230316 Meeting with Wildlife Health Networking, East Asia, WOAH

MPOX

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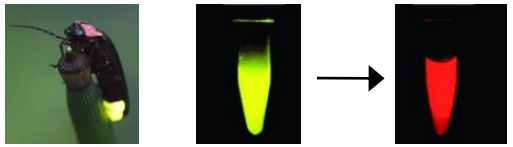
Excuse in advance

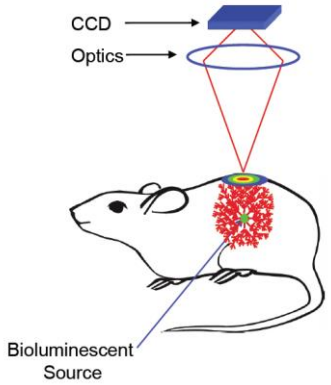
My main research topic is viral zoonotic diseases, **especially rabies, but not Mpox**

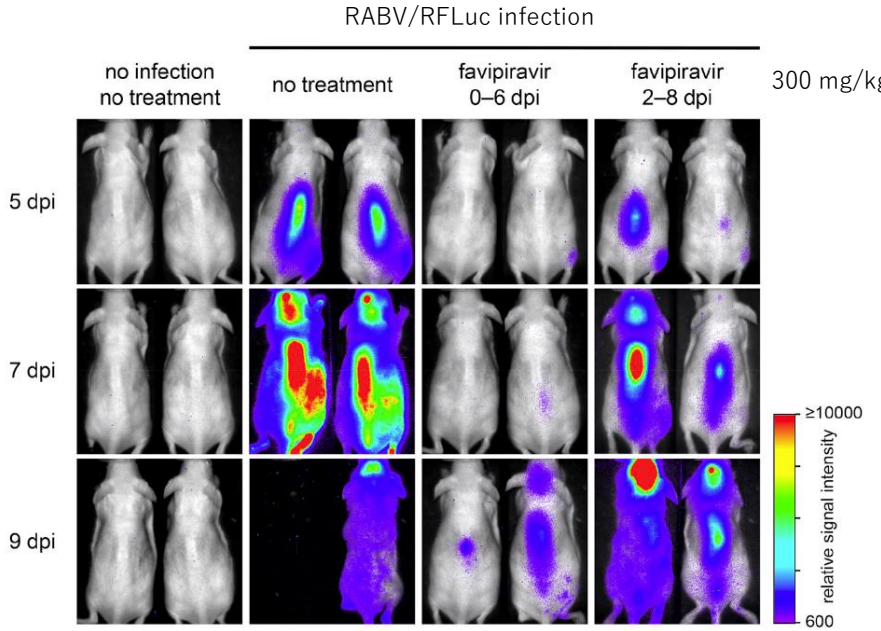
Evaluation of the efficacy of favipiravir against rabies virus using in vivo imaging

RABV/RFLuc (recombinant RABV expressing RFLuc)



Red Firefly luciferase (RFLuc) is a mutant of the firefly luciferase and has a red-shifted emission spectrum (Em peak 560 → 613 nm)
Red light is high transparency in tissues





Yamada et al, Antiviral Res, 2019

Today's my presentation is not based on my original information, but is based on various websites and papers

Summary of Mpox Outbreaks

Mpox virus was first isolated in late 1958 in Copenhagen during two outbreaks of a smallpox-like disease in a colony of cynomolgus monkeys

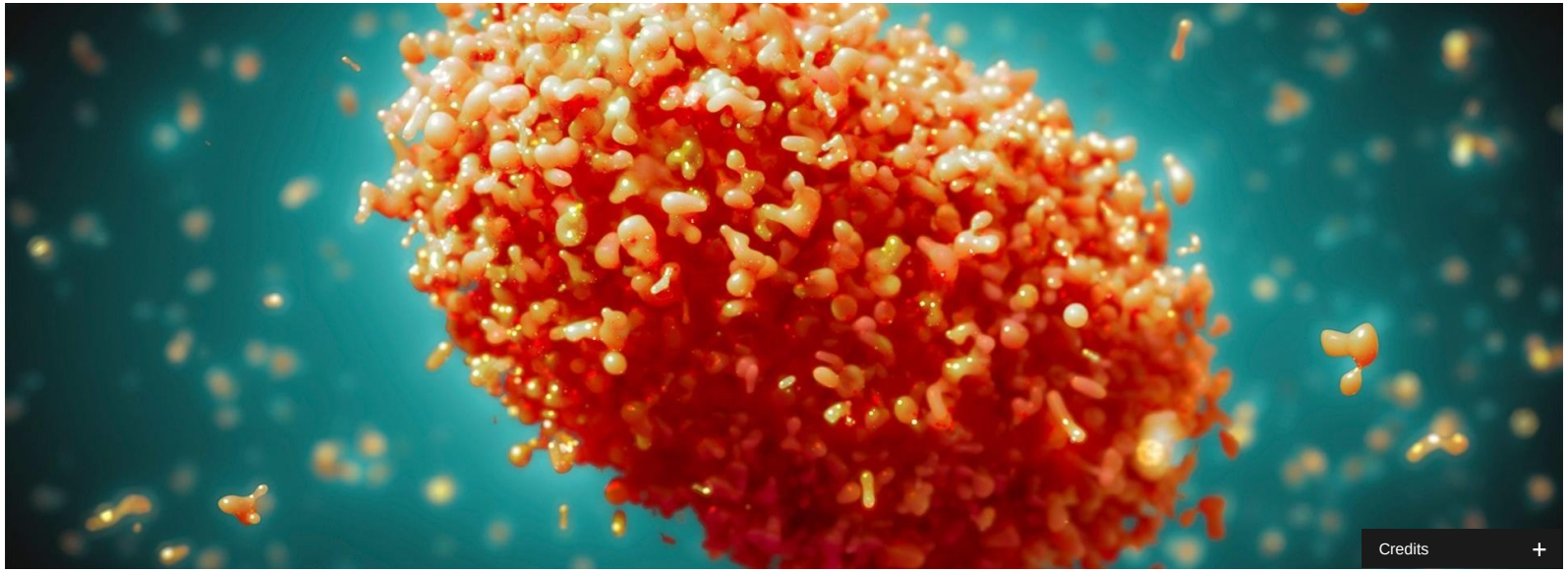
The first case of mpox in a human was reported in 1970, as part of the national smallpox surveillance and eradication program then under way in Africa

Mpox in humans remained an exclusively African disease, with sporadic cases diagnosed in forested areas of Central or West Africa and small outbreaks mainly in the Democratic Republic of Congo, until 2003, when the first cases outside Africa were reported

In 2018, five infected patients were identified:
three in the United Kingdom, one in Israel, and one in Singapore. These imported cases were linked to persons from Nigeria, where a large outbreak occurred in 2017–2018

In May 2022, a series of mpox cases was identified in the United Kingdom, Portugal, and Italy, mostly involving men who have sex with men (MSM)

Gessain A, et al. N Engl J Med. 2022



WHO Director-General declares the ongoing monkeypox outbreak a Public Health Emergency of International Concern

23 July 2022 | News release | Reading time: Less than a minute (51 words)

On July 23, the WHO Director-General declared the escalating global monkeypox outbreak a Public Health Emergency of International Concern (PHEIC). Currently, the vast majority of reported cases are in the WHO European Region. WHO/Europe remains committed to partnering with countries and communities to address the outbreak with the required urgency.

Related

WHO Director-General's statement on the Press conference following IHR Emergency Committee regarding the multi-country outbreak of monkeypox - 23 July 2022

BBC NEWS

Monkeypox: WHO declares highest alert over outbreak

By Robert Plummer (BBC News) 23 July 2022

There are only two other such health emergencies at present - the coronavirus pandemic and the continuing effort to eradicate polio.

Dr Tedros said the emergency committee had been unable to reach a consensus on whether the monkeypox outbreak should be classified as a global health emergency.

However, he said the outbreak had spread around the world rapidly and he had decided that it was indeed of international concern.

"The WHO's assessment is that the risk of monkeypox is moderate globally and in all regions, except in the European region, where we assess the risk as high," he added.

"This is an outbreak that can be stopped with the right strategies in the right groups," Dr Tedros said.

Health officials in the UK are already recommending people at highest risk of exposure to monkeypox - including some gay and bisexual men, as well as some healthcare workers **- should be offered a vaccine.**

https://www.bbc.com/news/health-62279436

BBC NEWS

Monkeypox: WHO declares highest alert over outbreak

Analysis
By **James Gallagher**
Health and science correspondent

Declaring a global emergency is a significant act.

It is a rallying cry for countries to take the virus seriously, it raises awareness around the world and it can help poorer countries get the tools they need to control monkeypox.

In principle, we have the tools to stop the virus. Monkeypox does not spread as easily as Covid and we already have a vaccine (developed for smallpox) that offers good protection.

And while anyone can catch monkeypox, the outbreak is overwhelmingly concentrated in gay and bisexual men, as well as other men who have sex with men.

This can make the outbreak easier to tackle, as efforts, including **vaccines** and public health information, can be targeted at those most at risk.

But remember, there are still countries where same-sex relationships are illegal - and stigma and persecution can act as a barrier to help.

Whether we can stop monkeypox is as much a societal and cultural challenge as it is about the virus.

https://www.bbc.com/news/health-62279436

Vaccines for Mpox are available

There are currently three vaccines approved by different regulatory agencies for the prevention of mpox, including modified vaccinia Ankara from Bavarian Nordic (MVA-BN, Denmark) and LC16 from KMB Biologics (Japan).
Recently, in November 2022, a third vaccine called OrthopoxVac was licensed in the Russian Federation for immunization against smallpox, mpox and other orthopoxviruses according to the rules for registration of medicines of the Eurasian Economic Union.

In addition, a smallpox vaccine ACAM2000 has been recommended for use in specific populations in the case where other vaccines may not be available.

At this time the vaccines for mpox are not prequalified by WHO but interim guidance for their use has been developed and issued with the advice and support of the WHO Strategic Advisory Group of Experts.

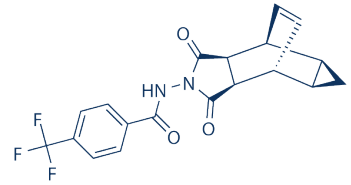
https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report---17---2-march-2023

Medical Countermeasures Available for the Treatment of Mpox

Currently there is no treatment approved specifically for mpox virus infections.

However, United States Government-stockpiled antivirals, developed for use in patients with smallpox, may be beneficial against mpox. The medical countermeasures currently available from the Strategic National Stockpile as options for the treatment of mpox include **tecovirimat**, **brincidofovir**, and **vaccinia immune globulin**. **Cidofovir** is also available commercially. Cidofovir is an antiviral medication that is approved by the FDA for the treatment of cytomegalovirus (CMV) retinitis in patients with Acquired Immunodeficiency Syndrome (AIDS).

Clinicians should first consider tecovirimat in treating mpox virus infections in people. Patients should be informed about the clinical trial for tecovirimat and encouraged to consider enrollment.



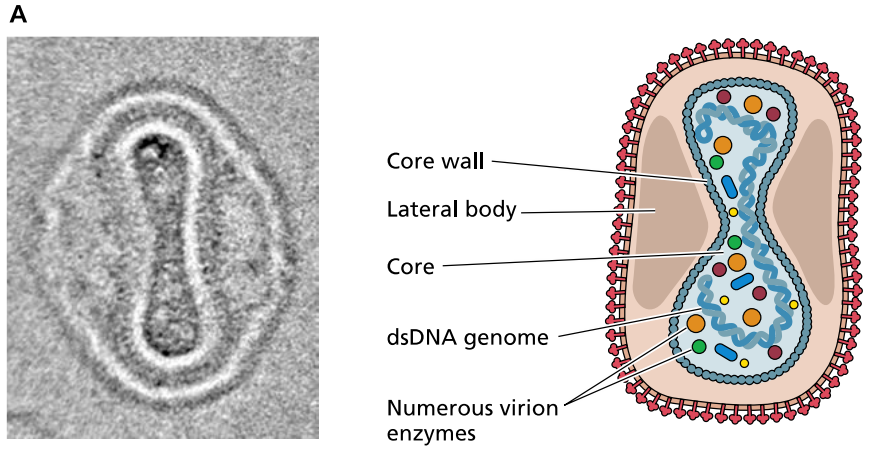
Tecovirimat

Tecovirimat (also known as TPOXX, ST-246) is an antiviral medication that is approved by the FDA for the treatment of smallpox. Data are not available on the effectiveness of tecovirimat in treating mpox infections in people, but studies using a variety of animal species have shown that tecovirimat is effective in treating disease caused by orthopoxviruses.

A clinical trial focused on safety in healthy people without mpox virus showed the drug had an acceptable safety profile; the effectiveness of tecovirimat was not studied in this trial. As mentioned above, there is an ongoing clinical trial (STOMP) to assess the effectiveness of tecovirimat for the treatment of mpox.

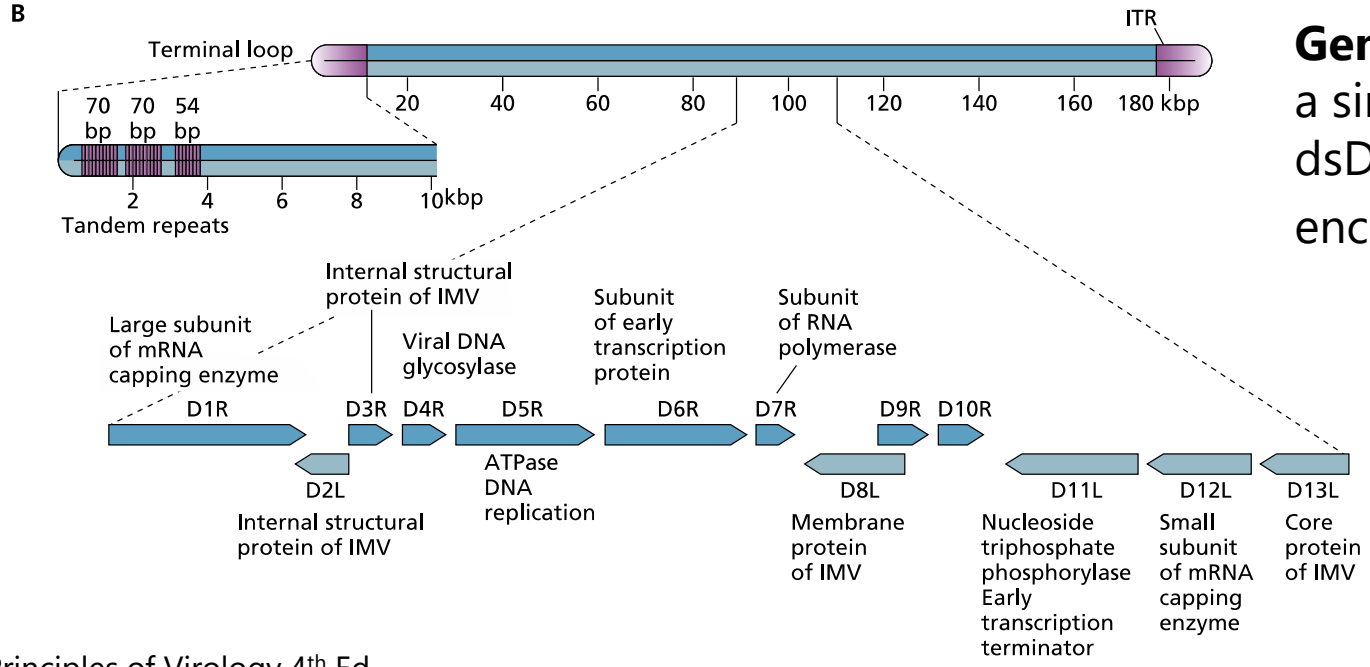
https://www.cdc.gov/poxvirus/mpox/clinicians/treatment.html

General Properties of Poxviruses



Virion

generally brick-shaped with a lipoprotein surface membrane
(220–450 nm long × 140–260 nm wide × 140–260 nm thick)



Genome

a single, linear molecule of covalently-closed, dsDNA, 130–375 kbp in length

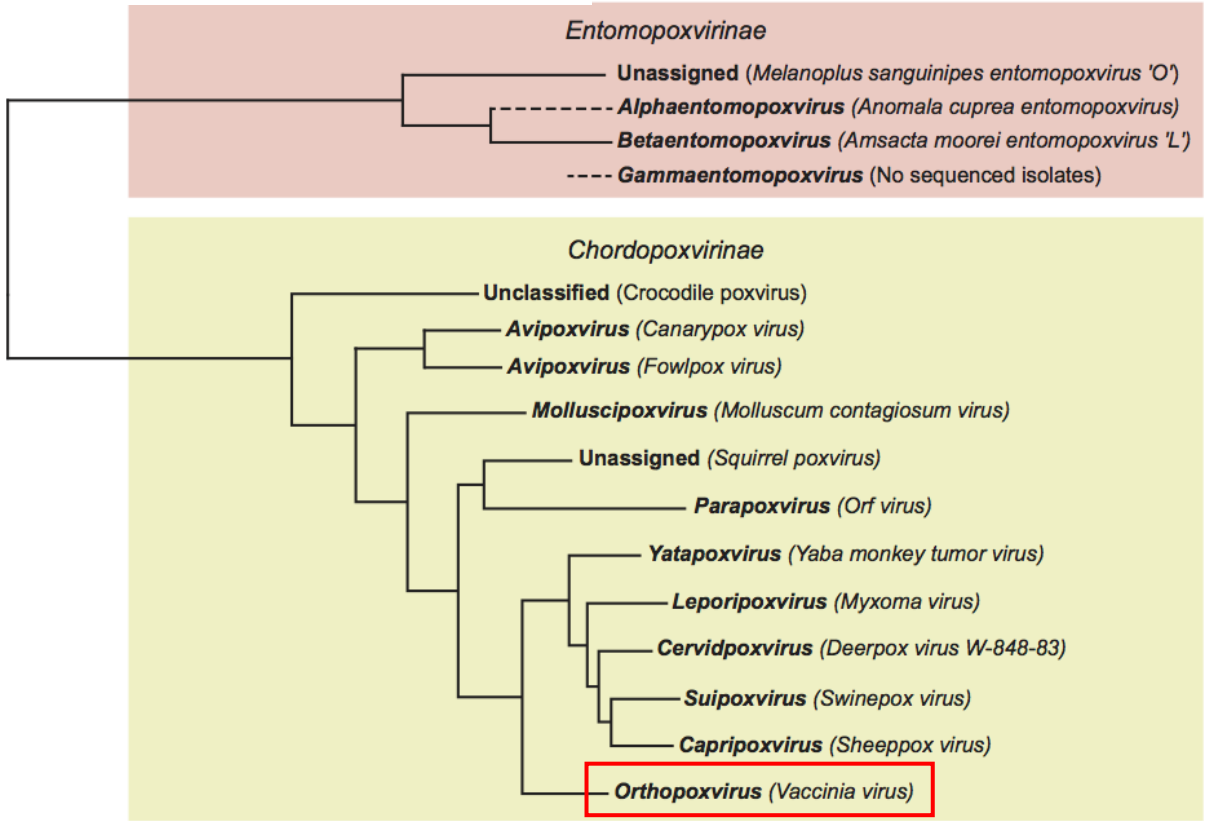
encoding 150-300 proteins

Principles of Virology 4th Ed.

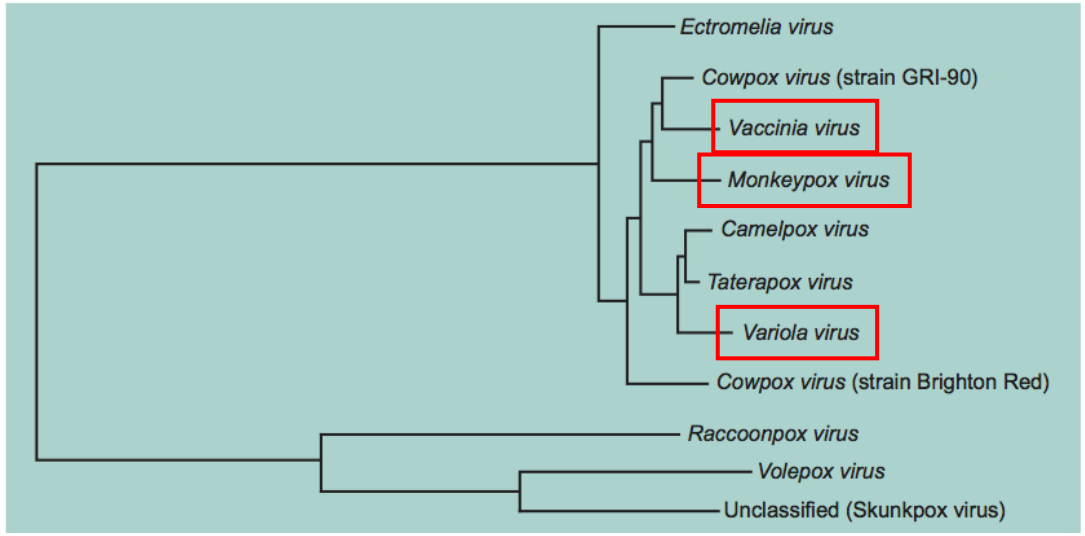
Phylogenetic relationships in the family *Poxviridae*

Mpox virus belongs to the **family**: Poxviridae, **genus**: orthopoxvirus (same as Variola virus)

family *Poxviridae*



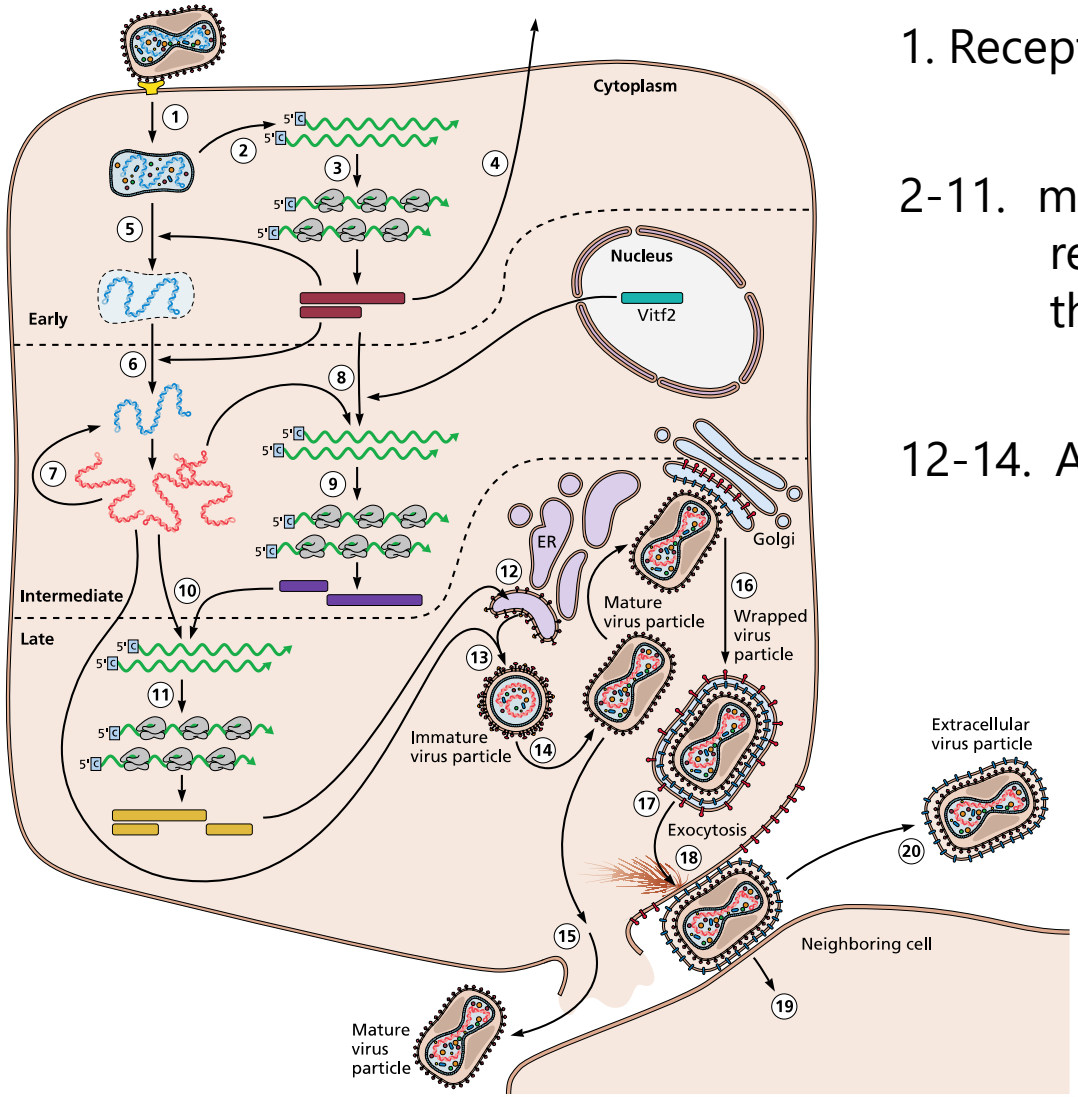
genus *Orthopoxvirus*



Antibodies directed against a member of the orthopoxviruses can provide cross-protection against other species

https://ictv.global/report_9th/dsDNA/poxviridae

Life Cycle of Poxvirus (Vaccinia Virus) in cells



Principles of Virology 4th Ed.

1. Receptor binding and entry of the viral core into the cytoplasm

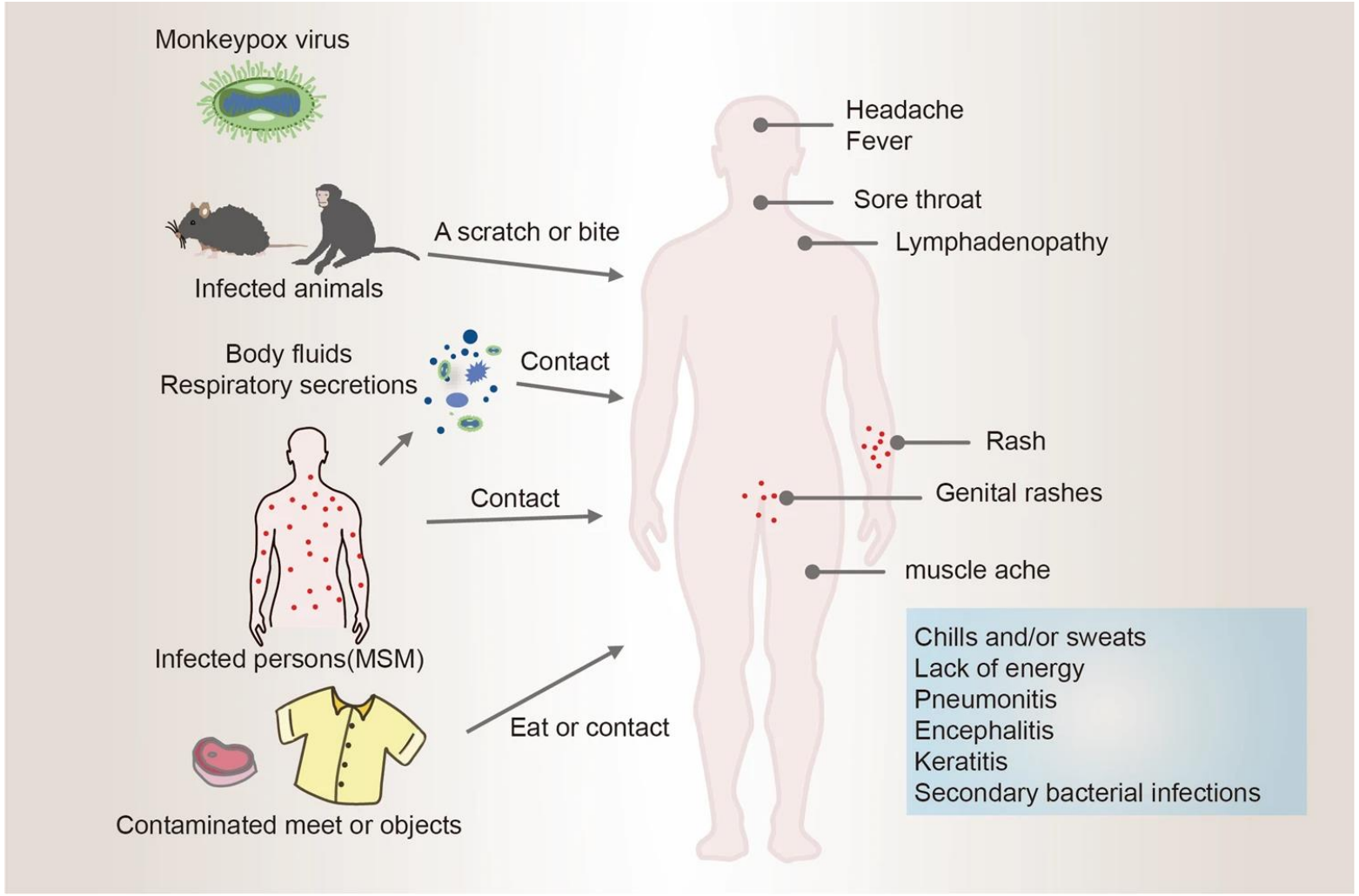
2-11. mRNA synthesis, viral protein production, and DNA genome replication: not only structural proteins but also viral proteins that modulate a cell function are produced

12-14. Assembly of progeny viral particles occurs in the termed viral factory

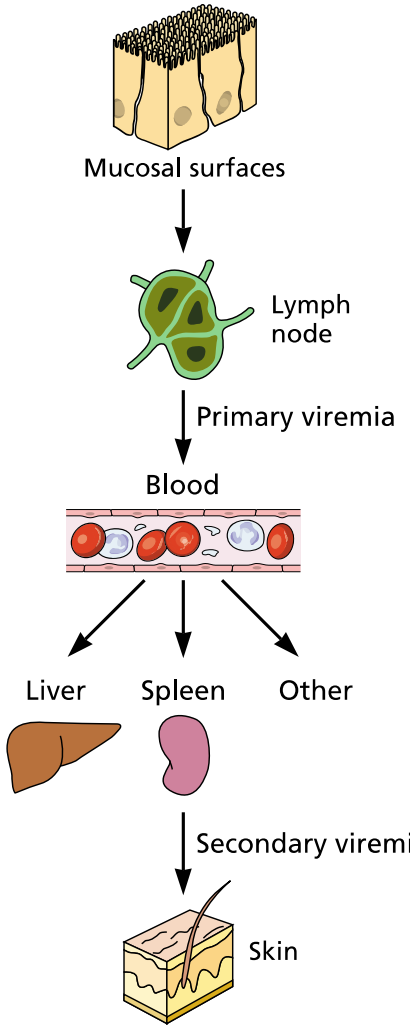
15. The brick-shaped intracellular mature viral particles are released upon cell lysis

16-20. Membrane-associated viral particles egress from cells through exocytosis and infect to neighboring cells

Transmission and Pathogenesis of Mpox



Huang Y, et al. Signal Transduct Target Ther. 2022



Virus spreads through lymphatics and blood

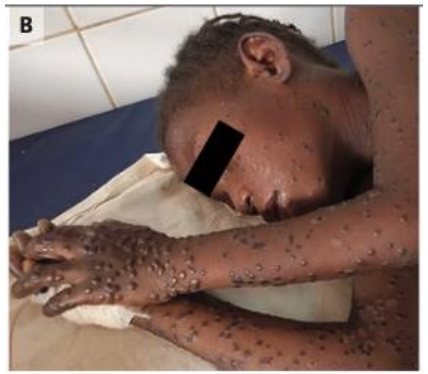
Sequential infection of multiple organs

Skin lesions are prominent

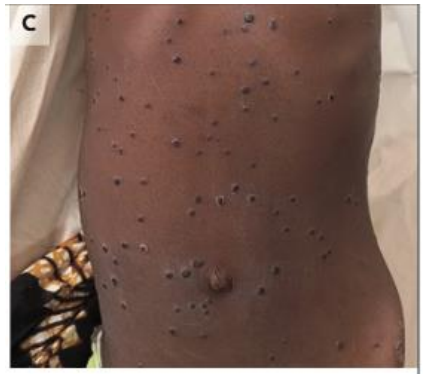
Principles of Virology 4th Ed.

Cutaneous and Mucosal Manifestations of Mpox in Humans

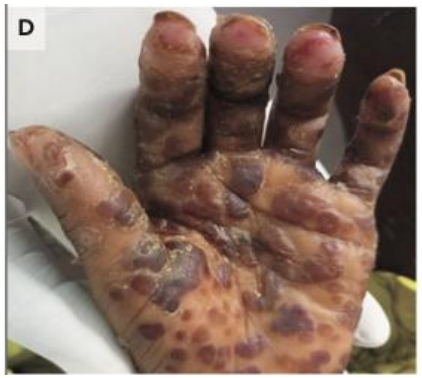
Umbilicated papules on the left hand of a young girl in the Central African Republic



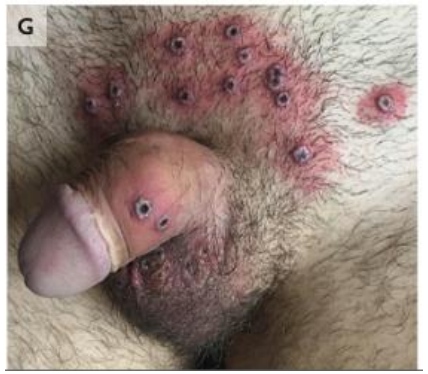
Extensive, disseminated papular lesions on the hands, arms, and face of a young girl



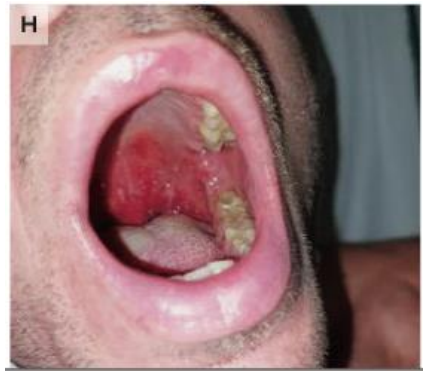
Disseminated skin lesions at different stages of evolution, including papules and crusts, on the abdomen of a young girl



Numerous skin lesions with hyperpigmentation, crusts, and desquamation on the left hand of a woman



Genital lesions, including scrotal and penile lesions, are present in a man who had sex with a man (MSM)



Pharyngitis in MSM

Gessain A, et al. N Engl J Med. 2022

Mpox in Animals

Mpox virus can infect a wide range of mammal species, including monkeys, anteaters, hedgehogs, prairie dogs, squirrels, and shrews.

We are still learning which species of animals can get mpox.
While we do not know if reptiles, amphibians, or birds can get mpox, it is unlikely since these animals have not been found to be infected with other orthopoxviruses.

Not all animals may have a rash when they have mpox.

Infected animals can spread mpox virus to people.
It is possible that people who are infected can spread mpox virus to animals through close contact.

Mpox virus can be found in the rash caused by mpox (scabs, crusts, fluids) and infected bodily fluids, including respiratory secretions, and potentially in urine and feces.

https://www.cdc.gov/poxvirus/monkeypox/veterinarian/monkeypox-in-animals.html

Mpox in Animals: Susceptibility

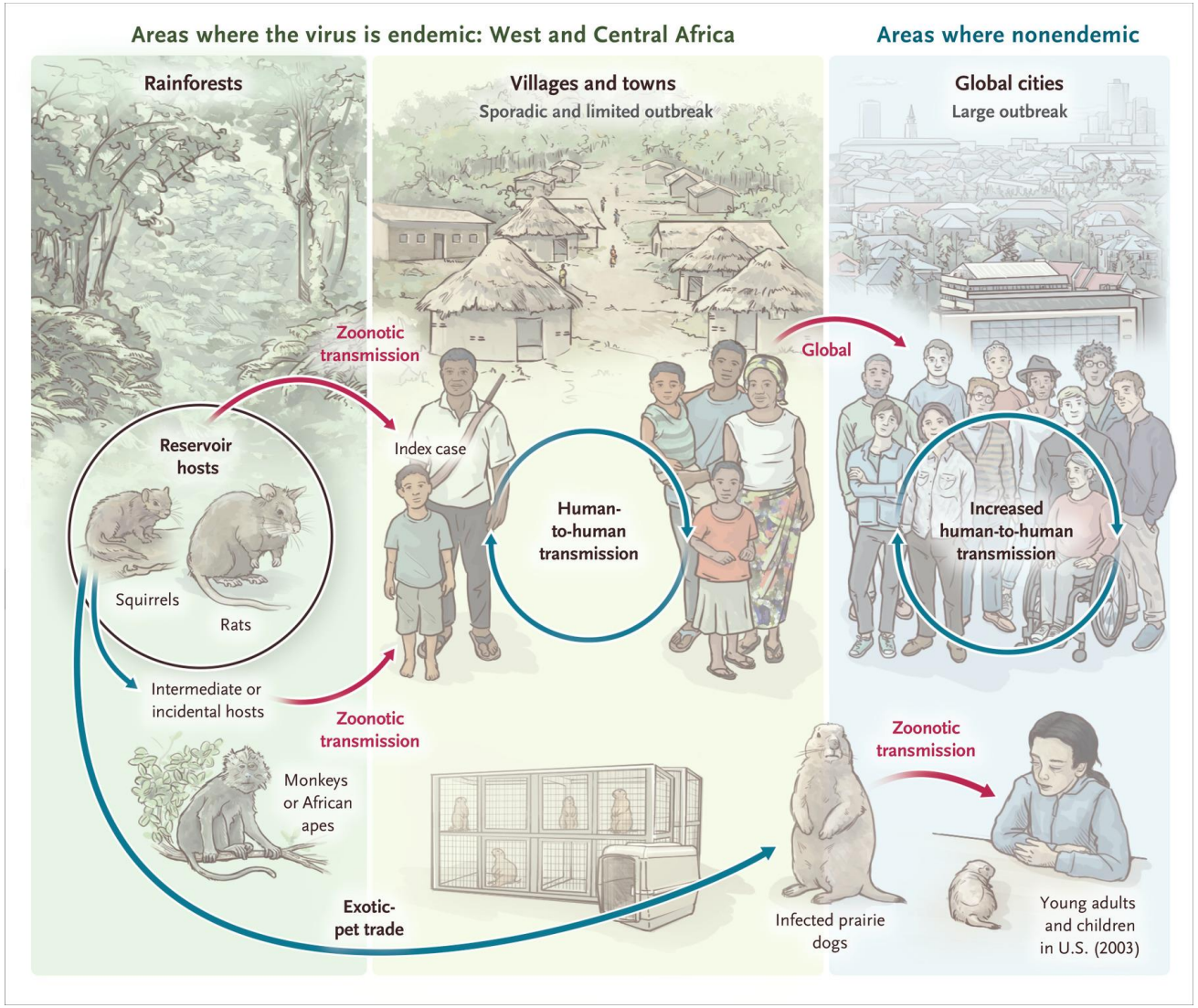
Rodents	
Prairie dogs	Yes
Squirrels	Yes
Marmots	Yes
Chinchillas	Yes
Giant-pouched rats	Yes
Gerbils	?
Guinea pigs	?
Hamsters	?
Mice	Possibly
Rats	Possibly
Carnivores	
Dogs	?
Cats	?

lagomorphs	
Domestic rabbits	Possibly
Insectivores	
Hedgehogs	Yes
Shrews	Yes
Non-human primates	
Monkeys	Yes
Apes	Yes
Livestock	
Cows	?
Camels	?
Goats	?
Sheep	?
Pigs	?

Wildlife	
Raccoons	?
Skunks	?
Voles	?
Badgers	?
Coyotes	?
Foxes	?

https://www.cdc.gov/poxvirus/monkeypox/veterinarian/monkeypox-in-animals.html

Natural History of Mpox



Gessain A, et al. N Engl J Med. 2022

The reservoir of the mpox virus has yet to be clearly identified, but **Rodents**, including various species of squirrels and rats living in the rainforests of Central and West Africa, are among the most likely candidates.

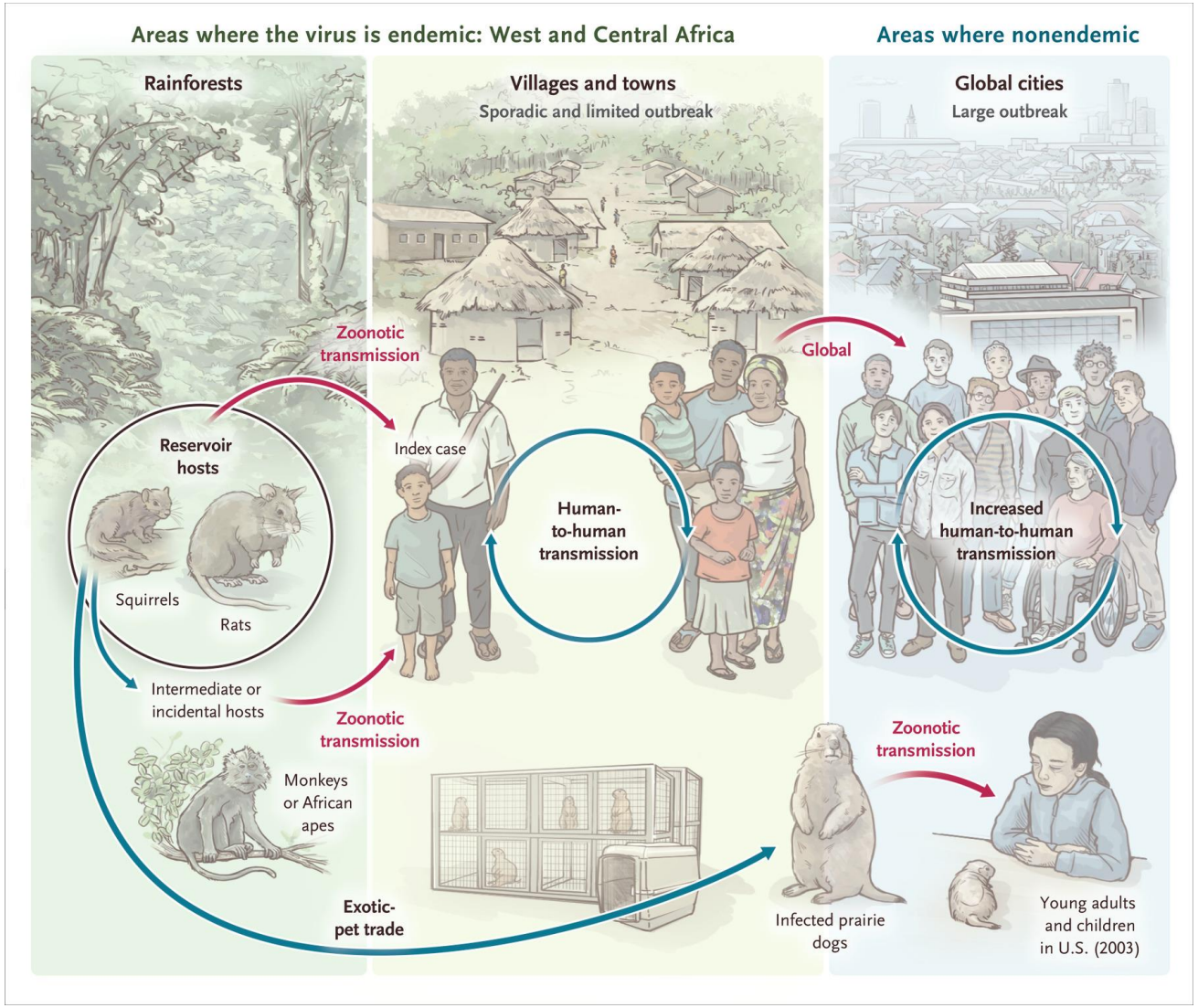
Mpox virus is transmitted through contact between the biologic fluids, lesions, or both of a reservoir animal or an incidentally infected host, such as a monkey, and a human being, the index patient.

The precise conditions of this viral spillover remain unclear, but contamination is thought to be most likely during hunting, as a result of bites from an infected animal, and during the transport, butchering, or consumption of infected animals.

Human-to-human transmission subsequently occurs, primarily among family members, but it may also occur in a nosocomial setting, at a clinic or hospital.

This human-to-human transmission can lead to sporadic cases of infection or epidemics, generally of moderate magnitude, which die out naturally within a few weeks or months, given the relatively low transmissibility of the virus in regions where it is endemic.

Natural History of Mpox



Gessain A, et al. N Engl J Med. 2022

On rare occasions, the mpox virus has emerged outside Africa.

The first time this is known to have occurred was in 2003, as a result of the importation into the United States of various rodents, including Gambian rats, from Ghana.

The rodents infected prairie dogs, which then infected young persons (young adults and children) in the United States.

Since 2017, the virus has again been escaping from Africa, this time in infected people, which resulted in the introduction of the virus into the gay, bisexual, and MSM community in 2022.

The rapid and extensive spread of mpox in this community, due to multiple contacts in the context of connected sexual networks, has contributed to the occurrence of the largest mpox epidemic ever observed.

Recent Situation of Mpox outbreak

World Health Organization

Table 1. Number of cumulative confirmed mpox cases and deaths reported to WHO, by WHO Region, from 1 January 2022 to 27 February 2023 17:00 CEST

WHO Region	Total Confirmed Cases	Total Deaths	Cases in past week[1]	7-day change in cases (%)
Region of the Americas	58 578	76	143	38%
European Region	25 843	5	5	-17%
African Region	1382	17	0	-
Western Pacific Region	248	0	3	200%
Eastern Mediterranean Region	82	1	0	-
South-East Asia Region	40	1	0	-
Total	86 173	100 0.1%	151	32%

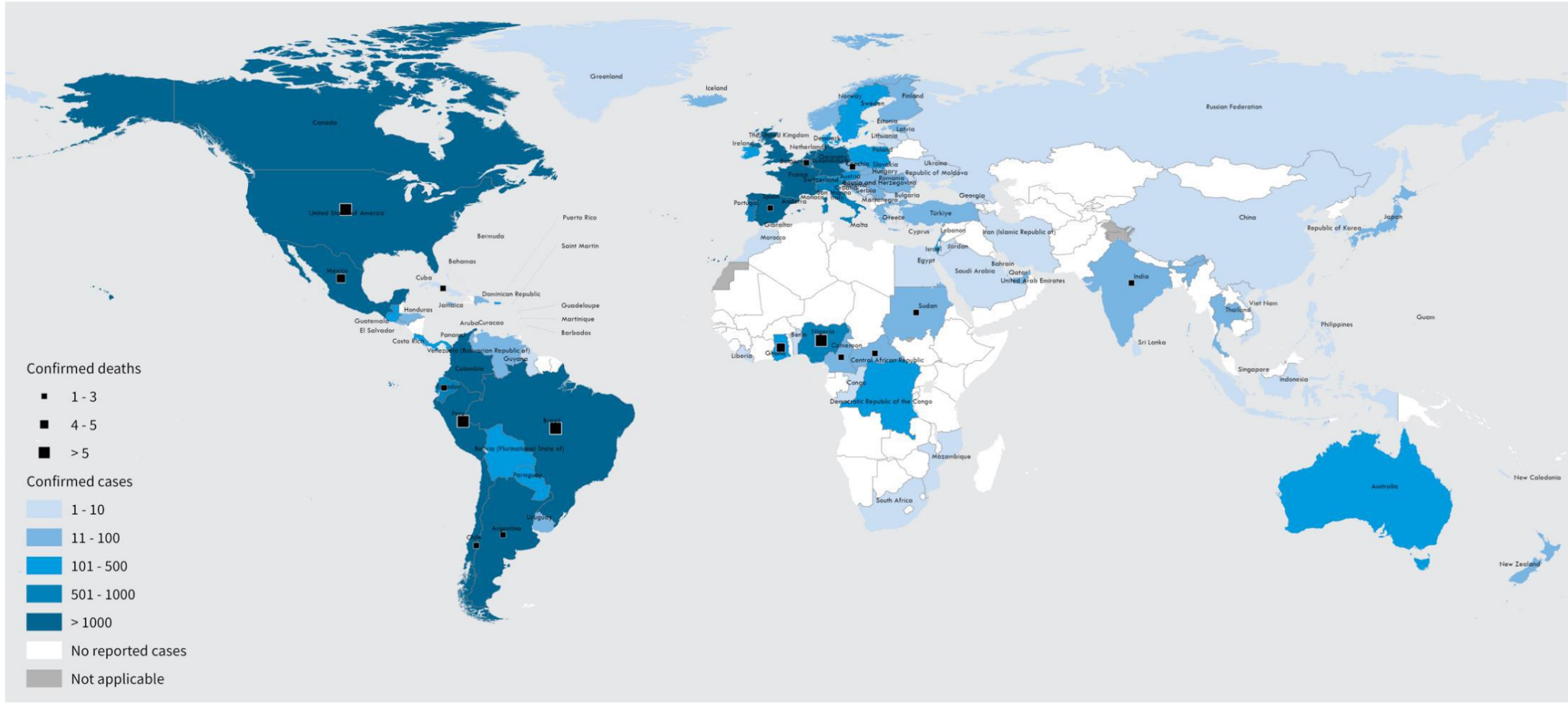
(-) Zero cases were reported in at least one week in the past two weeks

[1] Using the most recently completed international standard week (Monday - Sunday)

https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report---17---2-march-2023

Recent Situation of Mpox outbreak

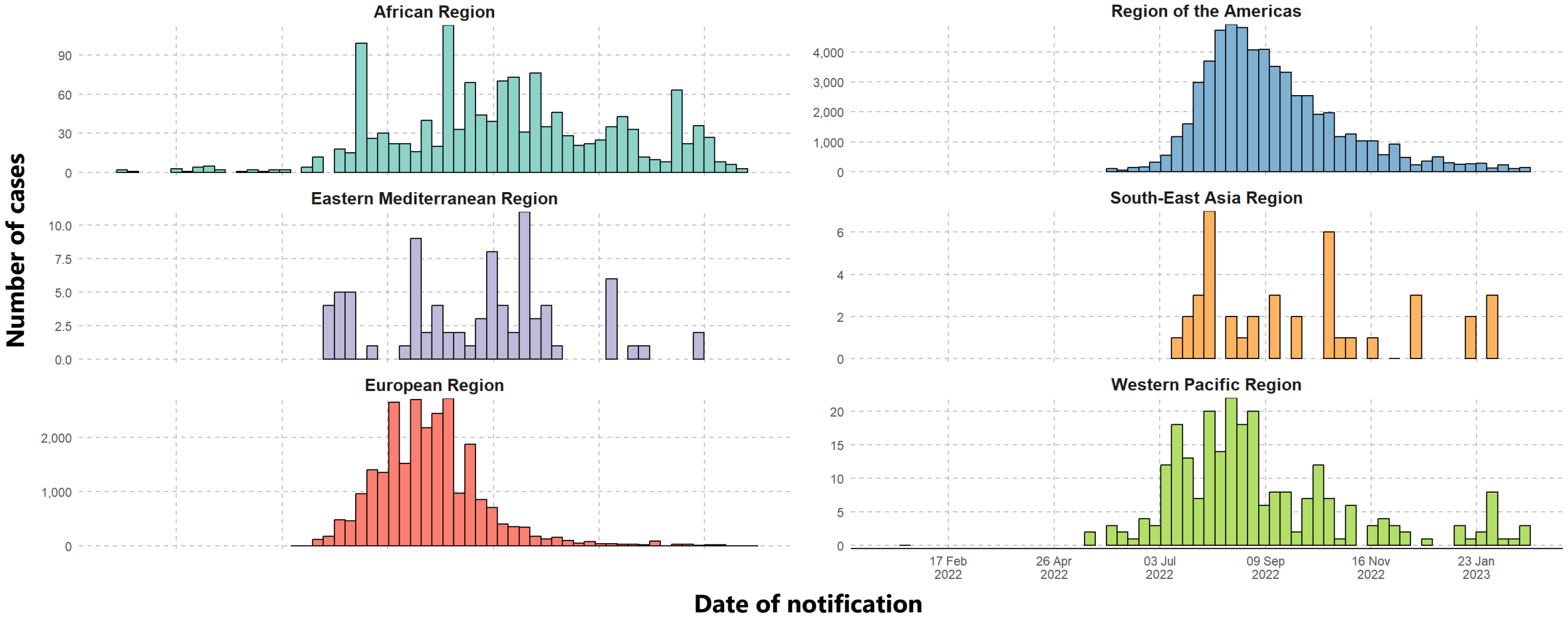
Figure 2. Geographic distribution of confirmed cases of mpox reported to or identified by WHO from official public sources from 1 January 2022 to 27 February 2023 17:00 CEST



https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report---17---2-march-2023

Recent Situation of Mpox outbreak

Epidemiological curves of weekly aggregated confirmed cases of mpox by WHO Region, from 1 January 2022 to 27 February 2023, 17:00 CEST*



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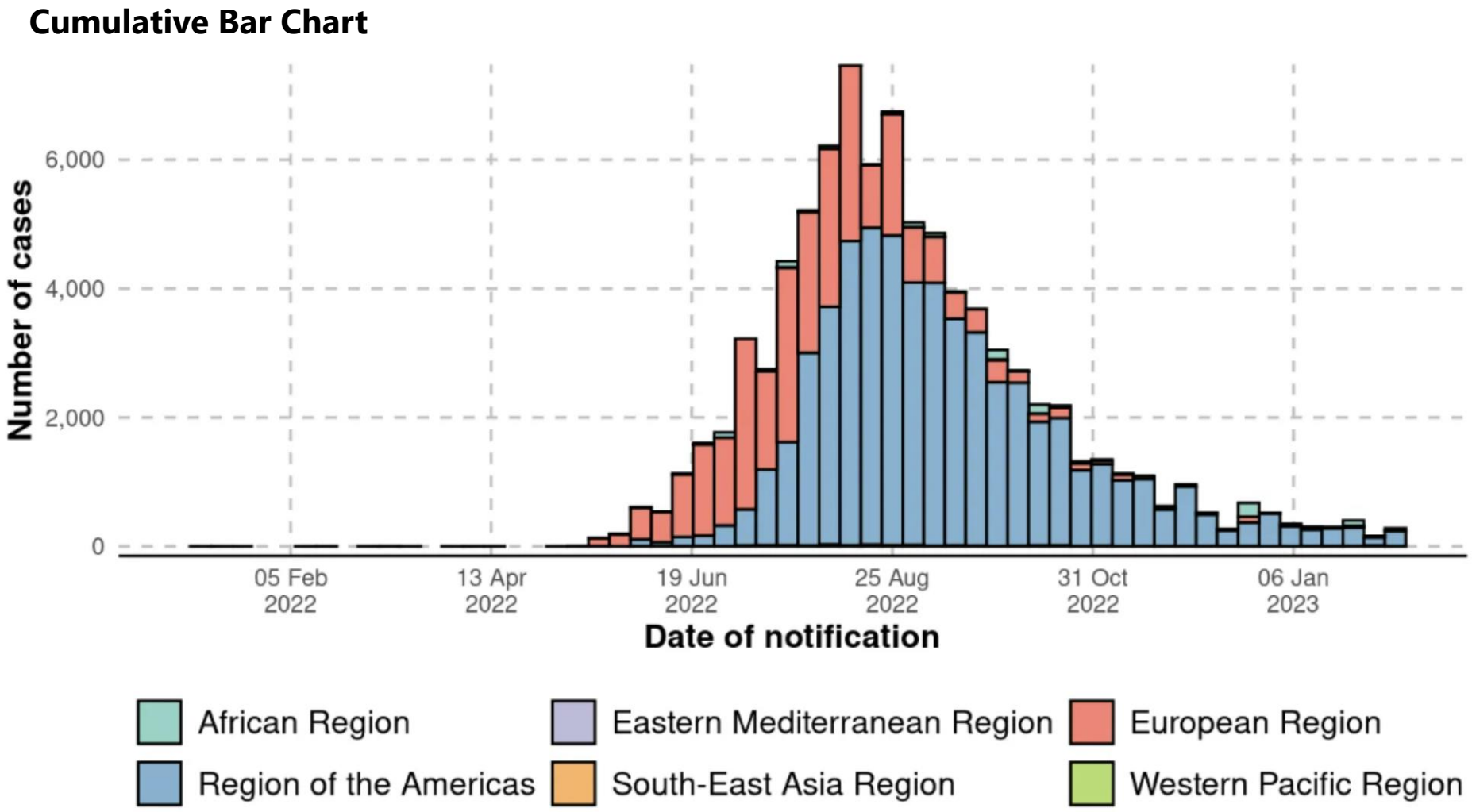
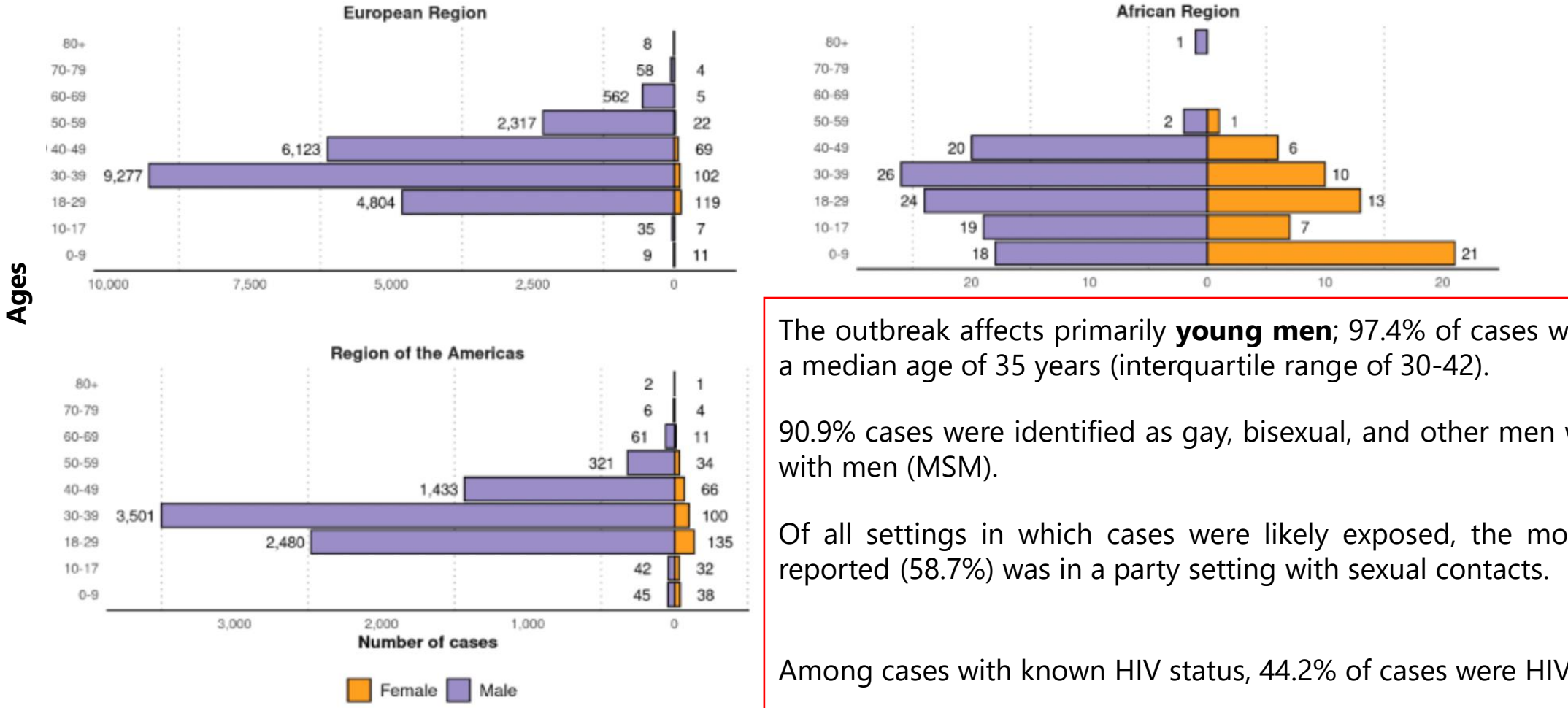
Recent Situation of Mpox outbreak



https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou/kekkaku-kansenshou19/monkeypox_00001.html

Age-sex pyramid of mpox cases

In the three WHO regions reporting the highest number of cases (n=31,012).



The outbreak affects primarily **young men**; 97.4% of cases were men with a median age of 35 years (interquartile range of 30-42).

90.9% cases were identified as gay, bisexual, and other men who have sex with men (MSM).

Of all settings in which cases were likely exposed, the most commonly reported (58.7%) was in a party setting with sexual contacts.

Among cases with known HIV status, 44.2% of cases were HIV-positive.

https://www.who.int/publications/m/item/multi-country-outbreak-of-monkeypox--external-situation-report--6---21-september-2022

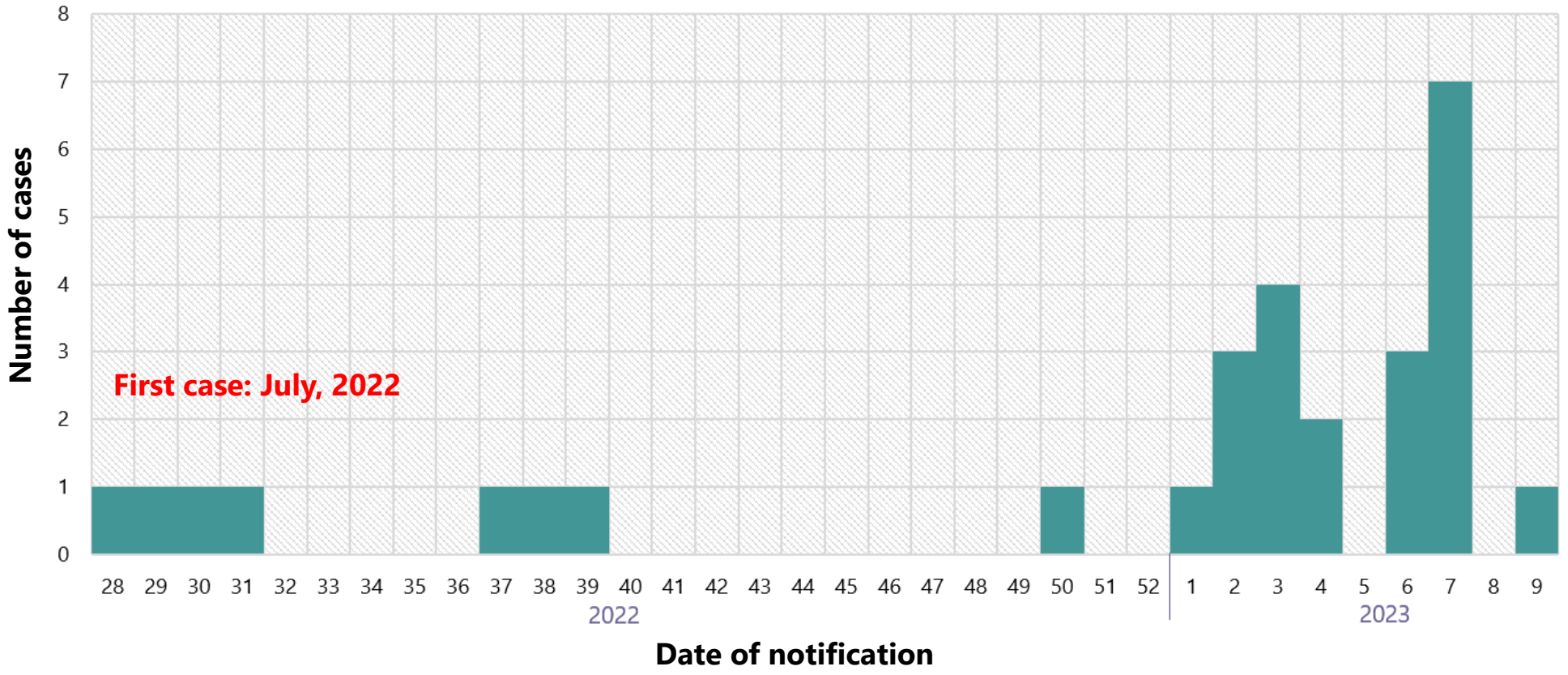
Recent Situation of Mpox outbreak in Japan

厚生労働省 Ministry of Health, Labour and Welfare

31 cases have been reported (March 7, 2023).

Since 2023, Mpox patients has been increasing especially in Kanto area (Tokyo, Kanagawa, Chiba, etc).

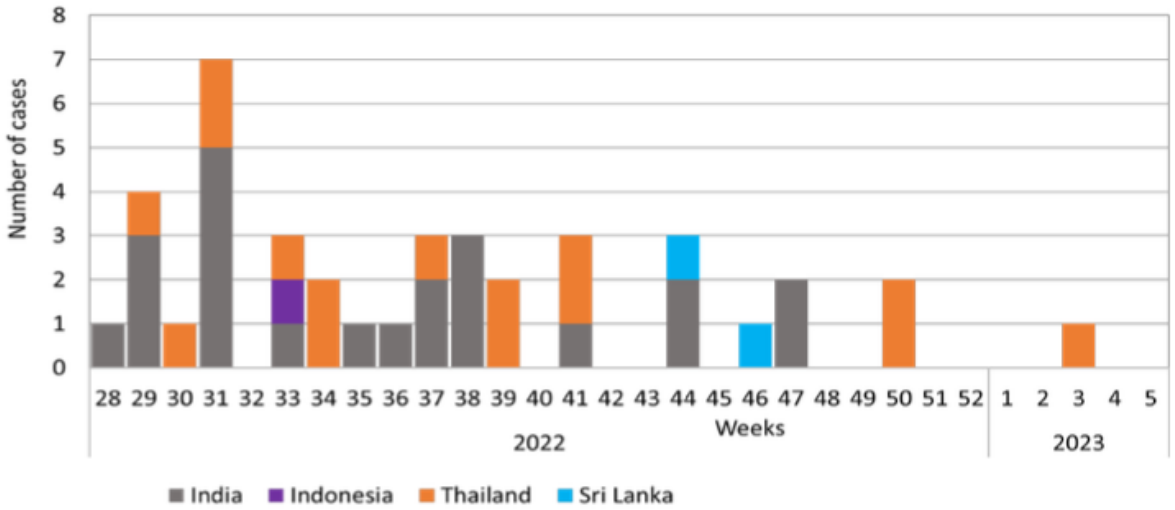
No history of international travel in most cases.



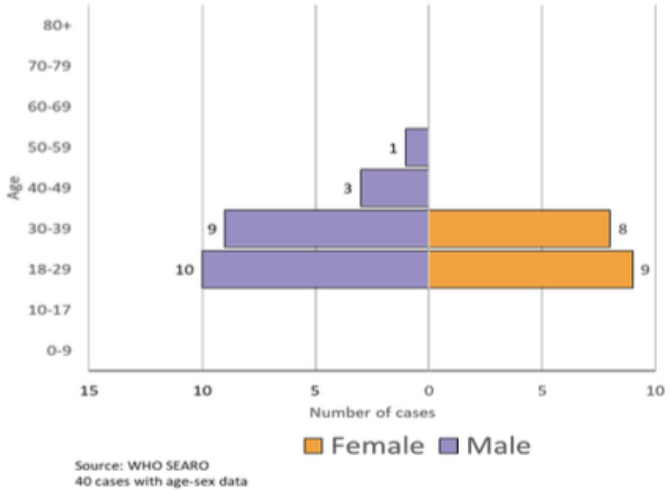
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou/kekkaku-kansenshou19/monkeypox_00001.html

Recent Situation of Mpox outbreak in WHO South-East Asia Region

Number of mpox cases reported in WHO South-East Asia Region by date of notification (14 July 2022 – 23 February 2023)

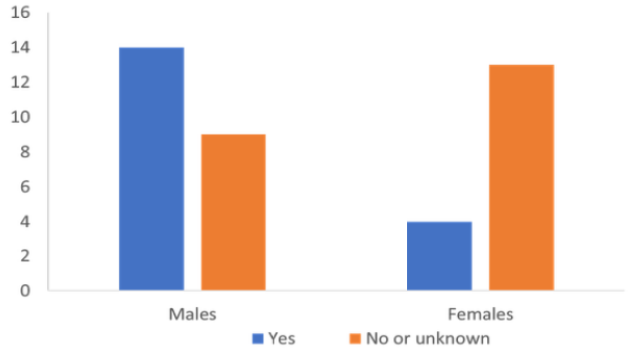


Age and gender distribution of mpox cases (as of 23 February 2023)



Men account for 58% of cases and women 43%, suggesting the proportion of males is much lower in the Region

Age and gender distribution of mpox cases (as of 23 February 2023)



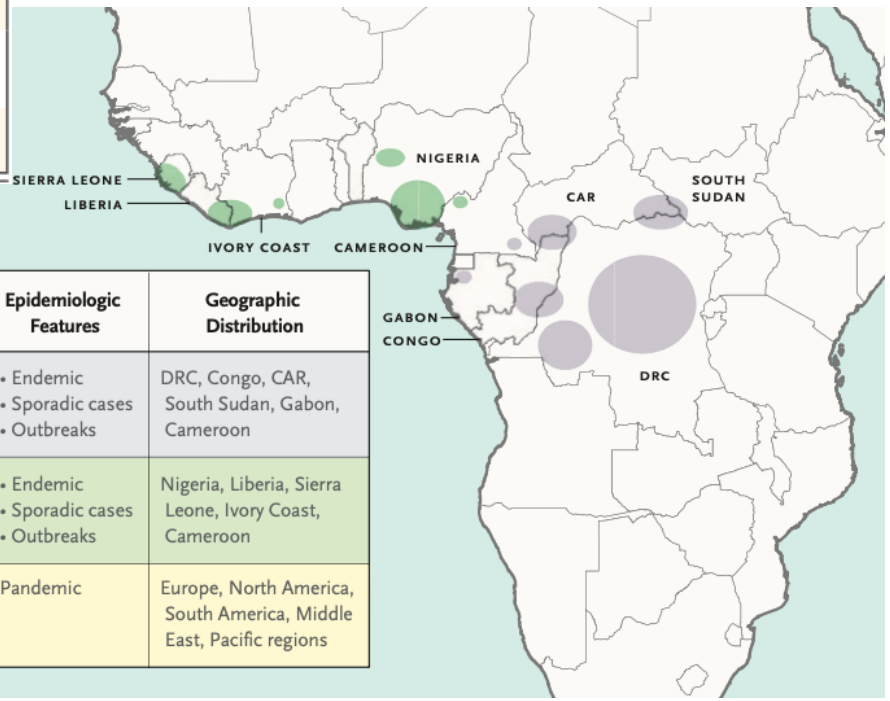
20 cases (50%) reported no recent travel history, suggesting they are likely locally acquired

Out of 18 cases reporting recent travel history, 89% report recent travel from countries in the WHO Eastern Mediterranean Region

https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report---17---2-march-2023

Table 1. Features of the Classic Form of Monkeypox and the New Clinical–Epidemiologic Form.

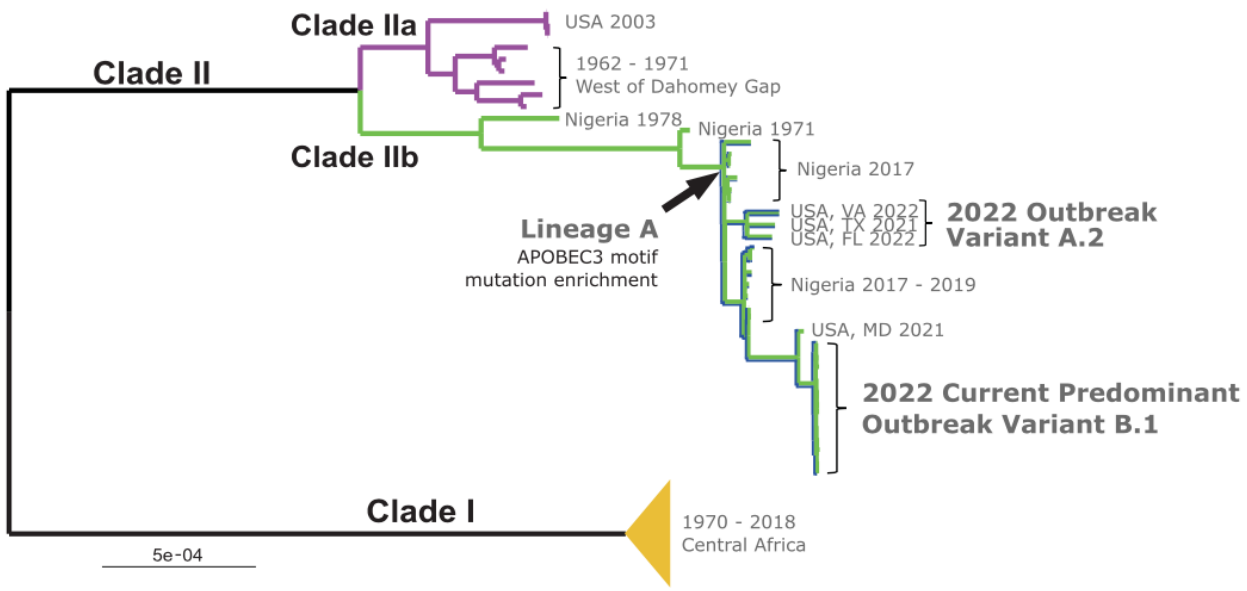
Variable	Classic Form, 1970s to the Present	New Clinical–Epidemiologic Form, 2022
Location	Central and West Africa	Countries where monkeypox is not endemic (Europe, North and South America, Middle East, Australia)
Affected population	Children and young adults (age at diagnosis increasing since 1980)	Young men who have sex with men (age, 31–40 yr)
Epidemiologic features	Sporadic cases and epidemics	Pandemic under way since May 2022
Transmission	Contact with infected animal reservoir (probably rodents), followed by human-to-human transmission	Exclusively human-to-human transmission
Dissemination	Mostly intrafamilial and limited nosocomial dissemination	Mostly sexual networking, condomless sex with multiple male partners
Clinical phase	Incubation, prodromal stage, eruption phase with skin lesions	Incubation, prodromal stage (not always present), eruption phase with lesions in an unusual distribution, especially on the genitals
Symptoms	Lesions on the face and extremities, with centrifugal distribution, often associated with cervical or axillary lymphadenopathy	Penile rash, perianal lesions, ulcerative lesions and vesicular rash, painful inguinal lymphadenopathy, pharyngitis, proctitis
Viruses	Central African and West African clades (clades 1 and 2, respectively)	West African variant (clade 3)
Case fatality rate (%)	1–15	0.025

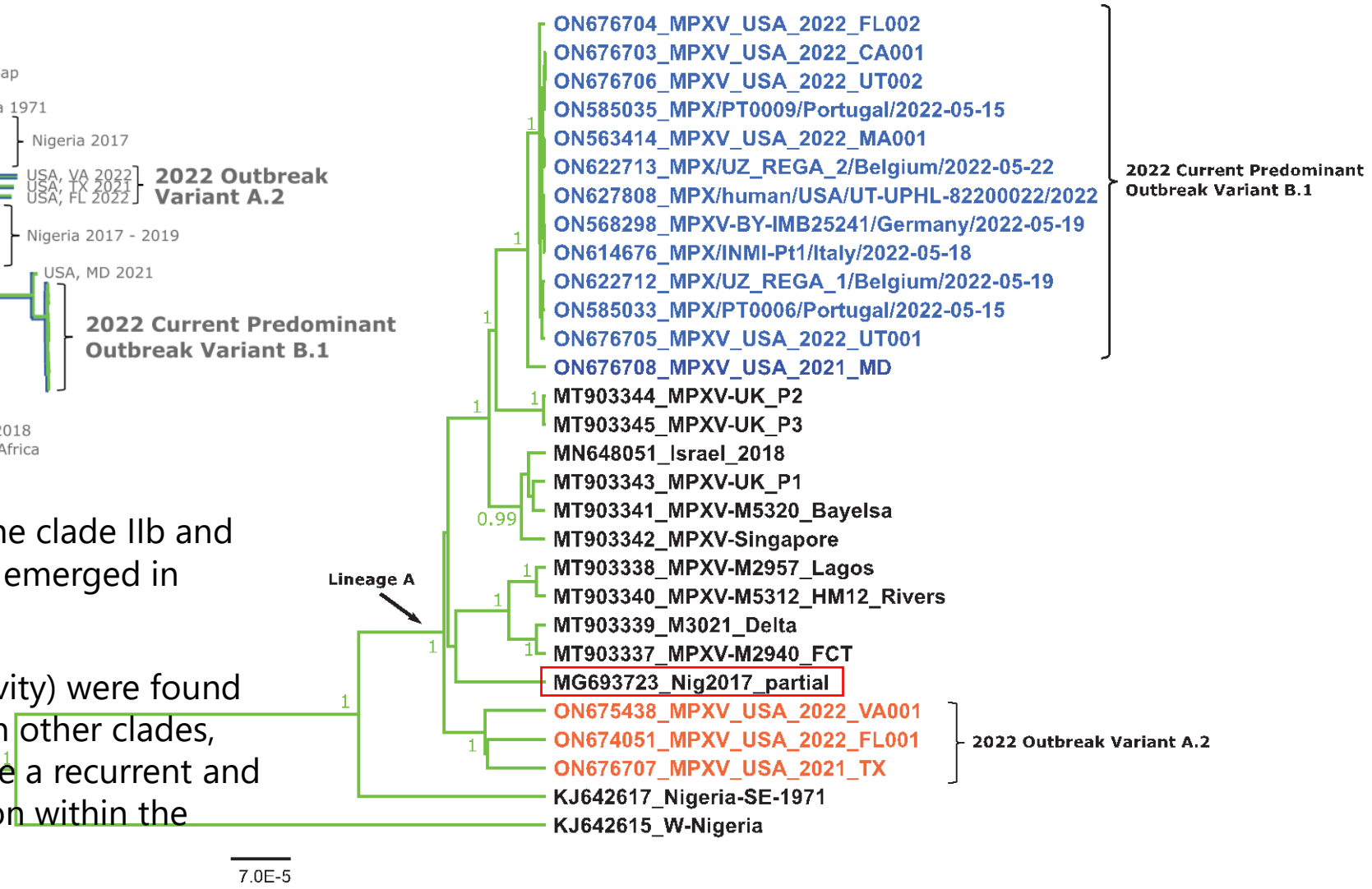


Original Clade Nomenclature	Revised Clade Nomenclature	Epidemiologic Features	Geographic Distribution
Central Africa	1	• Endemic • Sporadic cases • Outbreaks	DRC, Congo, CAR, South Sudan, Gabon, Cameroon
West Africa	2	• Endemic • Sporadic cases • Outbreaks	Nigeria, Liberia, Sierra Leone, Ivory Coast, Cameroon
New from West Africa	3	Pandemic	Europe, North America, South America, Middle East, Pacific regions

Gessain A, et al. N Engl J Med. 2022

The Lineage of Current Mpox Pandemic



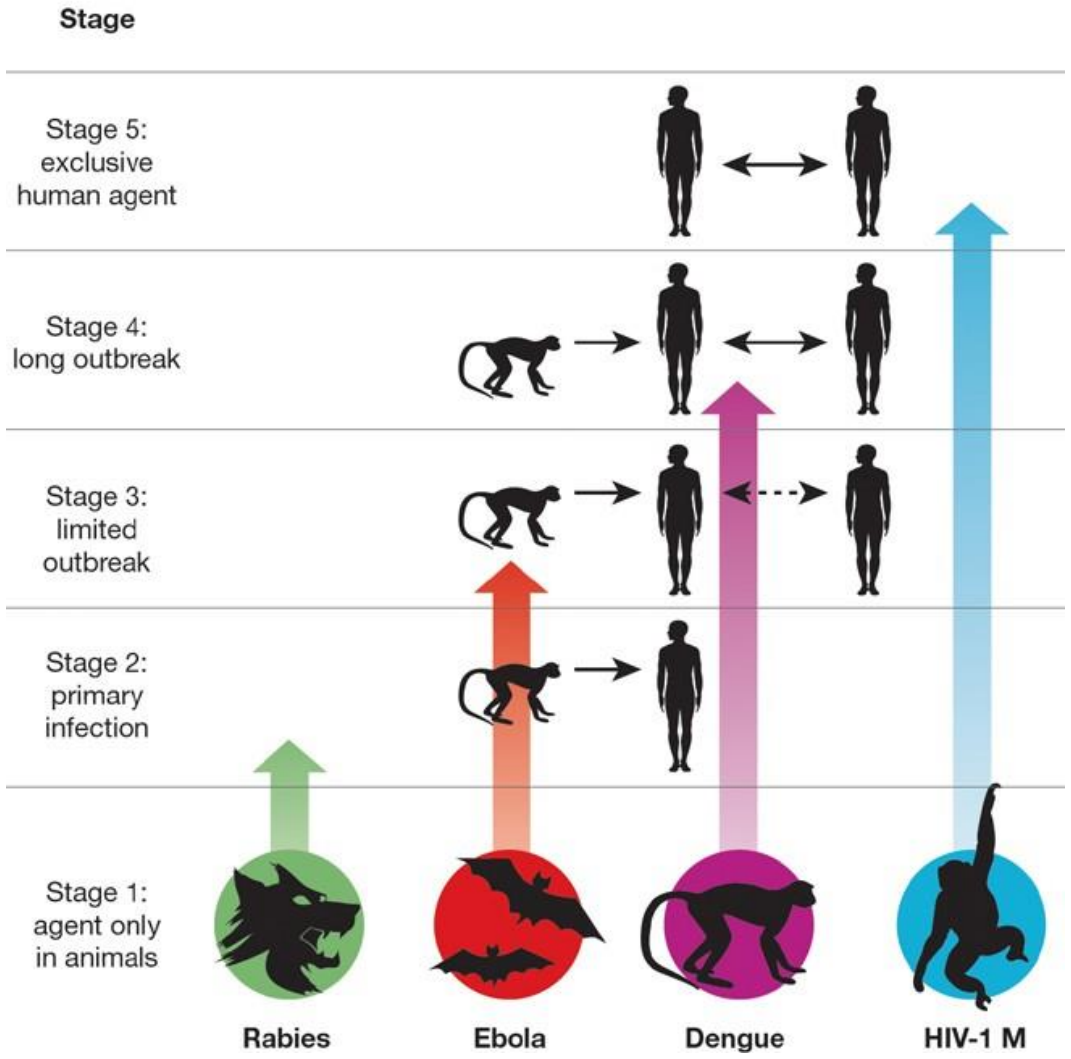


The pandemic mpox viruses belong to the clade IIb and are originated from the outbreak strains emerged in Nigeria in 2017

The GA-to-AA mutations (APOBEC3 activity) were found among Clade IIb, but not enriched within other clades, suggesting that APOBEC3 editing may be a recurrent and a dominant driver of mpox virus evolution within the current outbreak.

Gigante CM, et al. Science. 2022

Illustration of the five stages through which pathogens of animals evolve to cause diseases confined to humans



Stage 5. A pathogen exclusive to humans.

Stage 4. A disease that exists in animals, and that has a natural (sylvatic) cycle of infecting humans by primary transmission from the animal host, but that also undergoes long sequences of secondary transmission between humans without the involvement of animal hosts.

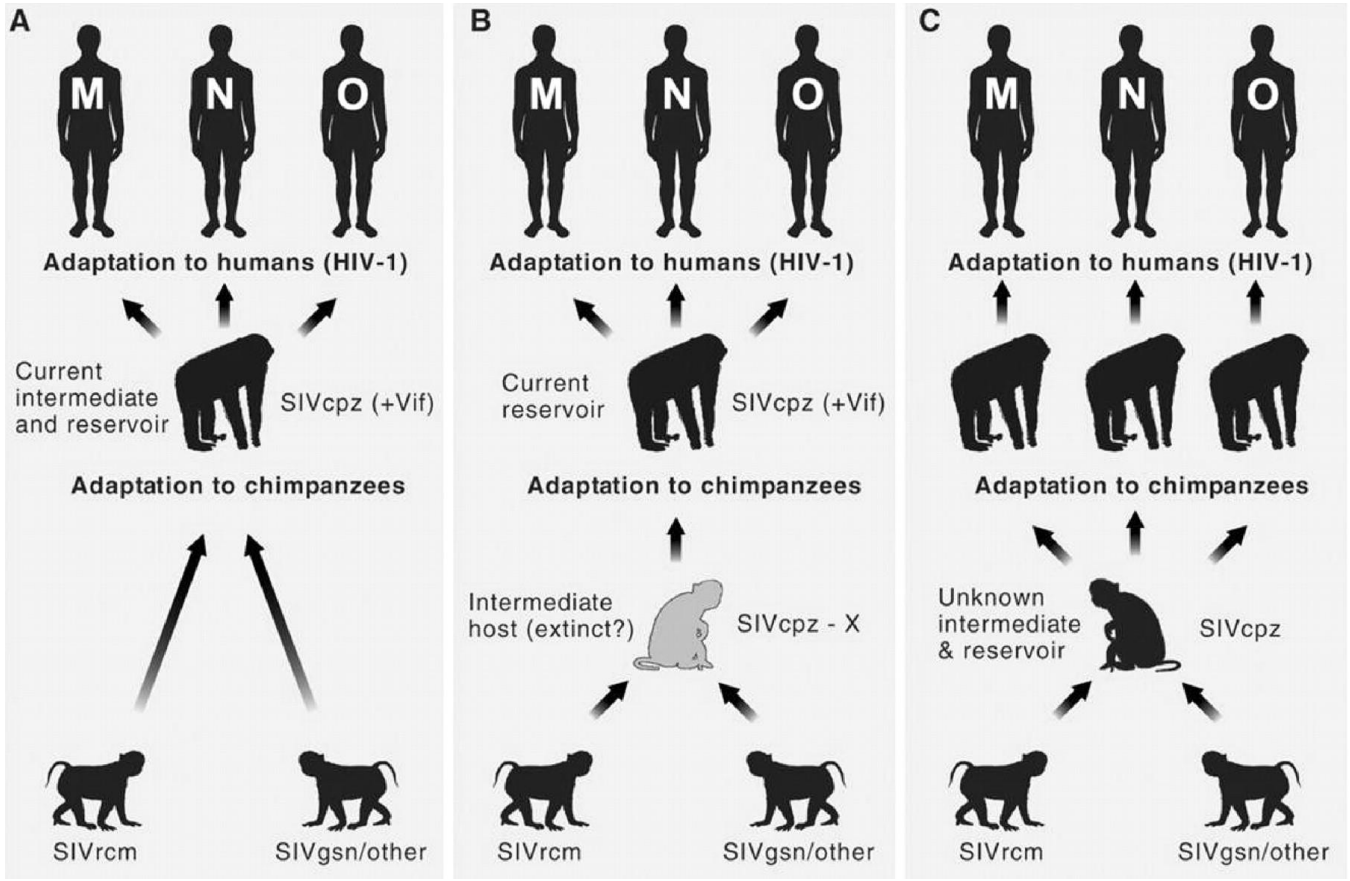
Stage 3. Animal pathogens that can undergo only a few cycles of secondary transmission between humans, so that occasional human outbreaks triggered by a primary infection soon die out.
Examples: Ebola, Marburg and monkeypox viruses.

Stage 2. A pathogen of animals that, under natural conditions, has been transmitted from animals to humans ('primary infection') but has not been transmitted between humans ('secondary infection'). Examples: Nipah and rabies viruses.

Stage 1. A microbe that is present in animals but that has not been detected in humans under natural conditions.

Wolfe ND, Dunavan CP, Diamond J. Origins of major human infectious diseases. Nature. 2007
https://www.nature.com/articles/nature05775#Sec3

HIV-1 was derived from Simian virus but not zoonosis now



The three major types of HIV (N, M, and O) each derived from a separate transfer event

repeated spillover
(through eating bushmeats?)

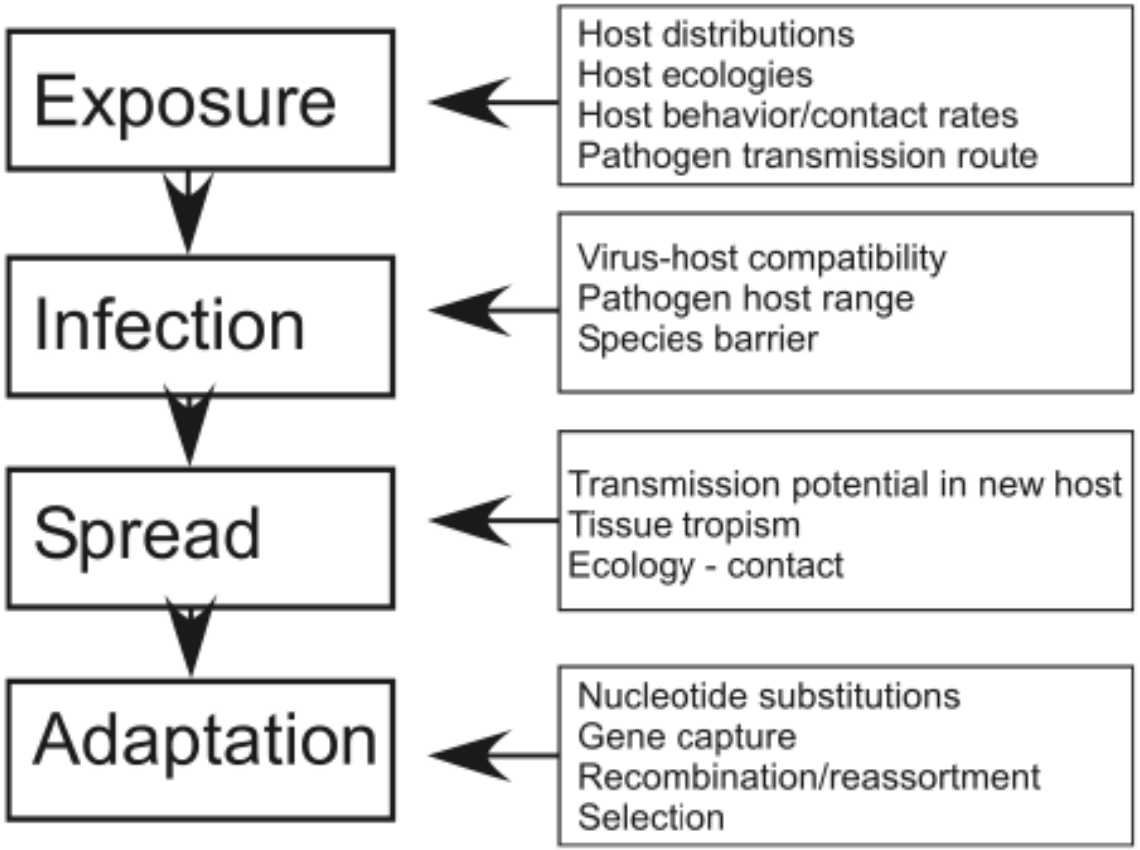
The recombinant SIVrcm/gsm that was adapted to chimpanzee

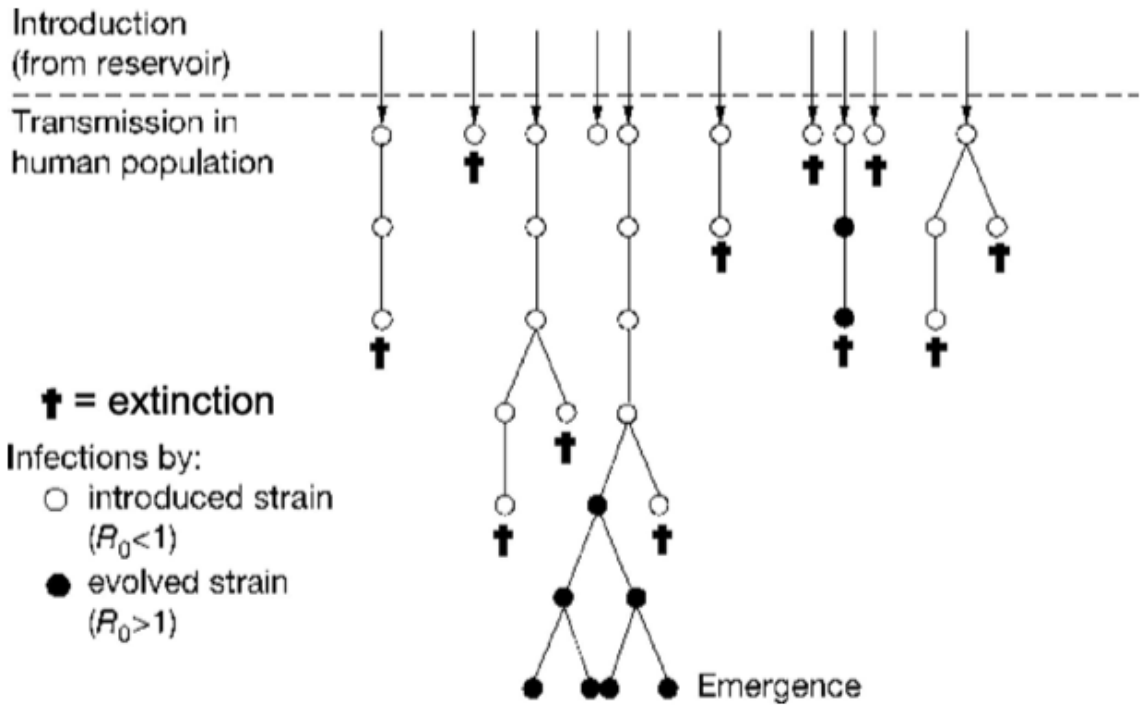
unknow intermediate host

The red-capped mangabeys (SIVrcm)
the greater spot-nosed monkeys (SIVgsn)

Parrish CR, et al. Microbiol Mol Biol Rev. 2008
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2546865/

The steps involved in the emergence of host-switching viruses





The transfer of viruses into the new host (e.g., human) population results in little or no transmission.
An occasional virus gains the ability to spread in the new host (R_0>1), and under the right circumstances for transmission those viruses will emerge and create a new epidemic.

Parrish CR, et al. Microbiol Mol Biol Rev. 2008
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2546865/

Genes of various poxviruses that have been found to be associated with the control of viral host range

Gene	Protein type[b]	Cultured cells with defect in virus tropism
Myxoma virus genes		
M-T5	Ankyrin repeats	Rabbit T cells; human tumor cells
M-T2	TNF receptor	Rabbit T cells
M-T4	ER localized	Rabbit T cells
M1 1L	Mitochondrial	Rabbit T cells
Vaccinia virus genes		
E3L	PKR inhibitor	Human HeLa cells, chicken embryo fibroblasts
K3L	dsRNA-binding protein	Hamster (BHK) cells
B22R/SPl-1 genes	Serpin	Human AS49 keratinocytes
C7L	Cytoplasmic	Hamster Dede cells
K1L	Ankyrin-repeats	Pig kidney: PK13 cells
Rabbitpox virus gene		
SPl-1	Serpin	Pig kidney: PK15 A594
Ectromelia virus gene		
p28	E3-ubiquitin ligase	Mouse macrophages
Cowpox virus gene		
C9L/CP77/CHOhr	Ankyrin repeats	Chinese hamster: W-CL9^{+} grows in CHO cells, W-K1L/C9L^{+} grows on PRK13 cells

Parrish CR, et al. Microbiol Mol Biol Rev. 2008
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2546865/

My question and concern

Will the pandemic mpox virus be the stage 4 virus or the stage 5 virus?

If the pandemic (human-adapted) virus can infect and maintained in animals (rodents) lived in a town/city, it will be a serious issue for veterinary public health.

Thank you for your attention!