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Perspective

Possible scenarios for the spread of mpox outside the endemic focus in Africa

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ABSTRACT

The recent expansion of mpox in Africa is characterized by a dramatic increase in zoonotic transmission (clade Ia) and the emergence of a new clade Ib that is transmitted from human to human by close contact. Clade Ia does not pose a threat in areas without zoonotic reservoirs. But clade Ib may spread widely, as did clade IIb which has spread globally since 2022 among men who have sex with men. It is not clear whether controlling clade Ib will be more difficult than clade IIb. The population at risk potentially counts 100 million but only a million vaccine doses are expected in the next year. Surveillance is needed with exhaustive case detection, polymerase chain reaction confirmation, clade determination, and about severe illness. Such data is needed to identify routes of transmission and core transmitters, such as sex workers. Health care workers are vaccinated to ensure their protection, but this will not curb mpox transmission. With the recent inequitable distribution of COVID-19 vaccines in mind, it is a global responsibility to ensure that low-income nations in the mpox epicenter have meaningful access to vaccines. Vaccination serves not only to reduce mortality in children but limit the risk of future mpox variants emerging that may spread in human populations globally.

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Introduction

Over the past 2 years, mpox has twice been declared a "Public Health Emergency of International Concern" (PHEIC) by the World Health Organization (WHO). In 2022, it was in response to a global outbreak of a new clade IIb primarily among men who have sex with men (MSM), ultimately with >100,000 cases reported worldwide centered in Europe and the US [1]. In August 2024, it was in response to a complex outbreak originating in the Democratic Republic of the Congo (DRC), and many fold increase in mpox cases caused by the original central African clade I variant (now designated Ia), but also the emergence of a human-to-human transmitted clade Ib that has since spread to neighboring countries [2]. On top of this, clade IIb continues to circulate at low levels globally [3].

From the first recognized human case in 1970, mpox in Africa was a zoonotic infection linked to exposure to a zoonotic reservoir and mostly affecting young children and only causing smaller outbreaks with person-to-person transmission often in household settings. In 2017, Nigerian physicians pointed to a marked change in the epidemiology of the mpox virus including more severe infections in people living with HIV, affecting young urban men rather than children; but testing and genetic characterization were not done at that time [4].

The growing mpox threat in the last years may in part be explained by waning population-level pox-virus immunity after the cessation of smallpox vaccine programs following the declaration of global smallpox eradication in 1980.

Now 45 years later, the majority of the population is susceptible. This is particularly pertinent in rainforest areas of Africa where mpox is enzootic. For instance, of 249 cases reviewed in Nigeria, those infected were between 1 and 52 years of age, with the average age range between 4 and 40 years [5]. Household transmission to children and adolescents is well known, and limited smallpox immunity in the wider population thus provides an opening for the spread of a new epidemic pox virus.

Many questions remain about the transmission of the emerging clades Ia, Ib, and IIb. The clade IIb outbreak in MSM in 2022 and achieving control of mpox by a combination of behavioral changes among infected persons in the MSM community and immunity from sexually transmitted infections (STI) and vaccination of MSM with a higher number of partners, though it is now endemic at low levels outside Africa [6].

Epidemic situational awareness and obtaining control of mpox is far more difficult in low-income settings where diagnostics are limited and stigma surrounds sexually transmitted diseases. The endemicity of clade IIb outside of Africa was demonstrated in an innovative study that analyzed virus content in used condoms found in parks and brothels in several nations from Southeast Asia and found that 1.3% contained clade IIb mpox virus [3]. Furthermore, two clade IIb cases of sexual infection in Dubai were reported from Vietnam [7], followed by the reporting of an additional 25 clade IIb cases without a travel history from Vietnam [8].

Genetics and molecular evolution

The emergence of clades Ib and IIb are both characterized by an elevated mutation rate and a gradual accumulation of mutations in the virus that are consistent with the effect of APOBEC3F, an mRNA editing enzyme, and part of the innate immune response in human cells [9,10]. This enzyme induces specific mutations (TC to TT, seen as GA to AA on the opposite strand) on the viral single-stranded DNA. The much higher rate of molecular evolution in clade Ib and IIb (about 28 times faster than the background rate) and the over-representation number of APOBEC3F mutations indicate that the virus has jumped to the human host and transmits from human to human (H2H) [10]. This is different from the original clades I and II (now Ia and IIa) where human cases infected by a zoonotic exposure resulted in limited chains of household transmission and then died out. Molecular clock analyses have estimated that the H2H-transmitted clade IIb emerged around the year 2015/2016 [10], while clade Ib emerged in 2023 [11]. These must be unrelated events, as the underlying clades I and II diverged an estimated 600-800 years ago and occurred in different geographies. Two studies uncovered the phylogenetic patterns of clade IIb [10,12], while 2024 studies described the new clade Ib in DRC [11]. Recent data from the DRC show sustained H2H transmission of clade Ib in Kinshasa [13].

The emergence of clade Ib

In Africa, clade Ib is on the rise and has so far caused substantial outbreaks in the DRC and several neighboring countries, especially Burundi [14]. In contrast to the MSM network transmission outside of Africa for clade IIb, including women and children in Africa, the spread of clade Ib outside Africa is not so clear.

Originally, from the DRC outbreak in a mining town, the clade Ib virus was found to be initially transmitted by intimate contact in a heterosexual network of sex workers [11]. But later reports, including from Burundi [15], have included many cases in young children, pointing to a role of close contact transmission from infected adults to their children within households [16,17]. Hence, Ib may not be an STI as such, but transmission merely reflects close skin contact. Sorting out the relative contribution of sexual transmission vs close physical contact to children is urgently needed.

Outside Africa there have been only a few travel-related cases of clade Ib detected and none of clade Ia. In Europe, on August 15, Sweden reported a clade Ib case imported from the DRC [18]. On November 4, the UK reported an imported case of mpox clade Ib with a travel history from Africa and subsequently three secondary cases, all household contacts to the index case [19]. On November 16, California reported a travel-related clade I case (presumably Ib) infected in Africa [20], on the November 22, a travel-related case of mpox clade Ib was reported from Canada, and on the December 16, Germany reported a family cluster of four clade 1b cases.

One possible scenario for the future epidemiology of clade Ib is the global spread of the variant in heterosexual high-risk networks. Another scenario is that clade Ib also gets into the MSM network, though the spread would be limited by immunity already obtained in the high-risk MSM population (from prior vaccination or clade IIb infection).

Mathematical models can be parameterized to predict the possible spread of clade Ib in a heterosexual network together with close contact infections to children [21,22], similar to models that have been done for clade IIb in the MSM network [5,6,21,22]. Such models can use observed data on sexual activity and actual

patterns of mpox in a country to validate outputs. Once validated, such models can be used to study different scenarios and predict the most effective use of limited vaccine doses.

Methods for the detection and typing of mpox clades

The diagnosis of mpox relies on polymerase chain reaction testing of material obtained from skin lesions or from the pharynx, anus, or rectum. Antigen tests and serology are at present not recommended. The accuracy of mpox antigen tests is not known, while the interpretation of antibody testing results between different orthopox viruses is challenging due to immunological cross-reactivity. Clade Ib has a deletion in one of the sites [23], which has been used for clade-specific polymerase chain reaction and thus, shows the importance of continuous whole genome sequencing to advance diagnostic assays [17].

Whole virus sequencing is crucial to describe the clade-specific epidemiological and virological evolution. There has been a recent accumulation of this data in GISAID in the context of recent phylogenetic studies [24]. However, only a few sequence data for clade Ib in Burundi are available in the public domain and the relationship between this clade and clade Ib in the eastern DRC is therefore at present uncertain.

Mortality and severe morbidity

There is also some uncertainty about the case fatality for the clade Ib variant, relative to the "old" clade I (now Ia). A study about case fatality of clade 1b variant infection, relative to clade I mortality in the DRC during 1980-1985 reported an overall case fatality of 11% and 15% in children under 5 years of age [25]. The discrepancy between the 1980s and the present situation may be explained by ascertainment bias. The case fatality in the current DRC outbreak is far lower, at about 2% but with many unknowns [17]. This apparent reduction over time may either be due to more effective surveillance in 2024 that catches less severe cases or the emerging clade Ib truly gives a lower case fatality rate.

This impression comes from surveillance data from Burundi where only clade Ib appears to be circulating. As of November 18, surprisingly no deaths have been recorded so far out of >1800 confirmed cases [17]. This absence of deaths was also reported earlier in Burundi cases up to September, although some hospitalized cases were not yet resolved [17].

Age-specific estimates up to November 2024 reported by the DRC show an overall mortality rate of 2.6% [15], however, the clade-specific data are not reported.

In Table 1, we compare transmission, transmissibility (R_0), status as a human pathogen in 2024, and case fatality in unvaccinated persons between smallpox and mpox clade Ia, Ib, and IIb.

Mortality should not be the only severe outcome of concern. In two studies, a 50% rate of miscarriage among mpox-infected pregnant women was reported in the DRC (subclade not known) [11]. Also, mpox cases may experience conjunctivitis, blepharitis, keratitis, corneal ulcers, and even loss of vision [15,27]. Anecdotal evidence suggests that clade I infections (unclear if Ia or Ib) may cause chronic vision problems in as many as 20% of the mpox cases [27]. This seems similar to a common issue of blindness after smallpox infections historically.

Clearly, a better understanding of the spectrum of severe outcomes such as spontaneous miscarriage and chronic vision problems, by clade and age stratification, is of key importance to better target high-risk populations with interventions including the use of vaccines. The antiviral drug tecovirimat has been used to treat mpox, but results of randomized, controlled trials are still awaited.

Transmission and epidemiology of clade Ib

By November 18, 2024, 20 African countries have reported 55,413 mpox cases [11]. Phylogenetic analysis of clade Ia isolates from DRC is consistent with repeated spillover events from zoonotic reservoirs and stuttering chains of transmission without an APOBEC3 mutation pattern. In contrast, for clade Ib, the APOBEC3 mutation pattern suggests that it has jumped to the human host and is seeing more sustained H2H transmission [11,28]. Already in January 2024, sexual transmission of clade Ib was reported from south Kivu and in September from Goma, north Kivu province (all in the DRC). The age patterns in the south Kivu outbreak suggest that close skin contact is also an important mode of transmission to young children. In an ongoing outbreak of clade Ib in Burundi, 55% were children, and many of these were under 5 years of age [15]. The study in Goma used contact tracing to show that clade Ib is transmitted between children in displaced person camps where hygiene is poor and people live close together [29].

The few travel-related clade Ib cases outside Africa seem in particular to originate from Kinshasa, the capital of the DRC [30]. Surprisingly, only a few international clade Ib cases have been reported so far, albeit with a small cluster of linked cases in London [19].

The spread of clade Ib in heterosexual sex workers may be the primary mode of transmission with the cases among young children being secondary contacts from infected household members. For clade IIb, modeling studies have clearly demonstrated the importance of the number of sexual partners as a main predictor for the basic reproduction number [6,21,22]. Other studies found that sexual transmission can explain the increased outbreak potential of clade Ib compared with clade Ia [21,22].

Control strategies: what to do and what about vaccines?

Two types of vaccinia virus vaccines are currently available, two replicating competent vaccinia virus vaccines (ACAM2000, LC16m8) that cannot be used in immunocompromised individuals and therefore require an HIV test before administration, and a non-replicating vaccinia virus vaccine, the modified vaccinia Ankara vaccine (MVA-Bavarian Nordic, JYNNEOS). A recent systematic review found that the MVA-Bavarian Nordic vaccine's effectiveness against clinical mpox was between 76% and 90% [31]. Randomized controlled trials are needed with the ACAM2000 and JYNNEOS vaccines, which are not yet approved for use in children, and proxy markers for protective immunity have not been defined. However, in Japan in 1975, the LC16m8 vaccinia virus vaccine was licensed for smallpox without age restriction and the indication has been extended for the prevention of mpox in 2022.

One model of clade I spread in the DRC (mostly clade Ia; the study predicted effects in 2023, which is before clade 1b became widespread) predicted that vaccinating 80% of all children under 5 years of age would be the best use of a vaccine, and would result in a 29% reduction in cases and a 43% reduction in deaths [32]. Such a strategy would currently require 33 million doses of vaccine, far more than what is expected to become immediately available and must await clinical trials to ensure safety and effectiveness in children. The model was created largely on clade 1a zoonotic transmission, therefore a model specifically for areas where clade Ib causes the outbreaks is needed [32]. In such models it would be important to also explore whether clade Ib might primarily be spreading in sexual networks and what contribution spread among children between households might be making.

If clade Ia continues to cause repeated introduction into children from the zoonotic reservoir and to prevent future H2H clades from emerging, consideration might be given to including mpox vaccination in a longer-term perspective into the childhood

Table 1
Comparison of smallpox, mpox clade Ia, Ib, and IIb.

Orthopox virus/variant	Emergence as a human pathogen	Transmission	Trans-miscibility (Ro)	Status as a human pathogen in 2024	Case fatality in unvaccinated persons
Smallpox	Emerged 1000s of years ago Eradicated in 1980	Respiratory, and close contact	~6	**Eradicated** In 1980, whereafter smallpox childhood vaccination program was ended	~30%[a]
MPXV -Clade Ia	Never emerged (zoonosis)	Contact with rodent reservoir; stuttering chains of transmission H-2-H	<1	**Never emerged** Over 20000 cases in west- and central DRC in 2024 (huge increase) No travel-related cases outside Africa	5-10%[b]
MPXV -Clade IIb	~2015	Sexually transmitted in global MSM network	~1.5-2	**Endemic** Spread among MSM since summer 2022; >100000 cases globally High-risk MSM segment vaccinated Endemic; controlled	0.2%[c]
MPXV -Clade Ib	~2023	Sexually transmitted in heterosexual networks, and by close contact	>1	**Emerging** Outbreaks are limited to Africa, largely eastern DRC, and Burundi Few travel-related cases outside Africa	1.9% and 0%[d]

DRC, Domanic Republic of Congo; MPXV, mpox virus; MSM, men who have sex with men.
Overview of Orthopox virus and variants that have affected the human population.
[a] Smallpox: In Denmark in the 1700s, about 30% of all young children died of smallpox; after the vaccine was introduced around 1800, the case fatality rate was 30% among unvaccinated persons [26].
[b] Mpox, clade Ia: Previously known as clade 1 and the more severe of two clades circulating Africa after smallpox eradication. A 5-10% case fatality rate for mpox clade 1a is likely an overestimate, as milder cases may not be counted.
[c] Mpox, clade IIb: Globally, 116000 cases and 255 deaths have been reported so far (OurWorldInData; https://ourworldindata.org/explorers/monkeypox) among the affected adults/MSM population.
[d] Clade Ib: In the first described outbreak in DRC, 1.9% (two of 108 confirmed cases) died in an outbreak affecting mostly adults [11]; however, in Burundi where only clade Ib is circulating there were no deaths reported among over 1800 confirmed cases in outbreaks involving mainly children [17].

vaccine program in mpox endemic areas. This would gradually build up pox-virus immunity in the wider population and support mpox (and other pox viruses) control in the longer time perspective. But it would probably not immediately reduce the spread of clade Ib through transmission in adults with multiple sex partners.

Alternative strategies for clade Ib vaccine control could be to limit transmission by offering vaccination to adults with many sexual partners. This strategy was used to control the clade IIb epidemic in MSM. This would include targeting for instance sex workers, which may be logistically challenging due to stigma, but could be done with a limited number of doses by targeting persons seeking treatment for any STI, as well as people on HIV pre-exposure prophylaxis and those on HIV treatment. This strategy is supported by a modeling study that conclude that to control sexually transmitted mpox, vaccination should target individuals with most partners [21].

With the recent unequal distribution of COVID-19 vaccines in mind, it is now a critical and global responsibility that low-income nations that are in the epicenter of the emerging mpox outbreaks (and the source of future novel emerging clades) have meaningful access to vaccines, not only to reduce morbidity and mortality locally but also to curb global spread. Only a handful of cases of clade Ib cases have been reported outside Africa, and vaccination is only potentially relevant for travelers to endemic areas, such as relief workers to high-risk settings.

Summary and conclusion

Over the past few years, two new mpox variants, clades IIb and Ib, have jumped from the animal (likely rodent) reservoir to the human host for the first time and are now capable of H2H spread through close contact and sexual encounters. In particular, nations that are characterized both by mpox endemicity due to the presence of the reservoir and a low median age are at particular risk, as persons born after 1980 (after the smallpox vaccination programs ended) have no (or very limited) immunity to pox virus. The clade IIb outbreak is now more or less under control globally although condom surveillance still found its presence in high-risk populations in several countries [3].

Clade Ib is now spreading in central Africa but with a less clear primary mode of transmission. This clade can clearly also spread in heterosexual high-risk networks, and to children and other contacts, possibly by skin-to-skin contact. Improved surveillance, including outbreak investigations and viral sequencing, is needed to support local control and prevention efforts.

It is likely that sex workers and other high-risk adults in affected areas should qualify for vaccination, but more data are needed in areas with clade Ib outbreaks. Consideration should be given for health workers also to be vaccinated in affected areas for ethical reasons to ensure their personal protection, although this will only minimally affect the spread of the viruses. The role of vaccination in children exposed to both clade Ia and Ib depends on more data from surveillance for instance on severe outcomes such as blindness in infected children. If clade Ia continues to cause repeated spillover events, incorporating mpox vaccination in the childhood vaccination program could be a prevention option in risk areas for such events if vaccination of children is found to be safe and efficacious.

Globally, clade Ib travel-related cases have been reported in a few countries outside Africa, but as long as the outbreak is not under control, the risk of introduction and spread in large cities, particularly with considerable sex worker industries increases.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

Not relevant.

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Author contributions

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