap and hot water.

Contaminated surfaces and objects should be cleaned and disinfected with a hospital-grade disinfectant or a 1:100 dilution of household sodium hypochlorite (bleach) [104,105].

WHAT IS THE PROGNOSIS OF MONKEYPOX IN HUMANS?

The case fatality rate of monkeypox has ranged from 0 to 11% in the general population of African countries, and is highest among young children. In addition, persons younger than 40 or 50 years of age (depending on the country may be more susceptible to monkeypox as a result of the end of routine smallpox vaccination worldwide following the eradication of smallpox.

The clade currently circulating in Spain, in adult patients, is associated with very low mortality [93].

FUNDING

None to declare

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

REFERENCES

1. von Magnus P, Andersen EA, Petersen KB, A. B-A. A pox-like disease in cynomolgus monkeys. Acta Path Microbiol Scand. 1958;46:159.
2. Arita I, Henderson DA. Smallpox and monkeypox in non-human primates. Bull World Health Organ. 1968;39(2):277-83. PMC2554549
3. Eke RA. Monkey-pox in a four-year old girl: case report. West Afr Med J Niger Pract. 1972;21(1):21-2.
4. Foster SO, Brink EW, Hutchins DL, Pifer JM, Lourie B, Moser CR, et al. Human monkeypox. Bull World Health Organ. 1972;46(5):569-76. PMC2480784
5. Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. Bull World Health Organ. 1972;46(5):593-7. PMC2480792
6. Marennikova SS, Seluhina EM, Mal'ceva NN, Cimiskjan KL, Macevic GR. Isolation and properties of the causal agent of a new variola-like disease (monkeypox) in man. Bull World Health Organ. 1972;46(5):599-611. PMC2480798
7. Lourie B, Bingham PG, Evans HH, Foster SO, Nakano JH, Herrmann KL. Human infection with monkeypox virus: laboratory investigation of six cases in West Africa. Bull World Health Organ. 1972;46(5):633-9. PMC2480791
8. Gispen R, Brand-Saathof BB, Hekker AC. Monkeypox-specific antibodies in human and simian sera from the Ivory Coast and Nigeria. Bull World Health Organ. 1976;53(4):355-60. PMC2366533
9. Arita I, Henderson DA. Monkeypox and whitepox viruses in West and Central Africa. Bull World Health Organ. 1976;53(4):347-53. PMC2366520
10. CDC. From the Centers for Disease Control and Prevention. Multistate outbreak of monkeypox-- Illinois, Indiana, and Wisconsin, 2003. Jama. 2003;290(1):30-1. doi: 10.1001/jama.290.1.30
11. Servicio de Microbiología Clínica y Enfermedades Infecciosas. Hospital General Universitario Gregorio Marañón. Documento para la respuesta frente al brote de viruela del mono (Monkeypox). 2022. Accessed 19 May 2022.
12. Stanford MM, McFadden G, Karupiah G, Chaudhri G. Immunopathogenesis of poxvirus infections: forecasting the impending storm. Immunol Cell Biol. 2007;85(2):93-102. doi: 10.1038/sj.icb.7100033
13. Alakunle E, Moens U, Nchinda G, Okeke MI. Monkeypox Virus in Nigeria: Infection Biology, Epidemiology, and Evolution. Viruses. 2020;12(11). doi: 10.3390/v12111257
14. Smith GL, Benfield CTO, Maluquer de Motes C, Mazzon M, Ember SWJ, Ferguson BJ, et al. Vaccinia virus immune evasion: mechanisms, virulence and immunogenicity. J Gen Virol. 2013;94(Pt 11):2367-92. doi:10.1099/vir.0.055921-0
15. Noyce RS, Lederman S, Evans DH. Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. PLoS One. 2018;13(1):e0188453. doi:10.1371/journal.pone.0188453
16. Noyce RS, Evans DH. Synthetic horsepox viruses and the continuing debate about dual use research. PLoS Pathog. 2018;14(10):e1007025. doi:10.1371/journal.ppat.1007025
17. Sadeuh-Mba SA, Yonga MG, Els M, Batejat C, Eyangoh S, Caro V, et al. Monkeypox virus phylogenetic similarities between a human case detected in Cameroon in 2018 and the 2017-2018 outbreak in Nigeria. Infect Genet Evol. 2019;69:8-11. doi:10.1016/j.meegid.2019.01.006
18. Smith GL, McFadden G. Smallpox: anything to declare? Nat Rev Immunol. 2002;2(7):521-7. doi:10.1038/nri845
19. Alcamí A. Was smallpox a widespread mild disease? Science. 2020;369(6502):376-7. doi:10.1126/science.abd1214
20. Henderson DA. The eradication of smallpox--an overview of the past, present, and future. Vaccine. 2011;29 Suppl 4:D7-9. doi:10.1016/j.vaccine.2011.06.080
21. Tewogbola P, Aung N. Revisiting the 1970 smallpox outbreak in Meschede, Germany: Lessons for a post-COVID world. J Emerg Manag. 2021;19(7):157-63. doi:10.5055/jem.0617
22. Ilic I, Ilic M. Historical review: Towards the 50th anniversary of the last major smallpox outbreak (Yugoslavia, 1972). Travel Med Infect Dis. 2022;48:102327. doi:10.1016/j.tmaid.2022.102327
23. Mühlemann B, Vinner L, Margaryan A, Wilhelmson H, de la Fuente Castro C, Allentoft ME, et al. Diverse variola virus (smallpox) strains were widespread in northern Europe in the Viking Age. Science. 2020;369(6502). doi:10.1126/science.aaw8977
24. Grigoryan YG, Krylov NN. COVID-19 and collective responsibility: a lesson from the Smallpox outbreak in Moscow in 1960. J Med Ethics Hist Med. 2020;13:32. doi:10.18502/jmehm.v13i32.5049
25. Foster SA, Parker S, Lanier R. The Role of Brincidofovir in Preparation for a Potential Smallpox Outbreak. Viruses. 2017;9(11). doi:10.3390/v9110320
26. Ilic M, Ilic I. The last major outbreak of smallpox (Yugoslavia, 1972): The importance of historical reminders. Travel Med Infect Dis. 2017;17:69-70. doi:10.1016/j.tmaid.2017.05.010

27. Bass SB, Ruzek SB, Gordon TF, Hanlon AL. Preparedness for a smallpox outbreak: comparing metrics for assessing levels of vaccination among health-care workers by state. Epidemiol Infect. 2007;135(4):622-33. doi:10.1017/s0950268806007229 P

28. Cobeljić M. Smallpox outbreak in Yugoslavia in 1972. Vojnosanit Pregl. 2004;61(5):569-73.

29. Tuells J, Duro-Torrijos JL. [The journey of the vaccine against smallpox: one expedition, two oceans, three continents, and thousands of children]. Gac Med Mex. 2015;151(3):416-25.

30. Mark C, Rigau-Pérez JG. The world's first immunization campaign: the Spanish Smallpox Vaccine Expedition, 1803-1813. Bull Hist Med. 2009;83(1):63-94. doi:10.1353/bhm.0.0173

31. Christenson B. Spanish royal philanthropic expedition and smallpox vaccination. Clin Infect Dis. 2006;42(5):731; author reply -2. 10.1086/500267

32. Sánchez Granjel L. [Balmis and the philanthropic expedition of the vaccine. Bicentennial of the Royal Philanthropic Expedition of Francisco Xavier Balmis to carry smallpox vaccine to America and Philippines]. An R Acad Nac Med (Madr). 2004;121(2):331-8; discussion 8-44.

33. Parker S, Buller RM. A review of experimental and natural infections of animals with monkeypox virus between 1958 and 2012. Future Virol. 2013;8(2):129-57. doi:10.2217/fvl.12.130 PMC3635111

34. Iowa State University. The Center for Food Security and Public Health. Monkeypox. Available at: https://wwwcfsphiastateedu/Factsheets/es/viruela_del_simiopdf. 2009.

35. Hutson CL, Lee KN, Abel J, Carroll DS, Montgomery JM, Olson VA, et al. Monkeypox zoonotic associations: insights from laboratory evaluation of animals associated with the multi-state US outbreak. Am J Trop Med Hyg. 2007;76(4):757-68.

36. Hobson K. Pet problems. From monkeypox to HIV, animals bring us new ills. US News World Rep. 2003;134(22):40-1.

37. Dumbell KR, Archard LC. Comparison of white pock (h) mutants of monkeypox virus with parental monkeypox and with variola-like viruses isolated from animals. Nature. 1980;286(5768):29-32. doi:10.1038/286029a0

38. Human monkeypox -- Kasai Oriental, Democratic Republic of Congo, February 1996-October 1997. MMWR Morb Mortal Wkly Rep. 1997;46(49):1168-71.

39. Mukinda VB, Mwema G, Kilundu M, Heymann DL, Khan AS, Esposito JJ. Re-emergence of human monkeypox in Zaire in 1996. Monkeypox Epidemiologic Working Group. Lancet. 1997;349(9063):1449-50. doi:10.1016/s0140-6736(05)63725-7

40. Mwanbal PT, Tshioko KF, Moudi A, Mukinda V, Mwema GN, Messinger D, et al. Human monkeypox in Kasai Oriental, Zaire (1996-1997). Euro Surveill. 1997;2(5):33-5. doi:10.2807/esm.02.05.00161-en

41. CDC. From the Centers for Disease Control and Prevention. Human monkeypox--Kasai Oriental, Democratic Republic of Congo, February 1996-October 1997. Jama. 1998;279(3):189-90.

42. Heymann DL, Szczeniowski M, Esteves K. Re-emergence of monkeypox in Africa: a review of the past six years. Br Med Bull. 1998;54(3):693-702. doi:10.1093/oxfordjournals.bmb.a011720

43. Yinka-Ogunleye A, Aruna O, Ogoina D, Aworabhi N, Eteng W, Badaru S, et al. Reemergence of Human Monkeypox in Nigeria, 2017. Emerg Infect Dis. 2018;24(6):1149-51. doi:10.3201/eid2406.180017 PMC6004876

44. Erez N, Achdout H, Milrot E, Schwartz Y, Wiener-Well Y, Paran N, et al. Diagnosis of Imported Monkeypox, Israel, 2018. Emerg Infect Dis. 2019;25(5):980-3. doi:10.3201/eid2505.190076 PMC6478227

45. Hobson G, Adamson J, Adler H, Firth R, Gould S, Houlihan C, et al. Family cluster of three cases of monkeypox imported from Nigeria to the United Kingdom, May 2021. Euro Surveill. 2021;26(32). doi:10.2807/1560-7917.Es.2021.26.32.2100745

46. Vaughan A, Aarons E, Astbury J, Brooks T, Chand M, Flegg P, et al. Human-to-Human Transmission of Monkeypox Virus, United Kingdom, October 2018. Emerg Infect Dis. 2020;26(4):782-5. doi:10.3201/eid2604.191164

47. Yong SEF, Ng OT, Ho ZJM, Mak TM, Marimuthu K, Vasoo S, et al. Imported Monkeypox, Singapore. Emerg Infect Dis. 2020;26(8):1826-30. doi:10.3201/eid2608.191387

48. World Health Organization. "Monkeypox – United Kingdom of Great Britain and Northern Ireland". 16 May 2022. Archived from the original on 17 May 2022 Retrieved 17 May 2022

49. Rao AK, Schulte J, Chen TH, Hughes CM, Davidson W, Neff JM, et al. Monkeypox in a Traveler Returning from Nigeria - Dallas, Texas, July 2021. MMWR Morb Mortal Wkly Rep. 2022;71(14):509-16. doi:10.15585/mmwr.mm7114a1

50. Mauldin MR, McCollum AM, Nakazawa YJ, Mandra A, Whitehouse ER, Davidson W, et al. Exportation of Monkeypox Virus From the African Continent. J Infect Dis. 2022;225(8):1367-76. doi:10.1093/infdis/jiaa559

51. La Nación. Viruela del mono: confirmaron el primer caso del virus en el país. Available at: https://wwwlanacioncomar/sociedad/viruela-del-mono-confirmaron-el-primer-caso-del-virus-en-el-pais-nid26052022/. 2022.

52. Velavan TP, Meyer CG. Monkeypox 2022 outbreak: an update. Trop Med Int Health. 2022. doi: 10.1111/tmi.13785

53. Kozlov M. Monkeypox outbreaks: 4 key questions researchers have. Nature. 2022. doi:10.1038/d41586-022-01493-6

54. Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis. 2022. doi:10.1016/s1473-3099(22)00228-6

55. Harris E. What to Know About Monkeypox. Jama. 2022. doi:10.1001/jama.2022.9499

56. Adalja A, Inglesby T. A Novel International Monkeypox Outbreak. Ann Intern Med. 2022. doi:10.7326/m22-1581

57. Kozlov M. Monkeypox goes global: why scientists are on alert. Nature. 2022. doi:10.1038/d41586-022-01421-8

58. Mahase E. Monkeypox: What do we know about the outbreaks in Europe and North America? Bmj. 2022;377:o1274. doi:10.1136/bmj.o1274

59. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. J Infect Dis. 1987;156(2):293-

8. doi:10.1093/infdis/156.2.293

60. W.H.O. The current status of human monkeypox: memorandum from a WHO meeting. Bull World Health Organ. 1984;62(5):703-13. PMC2536211

61. Breman JG, Kalisa R, Steniowski MV, Zanotto E, Gromyko AI, Arita I. Human monkeypox, 1970-79. Bull World Health Organ. 1980;58(2):165-82. PMC2395797

62. Jezek Z, Gromyko AI, Szczeniowski MV. Human monkeypox. J Hyg Epidemiol Microbiol Immunol. 1983;27(1):13-28.

63. Mutombo M, Arita I, Jezek Z. Human monkeypox transmitted by a chimpanzee in a tropical rain-forest area of Zaire. Lancet. 1983;1(8327):735-7. doi:10.1016/s0140-6736(83)92027-5

64. Durski KN, McCollum AM, Nakazawa Y, Petersen BW, Reynolds MG, Briand S, et al. Emergence of Monkeypox - West and Central Africa, 1970-2017. MMWR Morb Mortal Wkly Rep. 2018;67(10):306-10. doi:10.15585/mmwr.mm6710a5

65. Jezek Z, Arita I, Mutombo M, Dunn C, Nakano JH, Szczeniowski M. Four generations of probable person-to-person transmission of human monkeypox. Am J Epidemiol. 1986;123(6):1004-12. doi:10.1093/oxfordjournals.aje.a114328

66. Jezek Z, Marennikova SS, Mutumbo M, Nakano JH, Paluku KM, Szczeniowski M. Human monkeypox: a study of 2,510 contacts of 214 patients. J Infect Dis. 1986;154(4):551-5. doi:10.1093/infdis/154.4.551

67. Organización Mundial de la Salud. Viruela Símica. Datos y cifras. 19 de mayo de 2022. . Available at: https://wwwwhoint/es/news-room/fact-sheets/detail/monkeypox. 2022.

68. Stagles MJ, Watson AA, Boyd JF, More IA, McSeveney D. The histopathology and electron microscopy of a human monkeypox lesion. Trans R Soc Trop Med Hyg. 1985;79(2):192-202. doi:10.1016/0035-9203(85)90333-5

69. Yau TM, Rouhandeh H. Monkeypox virus (MPV). II. Uncoating and nucleic acid synthesis. Arch Gesamte Virusforsch. 1972;39(1):151-62. doi:10.1007/bf01241538

70. Yau TM, Rouhandeh H. Monkeypox virus (MPV). I. Propagation, purification, and further characterization. Arch Gesamte Virusforsch. 1972;39(1):140-50. doi:10.1007/bf01241537

71. Yang G, Pevear DC, Davies MH, Collett MS, Bailey T, Rippen S, et al. An orally bioavailable antipoxvirus compound (ST-246) inhibits extracellular virus formation and protects mice from lethal orthopoxvirus Challenge. J Virol. 2005;79(20):13139-49. doi:10.1128/jvi.79.20.13139-13149.2005

72. Duraffour S, Snoeck R, de Vos R, van Den Oord JJ, Crance JM, Garin D, et al. Activity of the anti-orthopoxvirus compound ST-246 against vaccinia, cowpox and camelpox viruses in cell monolayers and organotypic raft cultures. Antivir Ther. 2007;12(8):1205-16.

73. Quenelle DC, Buller RM, Parker S, Keith KA, Hruby DE, Jordan R, et al. Efficacy of delayed treatment with ST-246 given orally against systemic orthopoxvirus infections in mice. Antimicrob Agents Chemother. 2007;51(2):689-95. doi:10.1128/aac.00879-06

74. Quenelle DC, Prichard MN, Keith KA, Hruby DE, Jordan R, Painter GR, et al. Synergistic efficacy of the combination of ST-246 with CMX001 against orthopoxviruses. Antimicrob Agents Chemother. 2007;51(11):4118-24. doi:10.1128/aac.00762-07

75. Sbrana E, Jordan R, Hruby DE, Mateo RI, Xiao SY, Siirin M, et al. Efficacy of the antipoxvirus compound ST-246 for treatment of severe orthopoxvirus infection. Am J Trop Med Hyg. 2007;76(4):768-73.

76. Anonimous. Molecule of the month. Tecovirimat. Drug News Perspect. 2008;21(9):517.

77. Jordan R, Leeds JM, Tyavanagimatt S, Hruby DE. Development of ST-246® for Treatment of Poxvirus Infections. Viruses. 2010;2(11):2409-35. doi:10.3390/v2112409

78. Jordan R, Chinsangaram J, Bolken TC, Tyavanagimatt SR, Tien D, Jones KF, et al. Safety and pharmacokinetics of the antiorthopoxvirus compound ST-246 following repeat oral dosing in healthy adult subjects. Antimicrob Agents Chemother. 2010;54(6):2560-6. doi:10.1128/aac.01689-09

79. Jordan R, Goff A, Frimm A, Corrado ML, Hensley LE, Byrd CM, et al. ST-246 antiviral efficacy in a nonhuman primate monkeypox model: determination of the minimal effective dose and human dose justification. Antimicrob Agents Chemother. 2009;53(5):1817-22. doi:10.1128/aac.01596-08

80. Jordan R, Tien D, Bolken TC, Jones KF, Tyavanagimatt SR, Strasser J, et al. Single-dose safety and pharmacokinetics of ST-246, a novel orthopoxvirus egress inhibitor. Antimicrob Agents Chemother. 2008;52(5):1721-7. doi:10.1128/aac.01303-07

81. Wendt R, Tittelbach J, Schrick L, Kellner N, Kalbitz S, Ruehe B, et al. Generalized cowpox virus infection in an immunosuppressed patient. Int J Infect Dis. 2021;106:276-8. doi:10.1016/j.ijid.2021.03.076

82. Lindholm DA, Fisher RD, Montgomery JR, Davidson W, Yu PA, Yu YC, et al. Preemptive Tecovirimat Use in an Active Duty Service Member Who Presented With Acute Myeloid Leukemia After Smallpox Vaccination. Clin Infect Dis. 2019;69(12):2205-7. doi:10.1093/cid/ciz286

83. Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis. 2022. doi:10.1016/S1473-3099(22)00228-6

84. Russo AT, Grosenbach DW, Chinsangaram J, Honeychurch KM, Long PG, Lovejoy C, et al. An overview of tecovirimat for smallpox treatment and expanded anti-orthopoxvirus applications. Expert Rev Anti Infect Ther. 2021;19(3):331-44. doi:10.1080/14787210.2020.1819791

85. Russo AT, Berhanu A, Bigger CB, Prigge J, Silvera PM, Grosenbach DW, et al. Co-administration of tecovirimat and ACAM2000™ in non-human primates: Effect of tecovirimat treatment on ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge. Vaccine. 2020;38(3):644-54. doi:10.1016/j.vaccine.2019.10.049

86. Chan-Tack KM, Harrington PR, Choi SY, Myers L, O'Rear J, Seo S, et al. Assessing a drug for an eradicated human disease: US Food and Drug Administration review of tecovirimat for the treatment of smallpox. Lancet Infect Dis. 2019;19(6):e221-e4. doi:10.1016/s1473-3099(18)30788-6

87. Hoy SM. Tecovirimat: First Global Approval. Drugs. 2018;78(13):1377-82. doi:10.1007/s40265-018-0967-6

88. Mucker EM, Goff AJ, Shamblin JD, Grosenbach DW, Damon IK, Mehal JM, et al. Efficacy of tecovirimat (ST-246) in nonhuman primates infected with variola virus (Smallpox). Antimicrob Agents Chemother. 2013;57(12):6246-53. doi:10.1128/aac.00977-13

89. Duraffour S, Lorenzo MM, Zöller G, Topalis D, Grosenbach D, Hruby DE, et al. ST-246 is a key antiviral to inhibit the viral F13L phospholipase, one of the essential proteins for orthopoxvirus wrapping. J Antimicrob Chemother. 2015;70(5):1367-80. doi:10.1093/jac/dku545

90. Grosenbach DW, Honeychurch K, Rose EA, Chinsangaram J, Frimm A, Maiti B, et al. Oral Tecovirimat for the Treatment of Smallpox. N Engl J Med. 2018;379(1):44-53. doi:10.1056/NEJMoa1705688

91. Hutson CL, Kondas AV, Mauldin MR, Doty JB, Grossi IM, Morgan CN, et al. Pharmacokinetics and Efficacy of a Potential Smallpox Therapeutic, Brincidofovir, in a Lethal Monkeypox Virus Animal Model. mSphere. 2021;6(1). 10.1128/mSphere.00927-20 PMC7860987

92. Hutson CL, Kondas AV, Mauldin MR, Doty JB, Grossi IM, Morgan CN, et al. Correction for Hutson et al., "Pharmacokinetics and Efficacy of a Potential Smallpox Therapeutic, Brincidofovir, in a Lethal Monkeypox Virus Animal Model". mSphere. 2021;6(1). doi:10.1128/mSphere.00126-21

93. Bunge EM, Hoet B, Chen L, Lienert F, Weidenthaler H, Baer LR, et al. The changing epidemiology of human monkeypox-A potential threat? A systematic review. PLoS Negl Trop Dis. 2022;16(2):e0010141. doi:10.1371/journal.pntd.0010141

94. Centers for Disease Control and Prevention (CDC). Monkeypox.2022 . Available at: https://wwwcdcgov/poxvirus/monkeypox/indexhtml.

95. McConnell S, Herman YF, Mattson DE, Huxsoll DL, Lang CM, Yager RH. Protection of rhesus monkeys against monkeypox by vaccinia virus immunization. Am J Vet Res. 1964;25:192-5.

96. Vollmar J, Arndtz N, Eckl KM, Thomsen T, Petzold B, Mateo L, et al. Safety and immunogenicity of IMVAMUNE, a promising candidate as a third generation smallpox vaccine. Vaccine. 2006;24(12):2065-70. doi:10.1016/j.vaccine.2005.11.022

97. Frey SE, Newman FK, Kennedy JS, Sobek V, Ennis FA, Hill H, et al. Clinical and immunologic responses to multiple doses of IMVAMUNE (Modified Vaccinia Ankara) followed by Dryvax challenge. Vaccine. 2007;25(51):8562-73. doi:10.1016/j.vaccine.2007.10.017

98. Jones T. IMVAMUNE, an attenuated modified vaccinia Ankara virus vaccine for smallpox infection. Curr Opin Mol Ther. 2008;10(4):407-17.

99. Kennedy JS, Greenberg RN. IMVAMUNE: modified vaccinia Ankara strain as an attenuated smallpox vaccine. Expert Rev Vaccines. 2009;8(1):13-24. doi:10.1586/14760584.8.1.13

100. Garza NL, Hatkin JM, Livingston V, Nichols DK, Chaplin PJ, Volkmann A, et al. Evaluation of the efficacy of modified vaccinia Ankara (MVA)/IMVAMUNE against aerosolized rabbitpox virus in a rabbit model. Vaccine. 2009;27(40):5496-504. doi:10.1016/j.vaccine.2009.06.105

101. Frey SE, Winokur PL, Salata RA, El-Kamary SS, Turley CB, Walter EB, Jr., et al. Safety and immunogenicity of IMVAMUNE® smallpox vaccine using different strategies for a post event scenario. Vaccine. 2013;31(29):3025-33. doi:10.1016/j.vaccine.2013.04.050 PMC3755481

102. Arndtz-Wiedemann N. Myocardial effects of IMVAMUNE. Biosecur Bioterror. 2014;12(4):217-8. doi:10.1089/bsp.2014.0037

103. Kalthan E, Tenguere J, Ndjapou SG, Koyazengbe TA, Mbomba J, Marada RM, et al. Investigation of an outbreak of monkeypox in an area occupied by armed groups, Central African Republic. Med Mal Infect. 2018;48(4):263-8. doi:10.1016/j.medmal.2018.02.010

104. Petersen E, Kantele A, Koopmans M, Asogun D, Yinka-Ogunleye A, Ihekweazu C, et al. Human Monkeypox: Epidemiologic and Clinical Characteristics, Diagnosis, and Prevention. Infect Dis Clin North Am. 2019;33(4):1027-43. doi:10.1016/j.idc.2019.03.001

105. Gobierno de España. Protocolo para la derección precoz y manejo de casos ante la alerta de viruela de los monos (monkeypox) en España. Actualizado a 31 de mayo de 2022. Available at: https://wwwsanidadgobes/profesionales/saludPublica/ccayes/alertasActual/alertaMonkeypox/docs/ProtocoloMPX_20220520pdf.