6.1.1.4 Summary

The systematic review was conducted in two phases (see Annex 5 for details) and the data is not yet published but is available. The Summary of Findings table is based on non-comparative studies identified to indirectly informs the IPC PICO question. These studies described routes of transmission for suspected and confirmed mpox cases. Based on these studies, ten mpox transmission routes were identified amongst the 32317 cases of MPXV infection reported in these studies: confirmed sexual contact(65.1% of mpox cases), suspected sexual contact(30.3%), close contact (non-sexual)(2.9%), fomite/environment (0.36%), transplacental (0.01%), percutaneous injury (0.09%),direct deposition(formerly droplet) (0.003%), inhalation (0%) animal/animal products (0.48%) and multiple routes (0.83%) [26,27,47,57,86,87,97,102,103,128,130,131,132].Close contact (sexual /nonsexual) was the predominate mode of transmission (95.3 %). Transmission through percutaneous injury with contaminated object, fomite and transplacental and animal products were uncommon, accounting for approximately 0.1%. There was only one case of self-reported droplet exposure out of the 32, 317 cases that reported route of transmission data [74]. The single case was one of 12 breakthrough infections after postexposure vaccination against mpox. The study defined droplet transmission as occurring during the presence of the exposed person without masks at less than two meters for at least three hours with a PCR-confirmed mpox patient [74]. There were no reported inhalation exposures.

An additional sub-analysis was conducted to assess the route of transmission for each mpox clade: Clade I, Clade Ib, and Clade IIb. Only 29 out of 222 studies reported clade information, covering 23.6% of patients. No cases of Clade IIa were reported in the literature. Among the 10788 patients for whom the clades were identified, cases with clade Ib and IIb MPXV infection describe close contact (confirmed sexual, suspected sexual and non-sexual) as the primary modes of transmission. For clade 1a there was a total of 218 cases identified. Amongst these cases, the modes of transmission were primarily described as 40.6% (205 cases) as multiple routes, 30.9% (156 cases) as exposure to animals /animal products, 17% (86 cases) as close contact (non-sexual) and 11.5% (58 cases) as other routes of transmission. There was no description of droplet or inhalation transmission in any of the 29 clade specific studies. These findings align with the previous systematic review [68]

Outcome Timeframe	Study results and measurements	Comparator Respirators in addition to contact and droplet precautions	Intervention Medical masks as a part of contact and droplet precautions	Certainty of the evidence (Quality of evidence)	Summary
Mpox infection inferred from transmission route frequency data	(Observational (non-randomized))	1 reported case of transmission by droplet in 32318 patients (1/270 studies) Inferred odds ratio: 1		Low Due to serious indirectness, Due to serious risk of bias[1]	The use of a respirator probably makes little to no difference in preventing mpox transmission compared to a medical mask

1 Risk of Bias: serious. Inconsistency: no serious. Indirectness: serious. Imprecision: no serious. Publication bias: no serious.

6.1.2 Visitors to isolated mpox patients

Interim guidance *(Published 10 June 2022)*

WHO recommends that for patients isolated with mpox measures should be put in place to support patient interaction with family and visitors to promote well-being

- Visitors or caregivers should perform appropriate hand hygiene before and after entering/exiting the patient room, receive instruction and be closely supervised on the use (putting on and removal) of PPE for contact and droplet precautions.
- Vulnerable and high-risk individuals should be counselled regarding the risks in order to make an informed decision on whether to visit the patient.
- Alternate modes of communication such as videoconference to be offered.

6.1.3 Optimized supportive care

6.1.3.1 Admission to hospital

Interim guidance *(Published 10 June 2022)*

WHO recommends that patients at high risk for complications (i.e. young children, pregnant persons and those who are immunosuppressed) or those with severe or complicated mpox should be admitted to the hospital for closer monitoring and clinical care under appropriate isolation precautions to prevent transmission of mpox virus

For further details of systematic evaluation, see [1].

6.1.3.1.1 Practical info

A job aid describing systematic monitoring of patients is attached in Annex 7.

6.1.3.2 Optimised supportive care

Interim guidance *(Published 10 June 2022)*

WHO recommends that patients with mpox who develop complications or severe disease should be managed with optimized supportive care interventions.

6.1.3.2.1 Practical info

A table describing optimized supportive care measures for patients with complications or severe disease can be found in Annex 6.

6.2 Timing of ART initiation in people living with HIV (New recommendation)

6.2.1 Rapid ART initiation as the standard of care

WHO strongly recommends rapid ART initiation (≤ 7 days of HIV diagnosis) for adults, adolescents and children, including the offer of same-day start. This guidance is based on high-certainty evidence for adults and adolescents, low-certainty evidence for children (WHO consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring (2021) [160]). Three randomized clinical trials showed strong mortality benefits of rapid ART compared with delayed ART (RR 0.47, 95% CI 0.24–0.93) as well as positive impact on the frequency of ART initiation, retention in care and suppression of viral loads at 12 months.

The recommendation of rapid ART initiation acknowledges concerns of paradoxical immune reconstitution inflammatory system (IRIS) in the context of immunosuppression. Restoration of the immune function through ART is considered an important intervention in the management of opportunistic infections, especially if effective treatment is unavailable. However, for infections with central nervous system involvement such as TB and cryptococcal meningitis, and in case of TB, targeted antimicrobial treatment and delay of ART with a few weeks is recommended to reduce the likelihood of paradoxical IRIS with adverse outcomes.

6.2.2 Mpox and ART initiation

There are currently no randomized clinical trials comparing early vs delayed ART initiation in people with HIV and mpox.

One observational study of 19 patients with HIV and mpox showed uncertain effect of delaying the ART initiation; but it showed a higher rate of hospitalization compared with the early ART initiation group. There is low-certainty evidence that initiation of ART at the late stages of HIV infection may increase hospitalizations in mpox patients that were not on ART (5 non-randomized studies, 2037 participants, OR = 4.19, 95% CI 2.11–8.34).

Mpox IRIS following ART initiation may occur, but the frequency is uncertain. Differentiating between mpox IRIS and progressive mpox is complicated given the lack of clear case definition and overlapping manifestations.

In a technical meeting organized by WHO, expert consensus was that the general mortality reduction benefits of rapid ART initiation extend to patients with mpox,

accepting the risk of paradoxical IRIS, and noting that delaying ART initiation may possibly be harmful. These conclusions were based on the lack of available evidence-based effective therapy for mpox, the continued mpox viral replication and disease progression in patients with immunosuppression, the estimation that mpox central nervous system manifestations are uncommon, and the concurrence of other opportunistic infections with mpox that would benefit from rapid ART initiation.

People with symptoms of mpox should access health services and HIV testing early to reduce the risk of severe mpox disease.

Strong recommendation for, moderate certainty evidence (published May 2025)

WHO recommends rapid initiation of ART in people with mpox and HIV who are ART naïve or have had a prolonged interruption of ART *(Strong recommendation, moderate certainty of evidence)*

- Early HIV testing should be conducted when patients present with suspected or confirmed mpox infection.
- The patient should be referred to appropriate services for ART initiation as soon as possible, aiming to provide therapy within 7 days of HIV diagnosis including the offer of same-day start.
- In people who are already on ART and with undetectable viral load, ART regimen should be continued without interruption or change. The viral load test result should be less than 1 year old; if not, a new viral load test should be conducted.

6.2.2.1 Practical info

The latest guidance from WHO on HIV prevention, testing, treatment, service delivery and monitoring can be found here: https://www.who.int/publications/i/item/9789240031593.[160]

Disseminated cryptococcosis skin lesions may resemble mpox under some circumstances. Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV from WHO can be found here: https://www.who.int/publications/i/item/9789240052178.[53]

6.2.2.2 Evidence to decision

Benefits and harms — Substantial net benefits of the recommended alternative

There is high-quality indirect evidence of the mortality benefits of initiating antiretrovirals (ART) as soon as possible. In the absence of any effective mpox-specific treatment to lower the viral load, the panel judged there to be little benefit in delaying ART initiation.

The panel judged there to be harms from delay of ART initiation. Immune recovery is central to viral control and recovery from disease, and treatment delay will likely delay immune recovery. The panel judged harms from delay very likely, including reduced linkage and retention in care, and progression of mpox viral replication.

Despite the absence of direct evidence from patients with mpox, the harms of uncontrolled, progressive mpox infection in the context of advanced immunosuppression is very well documented and can be fatal. The panel judged that these harms likely outweigh any potential harm arising from IRIS.

Certainty of the evidence — Moderate

Current WHO recommendation for rapid ART initiation is based on high-quality evidence from three randomized controlled trials , with 7418 patients which inferred mortality benefits. The study populations within these trials did not include mpox patients, therefore, due to indirectness, the certainty in mortality benefit was assessed to be moderate.

IRIS can be severe when it occurs due to other opportunistic infections, but occurrence rates are uncertain in mpox.

Values and preferences — No substantial variability expected

The GDG inferred that most HIV patients with mpox would place a higher value on the mortality benefit of initiating antiretrovirals (ART) as soon as possible than on the possible increased risk of developing IRIS.

Resources and other considerations — No important issues with the recommended alternative

Resources

No issues in a system which already provides antiretrovirals.

Equity

No issues in a system which already provides antiretrovirals.

Acceptability

No issues in a system which already provides antiretrovirals.

Feasibility

No issues in a system which already provides antiretrovirals.

6.2.2.3 Justification

Currently, in contrast to other opportunistic infections in which delayed ART is recommended, direct evidence regarding the timing of ART for mpox is only very low certainty. There is low-certainty evidence from comparison of uncontrolled versus controlled HIV in mpox that delayed ART may increase hospitalizations in mpox patients (5 non-randomized studies, 2037 participants, OR = 4.19, 95% CI 2.11–8.34).

There is very low-certainty evidence regarding the impact of early treatment versus delay on occurrence and effects of IRIS in mpox/ HIV co-infected patients.

The GDG considered that the evidence from people who did not have mpox would pertain to those who did (with this high-quality evidence being rated down for indirectness, and therefore an overall moderate certainty evidence for benefits in mpox).

On values and preferences, the panel judged that all or almost all HIV patients with mpox would place a higher value on the likely mortality benefit of initiating ART as soon as possible than on the possible increased risk of developing IRIS.

The panel acknowledged that a strong recommendation would reduce the likelihood of accrual of direct evidence pertaining to the PICO. However, observational data from clinical case series would allow estimation of the incidence of IRIS.

6.2.2.4 Clinical question/ PICO

Population: HIV with Mpox

Intervention: Delayed ART

Comparator: Early ART

Outcome Timeframe	Study results and measurements	Comparator Early ART	Intervention Delayed ART	Certainty of the evidence (Quality of evidence)	Summary
Mortality (high risk)	Odds ratio 2.08 (CI 95% 1.08 — 3.99) Based on data from 7418 participants in 3 studies. (Randomized controlled)	46 per 1000	91 per 1000	**Moderate** Due to serious indirectness[1]	Delayed ART probably increases mortality in mpox patients as inferred from comparison of delayed versus early ART in HIV
		45 more per 1000 (CI 95% 3 more – 115 more)			
Mortality (low risk)	Odds ratio 2.08 (CI 95% 1.08 — 3.99) Based on data from 7418 participants in 3 studies. (Randomized controlled)	3 per 1000	6 per 1000	**Moderate** Due to serious indirectness[2]	Delayed ART probably increases mortality in mpox patients as inferred from comparison of delayed versus early ART in HIV
		3 more per 1000 (CI 95% 0 fewer – 9 more)			
Hospitalization	Odds ratio 7 (CI 95% 0.29 — 167.93) Based on data from 19 participants in 1 studies. (Observational (non-randomized))	82 per 1000	385 per 1000	**Very low** Due to serious risk of bias, Due to serious imprecision[3]	We are uncertain about the effect of delayed versus early ART initiation in mpox on hospitalisation
		303 more per 1000 (CI 95% 57 fewer – 856 more)			
IRIS	Odds ratio 1.13 (CI 95% 0.06 — 21.09) Based on data from 19 participants in 1 studies. (Observational (non-randomized))	100 per 1000	112 per 1000	**Very low** Due to serious risk of bias, Due to serious imprecision4	We are uncertain about the effect of delayed versus early ART initiation in mpox on occurrence of IRIS
		12 more per 1000 (CI 95% 93 fewer – 601 more)			

1, 2. Inconsistency: no serious. Indirectness: serious. Downgraded once for indirectness as population did not include mpox cases. Imprecision: no serious. Publication bias: no serious.

3. Risk of Bias: serious. Unadjusted estimate. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. One study with few events. Publication bias: no serious.

4. Risk of Bias: serious. Unadjusted estimate. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Downgraded once for risk of bias as the estimate is unadjusted, downgraded once for imprecision as there is one study with few events. Publication bias: no serious.

6.3 Breastfeeding and mpox (New recommendation)

The current recommendations on breastfeeding outside of the mpox context were summarized, by the technical working group (see Methods section) to provide foundational evidence for mpox guideline development. They noted that WHO has existing guidelines which pertained, specifically Recommendations on postnatal care of the mother and newborn (2013) [161].

- WHO recommends that "All babies should be exclusively breastfed from birth until 6 months of age. Mothers should be counselled and provided support for exclusive breastfeeding at each postnatal contact (Strong recommendation, based on moderate quality evidence).
- Remarks:
- This recommendation is applicable in all settings.
- Exclusive breastfeeding should be promoted during all antenatal and postnatal care contact.
- Particular support for exclusive breastfeeding should be provided when the mother has had a caesarean section or the baby is born preterm.
- WHO low-birth-weight feeding guidelines for LMIC recommend exclusive breastfeeding for all preterm and low-birth-weight infants (https://www.who.int/publications/i/item/9789241548366).[162]
- The GDG reviewed evidence for neonatal outcomes; the 6-month duration of exclusive breastfeeding is based on existing WHO recommendation and an updated Cochrane review.

The technical group structured the PICOs below to address separately the risk of mother to child transmission of mpox through two potential routes, via breastmilk or via direct contact. The final PICO addresses whether mothers who recover from mpox and who had withheld breastfeeding and direct contact, should resume breastfeeding and direct contact with the infant.

6.3.1 Breastfeeding

Conditional recommendation for, low certainty evidence (published May 2025)

WHO suggests that mothers with mpox continue breastfeeding, whilst limiting direct contact with their non-infected infant, until lesions are fully resolved (lesions are crusted, the scab of lesions have fallen off and a fresh layer of intact skin has formed underneath). (Conditional recommendation, low certainty evidence)

- If breastfeeding is continued between a suspected or confirmed mother with mpox and a non-infected infant, IPC measures must be established including limited contact between mother and infant except during breastfeeding and coverage of active lesions on other parts of the body whilst breastfeeding.
- The presence of areolar lesions should prompt careful consideration and mothers should not use that breast to breastfeed the infant. In the case of unilateral lesions, until lesions are healed per WHO criteria (lesions are crusted, the scab of lesions have fallen off and a fresh layer of intact skin has formed underneath), breastfeeding may take place from the unaffected breast whilst covering all active lesions.
- Health and care workers should inform the mother about the risk of infection to infants whilst breastfeeding and availability of appropriate alternatives.
- Context will drive the feasibility, availability and safety of alternatives to breast feeding. Whenever it is safe and feasible, expressed breastmilk or milk substitutes and no direct contact, may be pursued to reduce transmission.

6.3.1.1 Practical info

Additional guidance on breastfeeding can be found in WHO Recommendations on postnatal care of the mother and newborn and can be accessed here: https://www.who.int/publications/i/item/9789241506649.[161]

General protective IPC measures should be taken by mothers with mpox when handling and feeding their infants, e.g. washing hands before and after each feeding, wearing a medical mask and covering any lesions on the areola or on areas which have direct contact with the infant. Alternatively, if only one breast has lesions, mothers can express/pump from the breast with lesions on the areola and discard the milk and feed from the non-affected breast. In all cases, monitor the mother-infant pair closely for development of signs and symptoms of mpox and treat accordingly.

Infants of mothers with mpox should be closely monitored for signs and symptoms with the main goal of early supportive care to prevent the development of severe disease and poor outcomes.

In the event of replacement feeding with breastmilk substitute, it is essential to track the infant's growth, development and other illnesses as well as for signs and symptoms of mpox.

6.3.1.2 Evidence to decision

Benefits and harms

The benefits of continuing breastfeeding are based on the moderate quality evidence that exclusively breastfed neonates are at lower risk of all-cause mortality and infection-related mortality in the first month of life compared with partially breastfed neonates. Also, there is low-quality evidence that exclusively breastfed neonates are at lower risk of sepsis, acute respiratory infection and diarrhoea in the first month of life compared with partially breastfed neonates.

Harms of continuing breastfeeding include the risk of transmission of infection to the infant through contact with lesions or expressed milk. The evidence available about transmission through expressed milk (with no contact) due to presence of viable virus in the milk is limited.

Certainty of the evidence Low

The certainty of the evidence ranged between moderate and very low. Aside from the indirect evidence regarding the impact of breast feeding, seven publications providing potentially direct evidence were identified; five were case reports and two were case series. However, in none of these studies was there clarity about the existence of lesions specifically on the breasts.

Six of these studies report on breastfeeding and direct contact. In five of the studies, the infant was infected compared with no infant being infected in the one study that reported on no breastfeeding and no contact. There was moderate certainty evidence that breastfeeding and direct contact between mothers with mpox with no lesions on the breasts probably resulted in infection of some infants. However, there is less clarity about the frequency of this event. There was, however, very low certainty evidence of the magnitude of any increase of mpox infection in infants as a result of breastfeeding and direct contact with mother with mpox and no lesions on the breasts.

Regarding hospitalization of infants due to mpox infection, four out of six infants who were breastfed and had close contact were hospitalized compared with the no

breastfeeding and no direct contact (the case hospitalized in the group of no breastfeeding and no direct contact was to monitor the infant and not because of infection).

Concerning mortality, there was one death in the breastfeeding and direct contact group compared with the no breastfeeding and no direct contact. There was low certainty of evidence for breastfeeding and direct contact and increase of infant mortality and very low certainty regarding the magnitude of any increase in infant deaths that may occur as a result of breastfeeding and direct contact between mothers with mpox, with no lesions on the breasts and the infant.

There was only one case report that described breastfeeding and no direct contact. The certainty of evidence was rated very low due to lack of clarity of how breastfeeding and no direct contact (e.g. expressed milk) affects the risk of infection, hospitalization and mortality of the infant.

No adverse events were reported in any of the studies.

No studies reported on infants of mothers with confirmed mpox infection and lesions on the breasts. Therefore we do not have published evidence on the effect of breastfeeding and close contact with the infant when the mother has lesions on the breasts.

Values and preferences Substantial variability is expected or uncertain

There is likely to be substantial variability in values and preferences between mothers, and these are related to the availability and safety of the resources to use as milk substitutes, as well as beliefs, religion, culture and family traditions.

No formal studies are available to inform patient values and preferences in mpox. Nevertheless, the panel inferred that parents generally and strongly wish to avoid harms to their babies. At the same time, experience from Ebola virus disease and from mpox outbreaks in the Democratic Republic of the Congo reported by panel members suggests that when faced with competing priorities of harm reduction and the desirability of breastfeeding, mothers valued breastfeeding highly.

In settings in which alternatives to breastfeeding (appropriate milk substitutes) are not feasible, available and safe, the panel inferred that most parents would place a higher value on the possible beneficial effects of breastfeeding with direct contact

or expressed milk (no direct contact) over eliminating the uncertain magnitude of risk of infants getting infected with mpox.

Resources and other considerations Important issues, or potential issues not investigated

Resources

The affordability of alternatives to breastfeeding in many contexts may be limited, and costs will more likely fall on the family or the health care system. The GDG noted the complexities of providing safe breastmilk substitutes including the requirement for available safe water and equipment to provide it.

There were significant other resources required in terms of IPC measures irrespective of the choice of breastfeeding or not.

During the PALM007 study in the Democratic Republic of the Congo, breastmilk substitute was provided as part of the research, but that apart from this support, mothers would not usually have access to it. Outside of research settings, downstream events occurring as a result of not-breastfeeding may have a significant cost and resource implication especially following diarrhoeal disease or malnutrition.

Equity

Increasing costs associated with use of alternatives to breastfeeding could drive inequity or increase pre- existing inequities.

Acceptability

Breastfeeding is accepted and promoted in all settings and environments as the best option for infant feeding.

Feasibility

There is large heterogeneity in accessibility to alternatives to breastfeeding (see Resources, above). Specifically, the potential to pasteurize breastmilk was also noted, but felt to be not feasible in many contexts.

6.3.1.3 Justification

Overall, the certainty of evidence about breastfeeding of mothers with mpox to their infants was rated as moderate to very low. The GDG felt that no strong recommendation could be made given the certainty of the evidence available.

The GDG considered the benefits of continuing breastfeeding by a mother with mpox infection are based on moderate certainty evidence that exclusively breastfed neonates are at lower risk of all-cause mortality and infection-related mortality in the first month of life compared with partially breastfed neonates.

The GDG also considered in their deliberations that alternatives to breastfeeding may be not feasible or not safe and expose the infant to harm. In settings where alternatives to breastfeeding (appropriate milk substitutes) are not feasible, available and safe, the panel inferred that most parents would place higher value on the possible beneficial effects of breastfeeding with direct contact or expressed milk (no direct contact) over eliminating the uncertain magnitude of risk of infants getting infected with mpox via breastfeeding. The GDG also noted there is little research available on parent preferences and this should be highlighted as a further area of research.

In considering harms and risks, the GDG also reflected that in the pre-symptomatic stage, before the lesions emerge and before the mother has presented for treatment, the infant may have already been already exposed. If that is the case, there may be little benefit in subsequent avoidance of breastfeeding. Additionally, lesions in other parts of the body, in the context of intimate care of an infant may make an isolated recommendation on breastfeeding have little impact on the likelihood of the infant being infected.

All these considerations support the conditional recommendation for continuing breastfeeding.

6.3.1.4 Clinical question/ PICO

Population: People with suspected or confirmed mpox without lesions on the breast who are breastfeeding their infant

Intervention: Continue breastfeeding and direct contact

Comparator: Stop breastfeeding and no direct contact

Outcome Timeframe	Study results and measurements	Comparator No breastfeeding + no contact	Intervention Breastfeed + contact	Certainty of the evidence	Summary
Mpox disease in infant	Based on data from 7 participants in 5	0	83 per 100	Moderate for transmission (due to	Breastfeeding and direct contact between mpox infected mother with no

	studies. (Observational (non-randomized))			extensive evidence of transmission). Very low for magnitude of increase (due to very serious risk of bias and imprecision)[1]	lesions on the breasts probably results in infection of some infants. We are very uncertain of the magnitude of any increase in mpox infection in infants as a result of breastfeeding and direct contact between mpox infected mother with no lesions on the breasts and the infant.
Hospitalization of infant due to mpox	Based on data from 6 participants in 5 studies. (Observational (non-randomized))	0	67	Moderate for transmission (due to extensive evidence of transmission). Very low for magnitude of increase (due to very serious risk of bias and imprecision)	Breastfeeding and direct contact between mpox infected mother with no lesions on the breasts and the infant, probably results in some hospitalizations We are very uncertain of the magnitude of hospitalization of infants that occurs as a result of breastfeeding and direct contact of mothers with no lesions on the breasts and the infant.
Infant mortality	Based on data from 6 participants in 5 studies. (Observational (non-randomized))	0	17	Low for infant mortality (due to very serious risk of bias and imprecision). Very low for magnitude of increase (due to very serious risk of bias and very serious imprecision)	Breastfeeding and direct contact between mpox infected mother with no lesions on the breasts and the infant, may increase infant mortality We are very uncertain of the magnitude of any increase in infant deaths that may occur as a result of breastfeeding and direct contact between mpox infected mother with no lesions on the breasts and the infant
Adverse events of not breastfeeding for infant and mother					Not reported in included studies

Adverse events of not breastfeeding for infant and mother		Not reported in included studies

1. ***Risk of Bias: very serious.*** *due to risk of bias in reporting for case-reports and case-series.*

6.3.1.5 Clinical question/ PICO

Population: People with suspected or confirmed mpox with lesions on the breast who are breastfeeding their infant

Intervention: Continue breastfeeding and no direct contact (expressed milk)

Comparator: Stop breastfeeding and no direct contact

Outcome Timeframe	Study results and measurements	Comparator No breastfeeding + no contact	Intervention Breastfeed + no contact	Certainty of the evidence	Summary
Mpox disease in infant	(Observational (non-randomized))				No studies. We do not know the effect.
Hospitalization of infant due to mpox	(Observational (non-randomized))				No studies. We do not know the effect.
Infant mortality	(Observational (non-randomized))				No studies. We do not know the effect.
Adverse events of not breastfeeding for infant and mother					Not reported in included studies
Adverse events of not breastfeeding for infant and mother					Not reported in included studies

6.3.2 Resuming breastfeeding

Conditional recommendation for, very low certainty evidence (published May 2025)

WHO suggests that mothers who recover from mpox and who had withheld breastfeeding and direct contact, to resume breastfeeding and direct contact with the infant as soon as lesions are fully resolved (lesions are crusted, the scab of lesions have fallen off and a fresh layer of intact skin has formed underneath). *(Conditional recommendation, very low certainty evidence)*

- This recommendation applies to mothers with confirmed mpox who withheld breastfeeding and close contact with their infant.
- The mother needs to be supported to continue to express milk while not breastfeeding to maximize the likelihood of reinitiating breastfeeding once recovers and avoid complications (e.g. mastitis).

6.3.2.1 Practical info

Additional guidance on breastfeeding can be found in WHO recommendations on postnatal care of the mother and newborn (2013) and can be accessed here: https://www.who.int/publications/i/item/9789241506649 [233].

6.3.2.2 Evidence to decision

Benefits and harms — Substantial net benefits of the recommended alternative

The benefits of resuming breastfeeding are based in the moderate quality evidence that exclusively breastfed neonates are at lower risk of all-cause mortality and infection-related mortality in the first month of life compared with partially breastfed neonates. Also, there is low quality evidence that exclusively breastfed neonates are at lower risk of sepsis, acute respiratory infection and diarrhoea morbidity in the first month of life compared with partially breastfed neonates.

Harms of resuming breastfeeding after recovery include the risk of transmission of infection to the infant through persistence of virus in the breastmilk of recovered mothers. Evidence around presence of viable virus in the milk after is limited.

Certainty of the evidence — Very low

All evidence is of very low certainty, including infection, hospitalization and infant mortality endpoints, as it was derived from two case reports. One of these reports

was in the context of less than 2 weeks' post resolution of lesions and the other in more than 2 weeks' post lesion resolution.

There were no events in either group for infection, hospitalization or mortality of the infant. Adverse events were not reported.

Values and preferences Substantial variability expected or uncertain

There was likely to be a substantial variability in values and preferences, and these are closely related to the available resources.

No data are available from the literature to inform on patients' values and preferences in mpox specifically. The panel noted that parents generally and strongly wish to avoid harms to their babies. Experience from Ebola virus disease and mpox outbreaks in the Democratic Republic of the Congo reported by panel members suggests that in these circumstances, mothers valued breastfeeding despite the known potential for transmission of disease.

Most parents would place higher value on the possible beneficial effects of breastfeeding with direct contact over reducing the uncertain magnitude of risk of infants getting infected with mpox and the possible serious consequences with feeding infants expressed milk (no direct contact).

Resources and other considerations Important issues or potential issues not investigated

Resources

The affordability of alternatives to breastfeeding was questioned in many contexts, and these costs will more likely fall on the family or the health care system. The complexities of providing safe breastmilk substitutes include the requirement for available safe water and equipment to provide it.

There were significant other resources required in terms of IPC irrespective of the choice of breastfeeding or not.

It was noted that during the PALM007 study in the Democratic Re[ublic of the Congo, breastmilk substitutes were provided as part of the research, but that apart from this support, mothers would not usually have access to it. Outside of research settings, downstream events occurring as a result of not breastfeeding may have a

significant cost and resource implication especially following diarrhoeal disease or malnutrition if it occurs.

Equity

Increasing costs associated with alternatives to breastfeeding could drive inequity

Acceptability

Breastfeeding is accepted and promoted in all settings and environments as the best option for infant feeding.

Feasibility

There is large variability in access to alternatives to breastfeeding (see Resources, above).

6.3.2.3 Justification

Overall there was very low certainty evidence which precluded a strong recommendation.

The GDG discussed alternative ascertainment of the time point at which breastfeeding might be reinitiated. Two weeks was used as a initial practical threshold considering the ability to maintain lactation through expression of breastmilk and lesion resolution. However, the GDG agreed to adopt the dermatological definition of recovery: "when lesions have crusted over, the scabs have fallen off and a new layer of skin has formed underneath, and all the lesions on the eyes and in the body (in the mouth, throat, eyes, vagina and anus) have healed" as clinical progression may vary at the individual patient level.

Recommencing breastfeeding will benefit both mother and infant and infection of the infant once lesions are healed lesions is likely to be low.

6.4 Caring for people with mpox during and after pregnancy

6.4.1 Place of care during pregnancy

Interim guidance *(Published 10 June 2022)*

WHO recommends pregnant or recently pregnant persons with mild or uncomplicated mpox may not require acute care in hospital but monitoring in a health facility may be preferred; those with severe or complicated disease should be admitted to a health facility for care as they require optimized supportive care and/or interventions to improve maternal and fetal survival.

6.4.1.1 Practical info

Counsel patients about healthy diet, mobility and exercise, intake of micronutrients for herself and her infant, tobacco use and second- hand smoke exposure, use of alcohol and other substances, as per WHO recommendations on antenatal care for a positive pregnancy experience and WHO recommendations on maternal and newborn care for a positive postnatal experience [143,144].

6.4.1.2 Justification

Limited data suggest that mpox virus infection in pregnant women may lead to vertical transmission as well as adverse outcome for the fetus, such as spontaneous abortion and stillbirths [33,78,59,62,60].

6.4.2 Care during pregnancy

Interim guidance *(Published 10 June 2022)*

WHO recommends that pregnant and recently pregnant persons with mpox should have access to patient-centred, respectful, skilled care, including midwifery, obstetric, gynaecological, fetal medicine and neonatal care, as well as mental health and psychosocial support, with readiness to care for maternal and neonatal complications.

6.4.2.1 Practical info

- Patient-centred, respectful, skilled care refers to care organized for and provided to all patients in a manner that maintains their dignity, privacy and confidentiality, ensures freedom from harm and mistreatment, and enables informed choice.
- During labour and childbirth this includes a companion of choice, pain relief, mobility during labour and birth position of choice. Screen birth companions using the WHO case definition for mpox.
- If the companion has suspected or confirmed mpox, arrange for an alternative, healthy birth companion in consultation with the woman.
- Emphasize to any and all companions the importance of IPC measures during labour, childbirth and during the woman's and newborn's postnatal stay in the health facility. Include appropriate training on and use of PPE and limit movement in the health care facility.
- If a pregnant person has chosen to be cared for at home, then counsel the woman about maternal, fetal and newborn signs and to seek care if they develop worsening illness or danger signs. Self-care interventions should be encouraged.
- Counsel patient about healthy behaviours including diet, physical activity, intake of micronutrients, tobacco alcohol and other substance use, per WHO recommendations on antenatal and postnatal care [143,144]. For patient requiring abortion services, consider alternative modes of service delivery, including self-management of medical abortion up to 12 weeks' gestation, where women have access to accurate information and to a health care provider at any stage of the process, per the WHO Abortion care guideline [145].

6.4.3 Mode of birth

Interim guidance *(Published 10 June 2022)*
WHO recommends that mode of birth should be individualized, based on obstetric indications and the mother's preferences. WHO recommends that induction of labour and caesarean section should only be undertaken when medically justified and based on maternal and fetal condition. • Interventions to accelerate labour and childbirth (e.g. augmentation, episiotomy, operative vaginal birth) should only be undertaken if medically justified and based on maternal and fetal clinical condition per the WHO recommendations for intrapartum care [163].

- Delayed umbilical cord clamping (not earlier than 1 minute after birth) is recommended for improved maternal and infant health and nutrition outcomes. There is no evidence that delaying cord clamping increases the possibility of viral transmission from the mother to the newborn. The proven benefits of a 1–3 minute delay, at least, in clamping the cord outweigh the theoretical, and unproven, harms.
- Individualized decisions should be taken about postponing planned (elective) induction or caesarean section in pregnant person with suspected or confirmed mild mpox [171].
- Placenta and any pregnancy related tissue or fluids, such as amniotic or fetal tissue fluid, must be disposed of following specific IPC protocols for potentially infectious materials.

6.4.3.1 Justification

Emergency decisions about childbirth and pregnancy termination are complex and depend on various factors, including gestational age, the severity of the maternal condition, fetal viability and well-being, as well as regulatory and legal barriers in the country or state.

6.4.4 Pregnancy and postpartum period

Interim guidance *(Published 10 June 2022)*

WHO recommends that pregnant and recently pregnant persons who have recovered from mpox should be enabled and encouraged to receive routine antenatal, postpartum or abortion care, as appropriate. Additional care should be provided if there are any complications.

- Pregnant persons with or recovering from mpox should be provided with information related to the potential risk of adverse pregnancy outcomes and offered counselling when they request or desire it. Closer follow up is recommended, because of higher risk of stillbirth/pregnancy loss.
- Pregnant persons with mpox should be informed that it is unknown whether transmission can occur if others are exposed to pregnancy-related fluids or tissues, such as amniotic fluid, placenta or fetal tissue. Instructions should be provided on how to handle potentially infectious specimens.

- All pregnant persons with confirmed mpox and their infants should be followed up through national registries for signs of complications.
- Patient's choices and rights to sexual and reproductive health care should be respected, including access to contraception and safe abortion per the WHO Abortion care guideline [145].
- Counsel pregnant persons on safe sexual practices.

6.4.4.1 Justification

Limited data suggest that mpox virus infection in pregnant persons may lead to vertical transmission as well as adverse outcome for the fetus, such as spontaneous abortion and stillbirths [33,78,59,62,60].

6.5 Caring for infants and young children with mpox

6.5.1 Monitoring of newborn infants

Interim guidance *(Published 10 June 2022)*

WHO recommends that newborn infants of mothers with mpox should be monitored closely for evidence of potential congenital or perinatal infection. Mothers and infants or young children can also be exposed through close contact.

- Children should not sleep in the same room or bed or drink/eat from the same utensils as an individual with mpox.
- Young children should not be isolated alone. There should be one person (parent or caregiver), who is healthy and not at high risk, providing care to the child with mpox with appropriate IPC measures.
- Young children may be considered for care in health facility to monitor for disease progression, and if they occur to recognize and treat these complications with optimized supportive care.

6.6 Recommendations for patients with mpox that are sexually active

6.6.1 Sex and close physical contact

Interim guidance *(Published 10 June 2022)*

WHO recommends all patients should be advised to abstain from sex and close physical contact until ALL skin lesions from mpox have crusted, the scabs have fallen off and a fresh layer of skin has formed underneath.

- For patients who are sexually active: among persons presenting with rash or skin lesions that are suspected to have mpox, co- infection with other STIs should also be considered. The patient should have the following assessment:
  - Thorough sexual history.
  - Full physical examination using appropriate IPC measures with special attention on examination for: lymphadenopathy; rash or skin lesions in oral mucosae, genitals, anogenital region, and other parts of skin.
  - Testing should be performed for HIV, syphilis, genital HSV, and screening for STIs and managed per WHO Guidelines for the management of symptomatic sexually transmitted infections [184]; patients should be encouraged to use condoms consistently during sexual activity for prevention of HIV and other STIs but should be made aware that the use of condoms alone cannot offer protection against acquisition and transmission of diseases.
- For persons living with HIV, particularly those with poorly controlled disease, who have mpox may be at greater risk for severe disease [46]. Data suggest they may be at risk for genital ulcers, secondary bacterial infection and prolonged duration of illness [32].
  - If a person living with HIV is diagnosed with mpox, they should continue ART as before (see recommendation above of rapid initiation of ART in people with mpox and HIV who are ART naïve or have had a prolonged interruption of ART) [185]. People with lower CD4 counts are at greater risk of complications related to mpox so should be prioritized for starting ART [32].

- Should a person be diagnosed with both mpox and HIV at the same time, address the most urgent issues and treatment for mpox and consider drug-drug interactions.

6.6.1.1 Justification

The GDG acknowledged that the risk of transmission from direct contact with infected skin or mucocutaneous lesions can amplify transmission, and thus abstaining from sexual activity during the infectious period would curtail transmission. As well, the potential for sexual transmission is unknown and subject to further research.

Note: This recommendation is based on existing WHO recommendations from Clinical management and infection prevention and control for monkeypox: interim rapid response guidance (June 2022) [1].

6.6.2 Use of barrier contraception

Interim guidance *(Published 10 June 2022)*

Based on the precautionary principle, WHO suggests the use of condoms consistently during sexual activity (receptive and insertive oral/anal/vaginal) for 12 weeks after recovery to prevent the potential transmission of mpox.

- As there are no available data about after recovery sexual mpox transmission, the precautionary principle is being applied for this public health intervention. As more information becomes available and our understanding related to transmission improves the guidance will be updated accordingly.

6.6.2.1 Justification

Small case series have reported mpox virus DNA detection in bodily fluids after healing of skin lesions; this raises uncertainty about the persistence of mpox virus in bodily fluids such as semen, vaginal fluids, saliva and blood, and the risk of onward transmission. As this is an emergency guidance produced in a quickly evolving situation the precautionary principle is being applied for this public health intervention. As more information becomes available and our understanding related to transmission improves the guidance will be updated accordingly.

6.7 Recommendations for caring for mpox patients after acute infection

6.7.1 Follow-up care

Interim guidance *(Published 10 June 2022)*

WHO recommends that patients with suspected or confirmed mpox should have access to follow-up care. All patients with mpox (and their caregivers) should be counselled to monitor for any persistent, new or changing symptoms. If this occurs, they should seek medical care according to national (local) care pathways.

- National (local) coordinated care pathways should be established that can include primary care providers (e.g. general practitioners), relevant specialists (e.g. sexual health, infectious diseases, dermatologist, surgeons, wound care specialists), mental health and psychosocial providers, nutritionists and social care services for patients and families.
- Management should be tailored according to patient needs and be coordinated. Management interventions may entail education, advice on self-management strategies, caregiver support and education, peer-to-peer groups, stress management, stigma mitigation and home medication, and/or specialty management.

6.8 Recommendations on antiviral and other therapies (under revision)

Under revision[164,165,166,167,168,169,170].

The antiviral and therapeutics section of this guideline will be updated following the systematic review and meta-analysis of multiple ongoing therapeutic trials.

6.9 Recommendation on mental and psychosocial support of patients with mpox

6.9.1 Anxiety and depressive symptoms

Interim guidance *(Published 10 June 2022)*

WHO recommends prompt identification and assessment for anxiety and depressive symptoms in the context of mpox and to initiate basic psychosocial support strategies and first-line interventions for the management of new anxiety and depressive symptoms.

- Patients with mpox should receive compassionate, respectful, people-centred care consistently, while ensuring appropriate and adequate protection of household members, visitors and health workers.
- When a patient with mpox arrives at a health facility, the patient and family members should be informed about mpox and encouraged to remain calm. They should be informed about how the disease is transmitted and educated about the precautions that should be taken to prevent the disease from spreading. Families should be updated on the patient's condition and provided with any additional information.
- Ideally, a psychologist, social worker or nurse psychosocial provider fluent in the local language will be involved from the onset of the disease to counsel the patient on what will happen during any isolation. If this is not possible, then general nurses in the health centre should be trained and supervised to provide basic psychological support, using standardized resources.
- For people who are experiencing symptoms of depression, brief psychological interventions based on the principles of cognitive behavioural therapy (CBT), problem management and relaxation training can be considered [173]. Consider using remote mental health support (i.e. telephone therapy) when access to regular services is disrupted.
- If a person's anxiety or depressive symptoms persist beyond recovery from mpox, then an underlying anxiety or depressive disorder may be suspected, and a mental health professional should be consulted, and these conditions should be managed appropriately. Refer to the mhGAP humanitarian intervention guide for mental, neurological and substance use disorders in non-specialized health settings [174,175].

- It is important to ask about thoughts or acts of self-harm, particularly during mpox, due to risk factors for self-harm and suicide such as sense of isolation, loss of a loved one, job, or financial loss and hopelessness. Remove possible means of self-harm, activate psychosocial support, follow up with the person and consult a mental health professional as necessary. Refer to the mhGAP humanitarian intervention guide for mental, neurological and substance use disorders in non-specialized health settings [174,175].
- To ensure comprehensive care and based on the initial assessment, following discharge, link the person to employment, education, social services (including housing) and other relevant sectors [176].
- CBT with a trauma focus, eye movement desensitization and reprocessing or stress management should be considered for adults with post-traumatic stress disorder (PTSD) [174,177].

6.9.1.1 Practical info

- The WHO Psychological first aid: guide for field workers and Inter-Agency Standing Committee guidance on basic psychosocial skills [177,178] promote care according to the following principles:
  - Provide non-intrusive, practical care and support.
  - Assess needs and concerns.
  - Help to address basic needs (food, water, information).
  - Listen to patients and families, but do not pressure them to talk.
  - Provide accurate information on the patient's condition and treatment plan in easily understood and non-technical language, as lack of information can be a major source of stress.
  - Help people address urgent needs and concerns and help with decision-making as necessary.
  - Comfort patients and families while helping them feel calm. Inform them that the vast majority of mpox patients survive, so be sure to communicate to patients and their families that recovery is expected.
  - Help people connect to information, services and social supports. Information about mpox is important as it helps to dispel myths, share clear messages about healthy behaviour and improve understanding of the disease.
  - Encourage patients and caregivers to use evidence-based stress management and self-help tools such as the WHO stress management guide Problem management plus (PM+) [179].

- Following recovery, patients may suffer from lingering scars or disfigurement and psychological distress as a result. Psychological and social care should be included in the follow-up care plan and as part of a multidisciplinary team of care.

6.9.1.2 Justification

The mpox outbreak can lead to significant mental and psychosocial effects, similarly as observed in COVID-19 and EVD, [178,179] [180], including:

- Fear of the disease or death, loss of sense of meaning of life, or loss of faith.
- Physical and social isolation from family or community.
- Stigma associated with diagnosis and returning to the community.
- Scarring and disability (e.g. blindness) associated with the disease.

Basic psychosocial support skills are essential for management of all patients and represent an integral part of care that should be provided for all.

6.9.2 Sleep problems

Interim guidance *(Published 10 June 2022)*

WHO recommends psychosocial support strategies as the first-line interventions for management of sleep problems in the context of acute stress.

- Sleep hygiene advice (including avoiding the use of psychostimulants such as caffeine, nicotine or alcohol) and stress management (including relaxation techniques and mindfulness practices) are effective in reducing sleep problems and may be offered. Psychological interventions based on the principles of CBT may also be considered.
- For people who are hospitalized for mpox, additional causes of insomnia may include environmental factors (e.g. excessive light and noise at night), anxiety, persistent cough, delirium, agitation or pain. Identifying and promptly addressing underlying causes should be prioritized before using any pharmacological sleep aids.

6.10 Recommendation of deceased patient management

6.10.1 Handling of human remains

Interim guidance *(Published 10 June 2022)*

WHO recommends that the handling of human remains of deceased individuals with mpox should be done with appropriate IPC measures.

- Handling of the deceased should be kept to a minimum.
- Perform hand hygiene and wear PPE according to contact and droplet precautions (gloves, gown, medical mask and eye protection based on risk assessment) as patients with rashes that have not healed may still have infectious virus.
- Airborne precautions should be implemented when performing AGPs.

(This section has been modified from the interim guidance to reflect current recommendations)

6.10.1.1 Practical info

- Ensure that any leakage of body fluids is contained.
- The body should be wrapped in a cloth or shroud and transferred to the mortuary as soon as possible.
- The dignity of the dead, their cultural and religious traditions, and their families should be respected and protected. Family and friends may view the body after it has been prepared for burial, in accordance with local customs. They should not touch or kiss the body and should clean their hands with soap and water or alcohol-based hand sanitizer after the viewing [136,147]

6.10.1.2 Justification

This recommendation derives from the Clinical management and infection prevention and control for monkeypox: interim rapid response guidance (2022) [1], which recommended the use of airborne precautions in addition to droplet and contact precautions. In line with changes to WHO guidance, this recommendation has been revised from the interim guidance to remove the stipulation for airborne precautions.

6.11 Recommendations for health and care workers with occupational exposure to mpox

6.11.1 Occupational exposure to mpox

Interim guidance *(Published 10 June 2022)*

WHO recommends staff with an occupational exposure to mpox should have an assessment and management plan

- Health and care workers should notify infection control, occupational health and public health authorities of possible exposures to receive a medical evaluation and instructions on follow up.
- Health and care workers who have had an exposure to a person with confirmed mpox should undergo medical evaluation and consideration for possible interventions (vaccination or post-exposure prophylaxis [PEP]) under prospective data collection protocol or clinical trial.
- Health and care workers who have had an occupational exposure (i.e. not wearing appropriate PPE) do not need to be excluded from work if they are asymptomatic, but should undergo active surveillance for symptoms for 21 days post-exposure and be instructed not to work with vulnerable patients.

6.11.1.1 Practical info

These plans should be in accordance with national or subnational policies. The term national describes a government entity at national level and subnational describes any government entity below the national level (regardless of the political, financial and administrative design of the country) involved in the management of health workers in the context of mpox.

7. Methods: how was this guideline created

This guideline was developed according to the standards and methods described in the WHO Handbook for guideline development [181]. The initial content was derived from the Clinical management and infection prevention and control for monkeypox: interim rapid response guidance [1]; which did not undergo a formal Grading of Recommendations Assessment, Development and Evaluation (GRADE) process, given it was written as a rapid guidance in the context the first mpox Public Health Emergency of International Concern (2022).

The topical areas updated from the Clinical management and infection prevention and control for monkeypox: interim response guidance (10 June 2022) were revised based on priorities identified by the WHO mpox Steering Committee and the Safe Scalable Care Cluster in the Mpox Incident Management Support Team, which was established during the Public Health Emergency of International Concern declared by WHO on 1 4August 2024 [105]. For prioritized questions, the GRADE approach was used to rate the strength and direction of evidence, and to produce recommendations (see Stepwise approach - application of GRADE methodology). Several interim statements from the 2022 guidance were not subject to systematic reviews, as the WHO technical team determined they were appropriate for inclusion in the updated document as good practice statements (following GRADE methodology), as implementation considerations, or to be updated at a later date. These interim statements were reviewed and categorized in collaboration with the methodologist, the WHO technical unit and the GDG co-chairs. They were then presented to the GDG members for review and inclusion.

WHO convened a technical meeting with experts on the 15 November 2024 to discuss and interpret the available evidence on ART initiation in people living with HIV and mpox [188].. Additionally, WHO convened a technical meeting with experts on the 26 November 2024 to discuss and interpret the available evidence on breastfeeding and mpox. On 12 December 2024, the GDG was convened to make recommendations on breastfeeding and ART initiation after the presentation of the considerations summarized in the technical groups. On 27 November 2024, 10 December 2024 and 21 January 2025, the GDG convened to make recommendations on transmission-based precautions and home isolation.

The Steering Committee and GDG members agreed to retain many of the interim recommendations to ensure a consolidated and single- sourced guideline, supporting a more comprehensive emergency response.

The new recommendations are categorized as either strong or conditional recommendations (for or against), or as good practice statements. The interim statements will remain tagged as such.

7.1 Types of statements

7.1.1 Recommendations

Formal recommendations are actionable statements about the choice between two or more interventions in a specific population and if relevant, a specific setting. They are based on the best available evidence and follow a transparent methodology that considers the certainty of the evidence and determines the strength of the recommendation following the evidence to decision framework, see Table 6.

7.1.2 Good practice statements and implementation considerations

Good practice statements are necessary, actionable and clear guideline statements that are important but do not warrant formal ratings of evidence quality. Formulating a good practice statement includes adhering to five principles:

1) Is collecting and summarizing the evidence poor use of the panel's limited time, energy and resources?
2) Is the message necessary about health care practice?
3) Does implementing the good practice statement unequivocally result in a net positive consequence?
4) Is there a well-documented and clear rationale connecting the indirect evidence?
5) Is the statement clear and actionable?

Statements in the document for IPC that are identified as good practice statements were reviewed with the methodologist and GDG chairs to determine if they met the criteria for a good practice statement according the identified principles. The statements that were categorized as meeting the criteria were then presented to the panel for discussion and consensus.

Implementation considerations support the implementation of the recommendations and statements and describe the “who, what, when and how” of implementing the

recommendation. They may include tools and strategies relevant to supporting the implementation of the intervention but may not have a clear link to evidence. They translate standard and transmission-based precautions into practical guidance for managing mpox [7]. Many of these considerations are derived from WHO documents such as the *Transmission-based precautions for the prevention and control of infections: aide-memoire* [7] and the *Standard precautions for the prevention and control of infections: aide-memoire* [14] along with generic recommendations adapted to mpox transmission modes. These were validated by the GDG.

Table 6. Readership cues used for statements in the guideline

Interim	The purple "interim" indicated as a statement that was retained from the Clinical management and infection prevention and control for monkeypox: interim rapid response guidance (10 June 2022).
Strong recommendation	The green "strong recommendation" indicates an updated/new statement
Conditional recommendation	The yellow "conditional recommendation" indicates an updated/new statement
Good practice statement	The blue "good practice statement" indicates an updated/new statement

7.2 Step-wise approach - application of GRADE methodology

The GRADE process was followed for iterations after the interim guidance.

7.2.1 Step 1: Evidence monitoring and mapping and triggering of evidence synthesis

Guidelines are periodically updated to assess data that have undergone peer review in the intervening period and new data. Once practice-changing evidence, or increasing international interest, is identified, the WHO mpox Steering Committee triggers the guideline development process. The trigger for producing or updating specific recommendations is based on the following (any of the three may initiate a recommendation):

- likelihood to change practice;
- sufficient data to inform the high-quality evidence synthesis;
- relevance to a global audience.

This guideline is formulated as a “living” guideline", meaning revisions and updates will occur on an ongoing basis or are based on the availability of new evidence and evolving issues from the field leading to new PICOs. Other factors that may inform the need to update the guideline include changes in transmission intensity, changes in epidemiology and/or health systems' capacity to respond to new epidemiological scenarios.

7.2.2 Step 2: Convening the GDG

WHO selected GDG members to ensure global geographical representation, gender balance, appropriate technical and clinical expertise, and community representatives. For each intervention, the technical unit collected and managed declarations of interests (DOIs) and found no GDG member or co-chairs to have a conflict of interest that prevented or limited their participation. In addition to the distribution of a DOI form, during the meeting, the WHO Secretariat described the DOI process, and an opportunity was given to GDG members to declare any interests not provided in written form. No verbal conflicts were declared. Web searches did not identify any additional interests that could be perceived to affect an individual’s objectivity and independence during the development of the recommendations. One member was found to have an affiliation with a company that makes and sells simple, field usable tests to detect and quantify fecal bacteria in drinking water; however, since mpox is not a pathogen transmitted by contaminated drinking water, no conflict of interest was identified.

The GDG (see Acknowledgments) was convened to review analyses, including pre-specified subgroup analyses presented in summary of findings tables. In making recommendations, the GDG primarily took an individual patient perspective and secondarily a population, public health, or systems perspective. Issues of feasibility specific to proposed interventions were particularly relevant to this latter perspective. The GDG considered all issues in the GRADE evidence to decision framework in formulating recommendations.

Given the scope of the guideline, the GDG was divided into four sections: clinical management, IPC, breastfeeding and initiation of ART in HIV patients. Only GDG members with relevant expertise contributed to the recommendations (e.g. the IPC GDG formulated IPC recommendations, while the clinical management GDG made decisions on clinical management). For more details on the specific subgroups, see the section GDG topic-specific working groups.

7.2.3 Step 3: Evidence synthesis and assessment

An independent systematic review team conducted rapid systematic reviews of published literature and examined the benefits and harms of the interventions. This team includes systematic review, clinical experts and biostatisticians. The technical unit collected and managed DOIs and found no systematic review team members to have a conflict of interest. The certainty of evidence for each question was assessed using GRADE as outlined in the *WHO handbook for guideline development, 2nd edition* (Table 7 provides the definitions for the four levels of certainty of evidence). The GRADE assessment considers the risk of bias/study limitations, inconsistency, imprecision, indirectness and publication/reporting biases [182].

Table 7. Levels of certainty of evidence

High	We are very confident that the true effect lies close to that of the estimate of effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

7.2.4 Step 4: Recommendations

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations. Methods and clinical co-chairs facilitated deliberations to reach final recommendations. All GDG members were invited to participate and contribute to discussions in any GDG meetings. Decisions were made via consensus amongst the GDG members identified for the relevant recommendation. If consensus was not achieved, then the GDG members specific to the pertinent topic would be asked to vote.

The following key factors informed transparent and trustworthy recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables) that include effect estimates and confidence intervals for each outcome, with an associated rating of certainty in the evidence findings. If such data are not available, the GDG reviews narrative summaries [183];

- quality/certainty of the evidence [184,185];
- values and preferences of patients [186];
- resources and other considerations (including considerations of cost, feasibility, applicability, equity) [186];
- recommendations are rated as either conditional or strong, as defined by GRADE. If the GDG members disagree regarding the evidence assessment or strength of recommendations, WHO will apply voting according to established rules [186]. A pre- specified decision rule for making a strong recommendation of 70% of eligible GDG members was in place.

7.2.5 Step 5: External and internal review

An external review group reviewed the final guideline document to identify factual errors, and to comment on clarity of language, contextual issues and implications for implementation. The technical unit collected and managed DOIs of the external reviewers and found no external reviewers to have a conflict of interest. However, for certain therapeutics, pharmaceutical company technical representatives may be asked to comment on a new drug from industry perspectives, in line with the WHO handbook for guideline development, as comments from such individuals or organizations on a draft guideline may be helpful in anticipating and dealing with controversy, identifying factual errors and promoting engagement with all stakeholders. Comments on contextual issues were considered considering their interests. The affiliation of all individuals appears in the Acknowledgement section.

The guideline was finally reviewed and approved by the WHO Guideline Review Committee.

7.3 GDG topic-specific working groups

The process to develop this updated guideline was based in a structure that consisted on two working groups that functioned as GDG: Clinical Management and Infection Prevention and Control, engaged to specifically consider recommendations within their domain of expertise, i.e. the IPC working group primarily formulated IPC recommendations, while the clinical management working group focused on clinical management.

Besides, there were two technical groups: one on HIV and one on Breastfeeding. Both included some of the GDG members and several additional topical experts that were not GDG members (see Acknowledgements); they worked on bringing up the

considerations of these topics to be presented to the GDG members who were responsible for making the final recommendations for the guidelines.

While all perspectives and viewpoints were welcome in the discussions, the formulation of the recommendations for IPC were made specifically by the respective IPC GDG members; and in the Clinical Management GDG meetings only Clinical Management GDG members were responsible for making recommendations.

7.3.1 Infection prevention and control technical working group

The IPC working group members convened for three separate meetings (27 November 2024, 10 December 2024 and 21 January 2025) to review available evidence and formulate the recommendations, good practice statements and implementation considerations contained in this document.

7.3.1.1 Evidence synthesis

A commissioned systematic review underpins the current guideline and is an update of a previously published systematic literature review. The systematic review performed in 2023 assessed publications up to and including September 2022. A subsequent review was commissioned in 2024 given the evolution of new MPXV clades. Both reviews synthesize and update evidence for the three research questions outlined below and were developed in consultation with the GDG following the publication of the interim guidance in 2022.

1) Does the use of respirator versus a medical mask when interacting with a patient with suspected or confirmed mpox during the infectious period (as defined in the footnote) reduce occurrence of mpox in health and care workers in a household, congregate living or health care setting?
2) Does the use of an airborne precaution room versus an adequately ventilated room in a health care facility for a patient with mpox during the infectious period (as defined in the footnote) reduce the occurrence of mpox in health and care workers?
3) In the event that a person with non-severe mpox is being cared for at home, does isolating the person with non-severe mpox until all lesions are fully healed reduce occurrence of mpox in persons who are contacts, compared with not isolating when the patient wears a medical mask, covers all unhealed lesions, refrains from close contact and does not share any materials that could be contaminated?

The reviews occurred in two stages. The first stage appraised available evidence from comparative interventional trials, which yielded no evidence. In the absence of such data, the second stage was preformed to synthesize evidence on the reported routes of MPXV infection using non-comparative study designs to indirectly inform the three IPC intervention review questions. Details on the search strategy and key terminology can be found in Annex 5: Search strategy and terminology for reported routes of MPXV infection.

Throughout these discussions, research gaps were identified, prompting the development of the IPC research agenda and ongoing research prioritization efforts (see: Uncertainties, emerging evidence and future research).

7.3.2 Breastfeeding technical working group pre-GDG discussion

WHO convened a technical meeting with experts on 26 November 2024 to guide the review of relevant evidence and to support the update of recommendations concerning breastfeeding and mpox. The technical working group included external experts with experience in infant feeding and nutrition, paediatric care, with wide geographical representation and gender balance. The full meeting report can be found here [187].

A summary of synthesized evidence on the following PICO questions that relate to breastfeeding during and after recovery from mpox infection was presented and discussed:

- Should a mother with suspected/confirmed mpox and no lesions on the breast continue breastfeeding and direct contact with their non-infected infant?
- Should a mother with confirmed mpox and active lesions on the breast continue breastfeeding and direct contact with their non-infected infant?
- When after recovery from confirmed mpox (after stopping breastfeeding and close contact) should the mother resume breastfeeding and direct contact with their non-infected infant?
- Does pasteurization inactivate mpox in breastmilk to allow feeding the infant with expressed milk without direct contact with mother with mpox?

Overall there were very few studies to answer the four PICO questions. Identified studies were mostly observational, non- comparative study designs and with significant methodological limitations.

The meeting points are summarized below, and were presented to the GDG for further discussion and interpretation.

7.3.2.1 Routes of transmission

The TWG reiterated that guidance on breastfeeding and infant contact in mpox infection needs to differentiate between the following potential MPXV routes of transmission from mother to child:

- through breastmilk (presence and viability of virus in breastmilk is unknown)
- direct contact during the process of breastfeeding (from the breast)
- other direct contact with the infant (not from the breast) during care
- air droplets
- saliva through kissing.

7.3.2.2 What are the evidence gaps?

- It is still unknown if MPXV is secreted in milk although laboratory experiments have shown that it can be viable in milk. This was thought to be the first critical question because if studies show that breastmilk does NOT contain MPXV, then this would help to answer the question if breastfeeding should be recommended and if so how?
- If mpox can be transmitted via breastmilk, then there would be need for an additional PICO, whether heat treatment of expressed breastmilk can make it safe [?] and what is the feasibility of this intervention at an individual and population level.

7.3.2.3 What are the implementation considerations?

- There is a need to involve, where possible, another caregiver to take care of the infant particularly for mothers that are in isolation to limit the duration of contact with between the infant and a mother with mpox.
- The duration of infant-to-mother contact will vary depending on the age. Early initiation of breastfeeding requires longer contact, and later the infant may need shorter contact during breastfeeding. A newborn (up to 2, 6 or even 8 weeks) usually needs constant access to the breast to successfully breastfeed.
- A lesion on the areola would make breastfeeding very painful, and therefore for breast health, the mother should express from that breast in order to prevent engorgement or mastitis and preserve lactation for later resumption of breastfeeding.

- Alternative milk substitutes may not readily be available, or not affordable, or not safe in many locations.

7.3.3 HIV antiretroviral technical working group pre-GDG discussion

WHO convened a technical meeting with experts on 15 November 2024 to discuss and interpret the available evidence on ART initiation in people living with HIV and mpox. Participants included HIV medicine experts, infectious diseases specialists, and programme managers with significant mpox experience; a full list of participants and meeting report can be accessed here [188]. The technical meeting was led by an independent chair.

The objective of the meeting was to identify the evidence sources that would best inform the GDG and place these in the context of the current WHO guidelines that include a strong recommendation for rapid ART initiation, with the option of same-day initiation, in people living with HIV. To facilitate discussions, a literature review compiled by WHO technical staff summarized the available direct and indirect evidence.

The meeting reported the following findings, which were presented to the GDG for further discussion and interpretation.

7.3.3.1 ART initiation in people living with HIV with mpox

- ART is a life-saving intervention for people living with HIV, with or without mpox virus infection.
- Rapid ART initiation (within 7 days of HIV diagnosis) or re-initiation is the standard of care for people living with HIV that are ART-naive or have interrupted ART (WHO, strong recommendation). This includes people with opportunistic infections other than tuberculosis and central nervous system infections.
- Immune restoration through effective ART is important to control MPXV and delay in ART initiation may potentially be harmful.
- There is uncertainty about the incidence of mpox IRIS; mpox IRIS may occur but it is difficult to distinguish from progressive mpox given the lack of clear case definition, delayed clinical presentation and concurrence of other (opportunistic) infections.
- Central nervous system manifestations of mpox are estimated to be uncommon and based on clinical expertise not a reason to delay ART initiation provided that assessment of other etiologies is conducted.

- The expert group proposed the values and preferences statement that "Most HIV patients with mpox would place a higher value on the mortality reduction benefit of initiating ART as soon as possible than on the possible increased risk of developing IRIS".

7.3.3.2 What are the evidence gaps?

- Lack of direct evidence comparing rapid vs delayed ART initiation in people living with HIV and mpox. Only one small cohort study that directly addressed the question of timing of ART initiation was identified; this study did not show a difference in outcomes.
- Understanding progressive mpox, mpox IRIS and associated morbidity and mortality. There is limited evidence on viral pathogenesis, immune response and disease progression in people with and without ART initiation for HIV.

7.3.3.3 What are implementation considerations?

- Ensure all patients with presumed or confirmed mpox receive HIV testing at their first presentation to health care providers.
- Ensure individuals engage with health care services at an early stage of mpox symptoms to avoid disease progression and late ART initiation.
- Ensure clinical assessment is conducted in all patients prior to ART initiation to ensure comprehensive care of people living with HIV, in particular those with advanced HIV disease.

7.4 Risk factors for severe disease and prognosis methodology

To provide the GDG with a comprehensive understanding of mpox prognosis, a systematic review of observational studies published up to 20 September 2024, was conducted. The review aimed to: 1) establish baseline risk estimations for clinical adverse outcomes, including but not limited to hospitalization and mortality, in patients with mpox, differentiating between severe and non-severe cases as defined in the literature; and 2) identify adjusted risk factors associated with mpox prognosis [49].

With assistance from an expert librarian, the review team searched MEDLINE, Embase, CENTRAL, CINAHL, Global Health, medRxiv, bioRxiv, and SSRN from inception to September 2024, using search terms including "mpox", "cohort", "case-control ", "observational study", "cross-sectional", "epidemiologic", "population surveillance",

"retrospective", "prospective" and "randomized controlled tria"". To identify additional eligible studies, the review team screened the reference lists of included studies and relevant systematic reviews.

The review included studies of patients with laboratory-confirmed mpox virus infections that reported the rate of clinical adverse outcomes and adjusted risk factors for adverse outcomes.

To estimate pooled baseline risks and their associated 95% confidence intervals for each adverse outcome, the review team conducted meta-analyses of proportions using fixed effects models. The review team performed analyses for all patients, severe patients and non-severe patients separately. For every candidate risk factor, as most eligible studies reported odds ratios (OR) as the measure of association, if studies reported relative risks (RRs) or hazard ratios (HRs), the review team converted them to ORs and pooled ORs using the random effects model.

The review team examined different thresholds to classify studies as reporting on severe disease or non-severe disease and decided on a 50% threshold to categorize studies as severe disease or non-severe disease. Studies with fewer than 50% of participants classified as having severe mpox or hospitalized for treatment were categorized as non-severe; studies with 50% or more were categorized as severe.

8. How to access and use this guideline

This is a living guideline from WHO. The recommendations included here will be updated, and new recommendations will be added over time:

8.1 How to access the guideline

- WHO website: This is a full read out of the MAGICapp content for those without reliable web access. It can also be downloaded directly from MAGICapp (see cogwheel on top right).
- MAGICapp in online, multilayered formats: This is the fullest version of the guideline, as detailed below.

8.2 How to navigate this guideline

The guideline is written, disseminated and updated in MAGICapp, with a format and structure that ensures user-friendliness and ease of navigation [168]. It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline.

The purpose of the online formats and additional tools, such as the infographics, is to make it easier to navigate and make use of the guideline in busy clinical practice. The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making (clinical encounter decision aids) [168]

The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting information pertinent to applying the recommendations in practice. End-users will also need to understand what is meant by strong and conditional recommendations (displayed immediately below) and certainty of evidence (the extent to which the estimates of effect from research represent true effects from treatment).

For each recommendation additional information is available through the following tabs:

- Research evidence: Readers can find details about the research evidence underpinning the recommendations as GRADE Summary of Findings tables and narrative evidence summaries.
- Evidence to decision: The absolute benefits and harms are summarized, along with other factors such as the values and preferences of patients, practical issues around delivering the treatment as well as considerations concerning resources, applicability, feasibility, equity and human rights. These latter factors are particularly important for those in need of adapting the guidelines for the national or local context.
- Justification: Explanation of how the GDG considered and integrated evidence to decision factors when creating the recommendations, focusing on controversial and challenging issues.
- Practical information: For example, dosing, duration and administration of drugs, or how to apply tests to identify patients in practice.
- Decision aids: Tools for shared decision-making in clinical encounters.

8.3 Additional educational modules and implementation tools for health workers

- WHO Essential items estimator tool (https://partnersplatform.who.int/tools/essentialitemsestimator) assists governments, partners and other stakeholders to forecast the necessary volume of PPE, diagnostic test equipment, consumable medical supplies, biomedical equipment for case management, and essential drugs for supportive care and treatment of COVID-19.
- WHO website mpox clinical management (https://www.who.int/teams/health-care-readiness/clinical-management-of-monkeypox) includes multiple tools and infographics about clinical diagnosis and management of patients with mpox. Such as the Atlas of mpox lesions: a tool for clinical researchers, posters about screening, triage and differential diagnosis, skin care, etc. in patients with mpox infection. Also, it includes the link for the Global Clinical Data Platform for Mpox.
- Interim practical manual for designing, setting up and assessing health facilities in the context of mpox outbreaks (2024) (https://iris.who.int/handle/10665/380532).
- Health emergencies - infection prevention and control and water sanitation and hygiene (https://www.who.int/teams/health- care-readiness/infection-prevention-and-

control#:~:text=Infection%20prevention%20and%20control%20%28IPC%29%20and%20water,%20sanitation,%20and%20hygiene).

8.4 Collection of standardized data and the WHO Clinical Platform

As the cluster of mpox cases continues to expand in countries across WHO regions it is important that we understand the clinical features, prognostic factors and outcomes in patients so we can better inform our clinical management guidelines and inform public health. The WHO Global Clinical Platform collects patient-level anonymized clinical data and has been used to understand various emerging pathogens. As we work to understand more about the current cases, we have developed a case report form for mpox, and invite Member States to contribute data to this platform.

The objectives of the platform are:

- describe the clinical characteristics of mpox.
- assess the variations in clinical characteristics of mpox.
- identify the association of clinical characteristics of mpox with symptoms.
- describe temporal trends in clinical characteristics of mpox.

For more details, please see the WHO Global Clinical Platform for mpox website [link] [189]. A statistical analysis plan is available [link] [190].

9. Uncertainties, emerging evidence and future research

While formulating recommendations and prioritizing questions for this guideline, the GDG identified key areas of uncertainty, and in which they felt research would enable future recommendations to be made with higher certainty.

9.1 Transmission

- Limited epidemiological evidence on pre-symptomatic or asymptomatic phases of disease.
- Routes for human-human transmission, including how viral dynamics and trajectories correlate with viral culture in the various bodily fluids and the impact of this on transmission, infectious periods, subgroup by disease manifestation and disease severity.
- Potential for reverse zoonosis and spillback events.
- Natural history of disease: disease severity and risk factors for severe, disease in different subpopulations (neonates, children and young people, immunosuppressed, pregnant women and older persons).
- Difference and similarities in transmissibility between clade I (a and b), clade II (a and b).
- Risks related to particle and aerosol-generating activities (e.g. shaking linen).
- Infectious dose of MPXV in humans.
- Characterization of viral evolution.
- Wastewater sampling and predicting trends for outbreak response.

9.2 Clinical management

- Establish disease severity classification and risk factors for severity.
- Co-infection: other viruses (varicella zoster [VZV], HIV), STIs (such as herpes simplex virus [HSV], syphilis, chancroid, lymphogranuloma venereum [LGV]), and others, parasitic infections (malaria, dengue, filariasis) etc. Understand if co-infection impacts disease severity.
- Clinical management of patients with advanced HIV and mpox.
- The incidence of IRIS and its contribution to morbidity and mortality.
- Racial and ethnic disparities in incidence and access to countermeasure and care.
- Best symptomatic care for skin care, rash management, nutrition.

- Best optimized care package for complications such as ocular and central nervous system complications.
- Long-term outcomes for recovered patients, including mothers and babies, immunosuppressed patients. Evidence of post viral syndrome and clinical presentation.
- Efficacy and safety of therapeutics, including in pregnant and breastfeeding mothers and children.
- Presence and transmission of mpox through breastmilk. Measures to inactivate mpox virus to make the breastmilk safe (e.g. pasteurization).[129]

9.3 Infection prevention and control

- Description of close proximity and impact on transmission.
- Effectiveness of covering lesions and impact on fomite/environmental contamination.
- Health worker exposure risk categories and post-exposure prophylaxis (PEP).
- Susceptibility of the mpox virus to disinfectants and their virucidal properties (i.e. active ingredients and concentrations, contact time).
- Stability of virus in the environment and on surfaces.
- Optimal ventilation to reduce disease transmission.
- Duration of transmission-based precautions to maintain patients in isolation (when can transmission-based precautions be lifted).
- Effects of home-based care (what can be learned, models of care, etc.).
- Effectiveness of isolation at home to prevent transmission.

9.4 Methods questions

- Value and preference surveys of affected populations.

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Annex 1. WHO case definitions for mpox outbreak in non-endemic countries

Surveillance case definitions

The case definitions for use in this outbreak may be reviewed as more evidence becomes available.

For further guidance on testing please refer to Laboratory testing for the monkeypox virus (MPXV): interim guidance 2024 [191].

Suspected case

i) A person who is a contact of a probable or confirmed mpox case in the 21 days before the onset of signs or symptoms, and who presents with any of the following: acute onset of fever (> 38.5°C), headache, myalgia (muscle pain/body aches), back pain, profound weakness or fatigue.

OR

ii) A person presenting since 1 January 2022 with an unexplained acute skin rash, mucosal lesions or lymphadenopathy (swollen lymph nodes). The skin rash may include single or multiple lesions in the ano-genital region or elsewhere on the body. Mucosal lesions may include single or multiple oral, conjunctival, urethral, penile, vaginal or ano-rectal lesions. Ano-rectal lesions can also manifest as ano-rectal inflammation (proctitis), pain and/or bleeding.

AND

For which the following common causes of acute rash or skin lesions do not fully explain the clinical picture: varicella zoster, herpes zoster, measles, herpes simplex, bacterial skin infections, disseminated gonococcus infection, primary or secondary syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, molluscum contagiosum, allergic reaction (e.g. to plants); and any other locally relevant common causes of papular or vesicular rash.

NB It is not necessary to obtain negative laboratory results for listed common causes of rash illness in order to classify a case as suspected. Further, if suspicion of mpox is high due to either history and/or clinical presentation or possible exposure to a case, the

identification of an alternate pathogen which causes rash illness should not preclude testing for MPXV, as co-infections have been identified.

Probable case

A person presenting with an unexplained acute skin rash, mucosal lesions or lymphadenopathy (swollen lymph nodes). The skin rash may include single or multiple lesions in the ano-genital region or elsewhere on the body. Mucosal lesions may include single or multiple oral, conjunctival, urethral, penile, vaginal or ano-rectal lesions. Ano-rectal lesions can also manifest as ano-rectal inflammation (proctitis), pain and/or bleeding.

AND

One or more of the following:

- Has an epidemiological link to a probable or confirmed case of mpox in the 21 days before symptom onset.
- Identifies as gay, bisexual or other cis or trans man who has sex with men.
- Has had multiple and/or casual sexual partners in the 21 days before symptom onset.
- Has detectable levels of anti-orthopoxvirus (OPXV) IgM antibody (during the period of 4–56 days after rash onset); or a four-fold rise in IgG antibody titer based on acute (up to day 5–7) and convalescent (day 21 onwards) samples; in the absence of a recent smallpox/ mpox vaccination or other known exposure to OPXV.
- Has a positive test result for orthopoxviral infection (e.g. OPXV-specific PCR without MPXV-specific PCR or sequencing) .

Confirmed case

A person with laboratory-confirmed mpox virus infection by detection of unique sequences of viral DNA by real-time polymerase chain reaction (PCR) and/or sequencing.

Discarded case

A suspected or probable case for which laboratory testing of lesion fluid, skin specimens or crusts by PCR and/or sequencing is negative for mpox virus. Conversely, a retrospectively detected probable case for which lesion testing can no longer be adequately performed (i.e. after the crusts fall off) and no other specimen is found PCR-positive, would remain classified as a probable case. A suspected or probable

case should not be discarded based on a negative result from an oropharyngeal, anal or rectal swab or from a blood test alone.

1) The person has been exposed to a probable or confirmed mpox case. Please see below definition of a contact.
2) Serology can be used for retrospective case classification for a probable case in specific circumstances such as when diagnostic testing through PCR of skin lesion specimens has not been possible, or in the context of research with standardized data collection. The primary diagnostic test for mpox is PCR of skin lesion material or other specimen such as an oral or nasopharyngeal swab as appropriate. Serology should not be used as a first-line diagnostic test.
3) PCR on a blood specimen may be unreliable and should also not be used alone as a first-line diagnostic test. If blood PCR is negative and was the only test done, this is not sufficient to discard a case that otherwise meets the definition of a suspected for probable case. This applies regardless of whether the blood PCR was for orthopox viruses or was mpox virus-specific.

Annex 2. Medications and dosages for symptomatic care

Fever – paracetamol

Adults: 1 g PO/IV every 6–8 hours. Maximum dose 4 g every 24 hours or (max 2 g/24 h if history of chronic liver disease).

Neonates: Oral dose 10–15 mg/kg every 6 hours. Maximum dose 40 mg/kg/day; IV dose 7.5 mg/kg every 6 hours, maximum dose 30 mg/kg day.

All other children: 10–15 mg/kg every 6 hours, maximum dose 60 mg/kg /day.

Mild pain control – paracetamol

Adults: 1 g PO/IV every 6–8 hours. Maximum dose 4 g every 24 hours or (max 2 g/24 h if history of chronic liver disease).

Children: Orally or IV 10–15 mg/kg/dose every 4–6 hours as required, maximum usual dose 60 mg/kg/day, but 90 mg/kg/day can be given for short period with medical supervision.

Severe pain control – consider to add tramadol (PO or IV)

Adults: 50–100 mg PO/IV every 4–6 hours as needed, daily maximum 400 mg/day.

Children > 6 months: 1–2 mg/kg every 4–6 hours, maximum 400 mg/day.

Severe pain control – consider replacing tramadol for morphine (PO, IV, SC) (oral dose preferred if patient can tolerate; only use immediate release tablets for acute pain)

Adults: Oral dose is 10 mg every 4 hours as needed; maximum dose is 60 mg/day. IV dose is 1–4 mg SQ/IV every 4 hours as needed – monitor SBP and RR prior to administration of morphine (hold for low SBP or respiratory rate).

Children: Oral dose is 0.2–0.4 mg/kg/dose every 4 hours. Titrate dose to pain. IV dose is 0.05–0.1 mg/kg/dose every 4–6 hours as required.

Antihistaminic for itching

Adults: Loratadine 10 mg PO once daily.

Children (> 30 kg): Loratadine 10 mg PO once daily.

Nausea and vomiting

Ondansetron (associated with QT prolongation, thus it is important to note other medications that may also prolong the QT interval and to monitor regularly with ECGs if available).

Adults: 8 mg PO every 12 hours or 4 mg IV every 8 hours as needed.

Children: 0.15 mg/kg orally or IV 0.15 mg/kg every 12 hours, maximum dose 8 mg.

Promethazine

Only for adults: 12.5–25 mg orally every 4–6 hours as needed (can prolong QT interval).

Dyspepsia

Adult: Omeprazole 40 mg PO/IV every 24 hours.

Child: Omeprazole: 5–10 kg: 5 mg once daily; 10–20 kg: 10 mg once daily; ≥ 20 kg: 20 mg once daily.

Diarrhoea

Diarrhoea should be managed conservatively. The use of anti-motility agents is not generally recommended given the potential for ileus.

Anxiety

This may be a symptom patients experience particularly related to being in isolation or due to worsening symptoms.

First-line therapy is to talk with a mental health counsellor.

For moderate to severe anxiety, diazepam can be considered, but an evaluation of the patient's mental status should precede its use.

Benzodiazepines should not be given to patients with altered mentation.

Adults: Diazepam 5–10 mg PO every 8 hours as needed as long as mentation is unaffected.

Children: Diazepam 0.05–0.1 mg/kg PO every 6 hours as needed. Continual supervision by a health aid is indicated to keep the child calm. Sedatives should only be used if necessary to perform procedures and give interventions.

Agitation

If patient is agitated and becomes a danger to self, health care providers or other patients, consider pharmacotherapy.

Adults: Diazepam 2–10 mg PO/IV every 6–8 hours as needed as long as patient can protect their airway.

Adults: Haloperidol 0.5–5 mg every 4–6 hours, as needed.

Children > 6 years: Haloperidol IM 1–3 mg every 4–8 hours, as needed.

Children 3–6 years: Haloperidol PO 0.01–0.03 mg/kg once daily.

Haloperidol is associated with QT prolongation, thus it is important to note other medications that may also prolong the QT interval and to monitor with ECG regularly if available.

Note: Avoid the use of salicylates (e.g. aspirin) in children and adolescents < 18 years of age to avoid the development of Reye's Syndrome.

Annex 3. Antimicrobial recommendations and dosages for secondary bacterial skin infection

This is for the treatment of impetigo, erysipelas or cellulitis caused by a bacterial pathogen. It excludes skin infections caused by viral, fungal or parasitic pathogens, necrotizing fasciitis, pyomyositis, severe infections with sepsis and surgical site infections.

For further guidance on WHO recommendations for antimicrobial therapy please consult The WHO Essential Medicines List antibiotic book: improving antibiotic AWaReness [147]and The WHO Essential Medicines List antibiotic book: infographics. [192]

Adults

Antibiotic	Dose
Cloxacillin (flucloxacillin)	500 mg orally every 8 hours
Cephalexin	500 mg orally every 8 hours
Amoxicillin-clavulanic acid	500–125 mg orally every 8 hours
If concern for community acquired MRSA consider following treatment:	
Clindamycin	600 mg orally every 8 hours
Trimethoprim-sulfamethoxazole	800–160 mg orally every 12 hours
Doxycycline	100 mg orally every 12 hours

Note: In the case of penicillin or beta-lactam allergy: use clindamycin or trimethoprim-sulfamethoxazole.

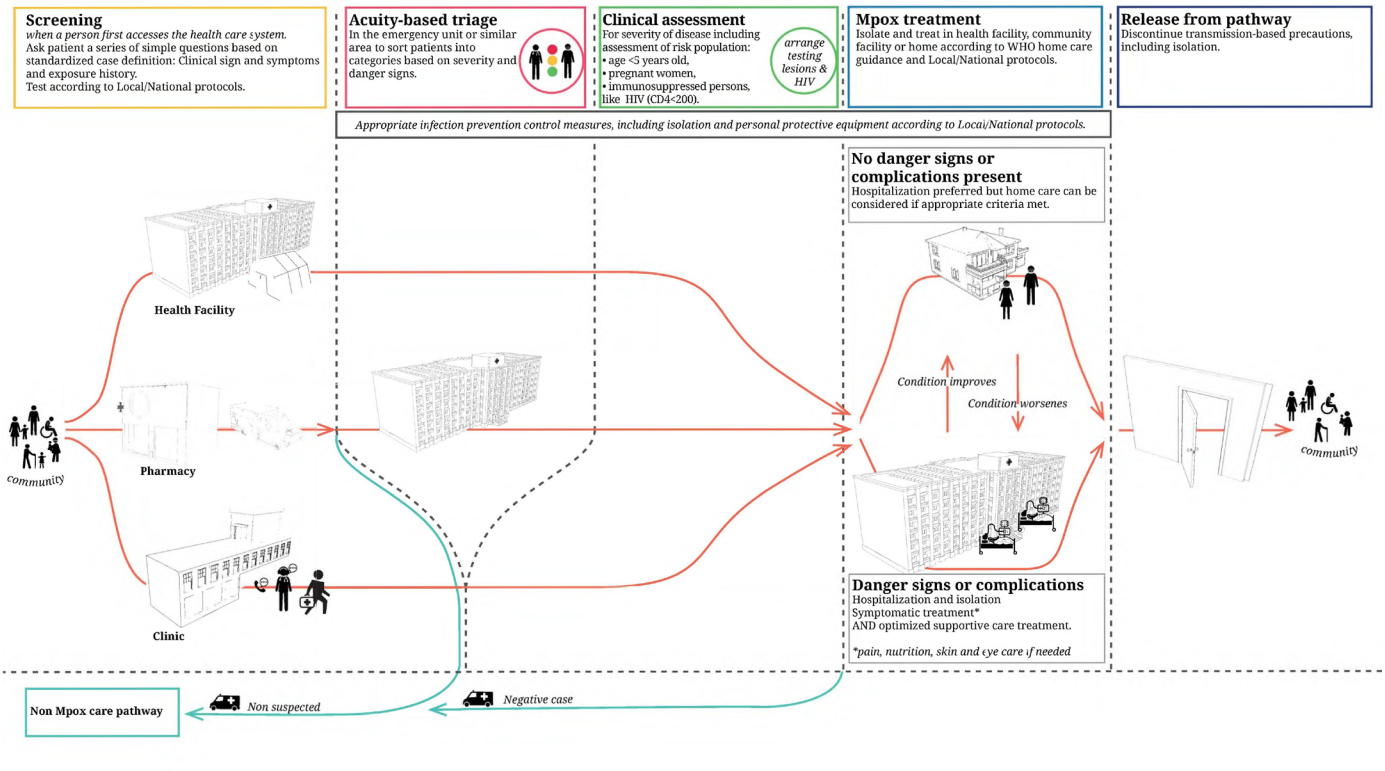
Children

Weight	Amoxicillin-clavulanic acid	Cefalexin	Cloxacillin (flucloxacillin)
	40–50 mg/kg/dose of amoxicillin component every 12 hours OR 30 mg/kg/dose every 8 hours orally	*25 mg/kg/dose every 12 hours orally*	*in neonates: 25–50 mg/kg/dose twice daily; in children: 25 mg/kg/dose every 6 hours*
3 < 6 kg	250 mg of amoxicillin/dose twice daily	125 mg every 12 hours	125 mg every 6 hours
6 < 10 kg	375 mg of amoxicillin/dose twice daily	250 mg every 12 hours	250 mg every 6 hours

10 < 15 kg	500 mg of amoxicillin/dose twice daily	375 mg every 12 hours	375 mg every 6 hours
15 < 20 kg	750 mg of amoxicillin/dose twice daily	500 mg every 12 hours	500 mg every 6 hours
20 < 30 kg	1000 mg of amoxicillin/dose twice daily	625 mg every 12 hours	750 mg every 6 hours
> 30 kg	Use adult dose	Use adult dose	Use adult dose

Note: If concern for community-acquired MRSA consider clindamycin: neonates 5 mg/kg/dose every 8 hours; children 10 mg/kg/dose every 8 hours.

Annex 4. Mpox care pathway



Annex 5. Search strategy and terminology for reported routes of MPXV infection

A commissioned systematic in 2024 review underpins the current guideline and is an update of a previously published review. It synthesized and updated evidence for the three research questions. The review occurred in two stages. The first stage appraised available evidence from comparative interventional trials, which yielded no evidence. In the absence of such data, the second stage was preformed to synthesize evidence on the reported routes of MPXV infection using non-comparative study designs to indirectly inform the three IPC intervention review questions.

Literature search strategy

The search was done at the end of September 2024 using broad search terms including terms for mpox-like viruses. The search included the following databases: MEDLINE (OVID), Embase (OVID), Biosis previews (Web of Science), CAB Abstracts (Web of Science) and Global Index Medicus.

Inclusion and exclusion criteria

All studies published in English and French between September 2022 and September 2024 that presented data on the mpox mode of transmission were eligible to be included. Both comparative and non-comparative studies in different settings (health care, households, congregate-living/community settings) were included. The following mpox studies were excluded; studies without transmission data, studies solely concerning animal-to-animal or animal-to-human transmission, studies solely examining laboratory transmission, non-original studies, and studies that published in a language other than English and French.

Given the potential for varying interpretations of key terminology, the following descriptions were used for the purpose of the systematic review:

i) Fully healed: mpox lesions have crusted, scabs have fallen off and a fresh layer of skin has formed underneath.
ii) Infectious period: until mpox lesions have crusted, scabs have fallen off and a fresh layer of skin has formed underneath.

iii) Isolation: the separation of infected people with a contagious disease from people who are not infected by keeping to a separate room or area within the home.
iv) Adequate ventilation in a single patient room: may be achieved by mechanical, natural or hybrid ventilation.
    - Mechanical ventilation rate: six air changes per hour in room.
    - Natural ventilation rate: 60 L/sec per patient.
    - Hybrid (mixed mode) ventilation is a combination of both mechanical and natural ventilation. It relies on natural driving forces to provide the desired (design) flow rate. Mechanical ventilation can be used when the natural ventilation flow rate is too low.
v) Airborne isolation room ventilation: mechanical ventilation to meet criteria for an airborne precaution room: negative pressure is created to control the direction of airflow. The ventilation rate should be at least 12 ACH.

Natural ventilation to meet criteria for an airborne precaution room: the airflow should be directed to areas free of transit or should permit the rapid dilution of contaminated air into the surrounding areas and the open air. The average ventilation rate should be 160 litres/second per patient.

From the data collected from stage two, several subgroup analyses were conducted based on different contexts:

- Setting: Review considered: household, congregate living, or health care settings community settings.
- Clade (where known or presumed): The analysis included Clade I, Clade II, and its subtypes Clade IIa and Clade IIb (and all sub lineages, including but not limited to IIb.lineage A, IIb.lineage B, and IIb.lineage C).
- Route of transmission: Transmission routes were analysed based on the information detailed in the paper(s).
- Region and/or country: Data were categorized by WHO regions, including the African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region and the Western Pacific Region.
- Context: Cases reported in the global mpox outbreak since 2022, categorized as the West African clade, were classified as likely Clade IIb unless evidence emerged to the contrary.

The review conducted in 2024 followed a similar search strategy as the one in 2023, the main difference being the extended timeframe.

Annex 6. Optimized supportive care measures

Complication	Treatment
Skin exfoliation	• Patients with heavy rash burden may develop exfoliation (in severe cases similar to partial thickness burns), which can be significant leading to dehydration and protein loss *[146]*. • Estimate percentage skin affected and consider treatment like burns. • Minimize insensible fluid loss and promote skin healing. • Ensure adequate hydration and nutrition. • Obtain consultation with appropriate consultants such as surgeon, dermatologist and/or wound care specialists. • Bedside or surgical debridement as needed. • Skin grafting in rare and severe cases
Necrotizing soft tissue infection	• This is a life-threatening condition of the deep soft tissue that affects the muscle fascia which causes necrosis, tissue destruction and systemic toxicity. Suspect if patient develops oedema, crepitus, malodorous discharge or pain out of proportion to appearance of infection. Though can be caused by mpox virus, consider bacterial pathogens as well. Start broad spectrum antibiotics to cover *Staphylococcus sp*. and *Streptococcus sp*. Consult surgeon for further management. • See the WHO Essential Medicines List antibiotic book for guidance on correct antimicrobial selection and appropriate use *[192]*.
Pyomyositis	• This occurs when pus develops within the muscle and should be suspected when the patient has muscle tenderness. Though this can be caused by mpox virus, it may also commonly be caused by skin flora such as *Staphylococcus sp*. or *Streptococcus sp*. *[141,192]*. Ultrasound can assist in diagnosis. Collect blood cultures, start broad spectrum antibiotics, and proceed to surgical incision and drainage. Send sample for microbiology and culture to support antimicrobial therapy selection. • See the WHO Essential Medicines List antibiotic book for guidance on correct antimicrobial selection and appropriate use *[192]*.
Cervical adenopathy	• Can occur in up to 85% of cases with lymphadenopathy *[33]*. • When large cervical adenopathy is combined with multiple oropharyngeal lesions patients may be at risk for complications such as respiratory compromise and retropharyngeal abscesses. Patients are also at risk for dehydration due to decreased food and water intake *[33,146]*. • Obtain consultation with appropriate specialists, such as surgeon, ENT, anesthesiologist and infectious disease clinicians. Under their care, in severe cases, steroids may be used *[33]*.
Ocular lesions	• One of the most significant sequelae of mpox is corneal scarring and loss of vision *[29,85,146,63,135]*. • Patients may present with non-specific ocular symptoms such as conjunctivitis. • Eye care with ophthalmologist evaluation *[135]*. • Ophthalmic antibiotics/antivirals if indicated for co-infection.

	• Vitamin A supplementation, especially to malnourished children *[141]*. • Good eye care that includes eye lubrication and saline-soaked protective eye pads *[141]*. • Avoid steroid ointments (may prolong presence of mpox virus in ocular tissue) *[146,193]*. • Trifluridine eye drops (sometimes used for other orthopoxviruses or herpetic eye infections) may be considered to hasten resolution of symptoms and prevent long-term damage from scarring, where available *[146,63,193,194]*.
Pneumonia	• Manage according to the WHO Clinical care for severe acute respiratory infection toolkit *[111]*. • See the WHO Essential Medicines List antibiotic book for guidance on correct antimicrobial selection and appropriate use *[192]*.
Acute respiratory distress syndrome (ARDS)	• Oxygen, non-invasive ventilation, mechanical ventilation. • Manage according to the WHO Clinical care for severe acute respiratory infection toolkit *[111]*.
Severe dehydration	• Severe dehydration and hypovolemic shock can be seen in patients with mpox due to intravascular volume loss due to extensive rash and/or gastrointestinal losses due to diarrhoea and vomiting accompanied by poor oral intake. • The treatment for severe dehydration is resuscitation with intravenous or intraosseous (IV/IO) fluid, given as one or multiple boluses with close monitoring of fluid responsiveness. Adequate IV fluid intake refers to the volume that will correct signs of hypovolemia. See Pocket book of hospital care for children *[146,141]*.
Sepsis and septic shock	• Sepsis and septic shock differ from severe dehydration as it results from an immune response to an infection. Management of sepsis requires early identification, management of infection and supportive care, including fluid resuscitation to maintain organ perfusion to reduce and prevent further organ injury; and may also require vasopressors as well as control of infection *[146]*. • See the WHO Clinical care for severe acute respiratory infection toolkit for more information about sepsis *[111]*. • See the WHO Essential Medicines List antibiotic book for guidance on correct antimicrobial selection and appropriate use *[192]*.
Encephalitis	• Consider lumbar puncture for cerebrospinal fluid (CSF) evaluation to evaluate for other treatable conditions. • Monitor and assess airway, breathing, circulation, disability (ABCD) and give emergency treatments. • Monitor neurological status (AVPU). • Control seizures with anti-epileptics *[135]*. • Antibiotics/antivirals if indicated for co-infections. • See WHO Essential Medicines List antibiotic book for guidance on correct antimicrobial selection and appropriate use *[192]*.

Nutritional considerations	• Assess the nutritional status of all patients. If food intake is limited due to weakness, the patient should be assisted with feeding by a health care provider. If the patient is unable to tolerate oral nutrition, consider enteral nutrition. The placement of a nasogastric tube by an experienced provider could be considered along with nasogastric feeding. Always ensure proper placement of nasogastric tube before administering feeds to avoid risk of aspiration. Paediatric mpox patients diagnosed with severe acute malnutrition should be treated according to the national protocol on management of severe acute malnutrition. • Take special care with patients at risk for refeeding (critically unwell, low BMI, reduced food intake for > 5 days, a history of alcohol abuse or receiving the following drugs: insulin, chemotherapy, antacids or diuretics) and start enteral feeding slowly with close monitoring. • Patients with reduced levels of consciousness are at risk for aspiration and should not be forced to eat. If severe malnutrition is present, refer to WHO published guidelines [135,141].

Clinical management of complications and severe forms of mpox

Annex 7. Systematic monitoring of patients

Vital signs and pain assessment	**Temperature, heart rate, blood pressure, respiratory rate, peripheral oxygen saturation, level of consciousness using the alert, voice, pain, unresponsive scale (AVPU), point of care glucose, and body weight and height to calculate BMI and children's mid-upper arm circumference (MUAC)** **Pain scale**
General condition	• Is the patient able to eat and drink without support? • Is the patient able to sit and walk independently? • Has the patient had recent weight loss since onset of symptoms?

Rash characterization	• Stage of rash: macules, papules, vesicles, pustules, crusted over, exfoliation
	• Location of the rash (face, arms, torso, genitals, legs, mucosa)
	• Number of lesions [59,107]:
	  • Mild (< 25 skin lesions)
	  • Moderate (25–99 skin lesions)
	  • Severe (100–250 skin lesions)
	  • Very severe (> 250 skin lesions)
	• If exfoliation present: % body affected (> 10% is concerning)

Presence of bacterial secondary infection	• Cellulitis, abscess, pyomyositis, necrotizing soft tissue infection
Neurologic status	• AVPU, seizures, coma
Volume status	• Presence of dehydration: mild, moderate, or severe
Signs of perfusion	• Pulse rate, strength, capillary refill • Urine output (> 0.5 mL/kg/h = good in adults; 1.0 mL/kg/h in children) • Mottling of skin
Respiratory system	• Respiratory rate, SpO2, signs of respiratory distress
Nutritional assessment	• Change in appetite, weight loss, body weight, height, calculation of BMI, MUAC in children • Signs of malnutrition – use standardized tool (e.g. Malnutrition Universal Screening Tool)
Ophthalmological examination	• One of the most frequent complications, for early diagnosis and management
Laboratory tests	• Hematology: white blood count, haemoglobin, platelet. Biochemistry: urea, creatinine, ALT, AST, glucose, albumin. Electrolytes: sodium, potassium, bicarbonate, calcium, chloride. Coagulation: prothrombin time/INR.

Vital signs and clinical features to monitor systematically *(Source: This table is modified from the WHO Optimized supportive care for Ebola virus disease [180] and includes information from the WHO Pocket book of hospital care for children [141]).*

World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

cmtm@who.int