Annexes to the Vaccines and immunization for monkeypox interim guidance

Grading of evidence – Evidence to recommendation tables

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Annex 1: Summary of findings: Primary preventive vaccination with ACAM2000 compared to no vaccination for persons with a high risk of exposure to monkeypox

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Local adverse events							
13.952 (8 studies)[a]	very serious[b]	not serious[c]	not serious[d]	not serious[e]	none	⨁⨁◯◯ Low	• Local adverse events may be very frequent in ACAM2000 vaccines, but the evidence is uncertain. • ACAM2000 vaccination leaves a permanent scar (known as "take") at the injection site following successful inoculation. • Examples of local adverse events commonly reported were injection site pain (up to 77%), redness (up to 74%), pruritus (up to 97%), injection site swelling (up to 48%), and rash (up to 20%).
Systemic adverse events							
848.417 (9 studies)[f]	very serious[b]	not serious[c]	serious[g]	not serious[e]	none	⨁◯◯◯ Very low	• Systemic adverse events may be frequent in ACAM2000 vaccinees, but the evidence is very uncertain. • Constitutional symptoms were frequent, such as muscle pain (up to 60%), fatigue (up to 49%), malaise (up to 37%), feeling hot (up to 37%), fever (up to 11%), chills (up to 17%), rigors (up to 21%), exercise tolerance decreased (up to 11%) • Dyspnea (up to 4%), lymph node pain (up to 73%), headache (up to 60%), nausea (up to 23%), vomiting (up to 7%), diarrhoea (up to 23%), and constipation (up to 6%).

Myopericarditis

1743620 (8 studies)[h]	very serious[b]	serious[i]	serious[g]	serious[j]	none	⨁◯◯◯ Very low	• Myopericarditis may be very rare in ACAM2000 vaccinees, but the evidence is very uncertain. • A random-effects model meta-analysis found an overall incidence of myopericarditis of 131 cases per 100,000 ACAM2000 vaccinees, 95% CI 28 to 607. • A total of 269 cases of myopericarditis were reported across eight studies with a total of 1,743,620 vaccinees.

Serious adverse events: Neurological serious adverse events[k]

843744 (4 studies)[l]	very serious[b]	not serious	serious[g]	not serious[m]	none	⨁◯◯◯ Very low	• Neurological serious adverse events may not occur in ACAM2000 vaccinees, but the evidence is very uncertain. • No neurological adverse events were reported in the four studies explicitly informing this outcome.

Serious adverse events: eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia

843744 (4 studies)[l]	very serious[b]	not serious	serious[g]	not serious[m]	none	⨁◯◯◯ Very low	• Eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia may be very rare in ACAM2000 vaccinees, but the evidence is very uncertain. • We found five cases of generalized vaccinia (McNeil 2014), one case of eczema vaccinatum (McNeil 2014), one case of progressive vaccinia (McNeil 2014) in the studies explicitly informing these outcomes. • Beachkofsky 2010 (excluded from this review as it was a case study) described another case of ACAM2000 generalized vaccinia.

Serious adverse events: autoinoculation

843714 (3 studies)[n]	very serious[b]	not serious	serious[g]	not serious[m]	none	⨁◯◯◯ Very low	• Autoinoculation may be very rare in ACAM2000 vaccinees, but the evidence is very uncertain. • A total of five cases of autoinoculation were described in the studies informing this outcome. • No case of ocular vaccinia was reported.

Serious adverse events: vaccine-related deaths

1732264 (6 studies)[o]	very serious[b]	not serious	serious[g]	not serious[m]	none	⨁◯◯◯ Very low	• Vaccine-related deaths may not occur in ACAM2000 vaccinees, but the evidence is very uncertain. • In the six studies reporting this information, two out of 1,732,264 vaccinees died (not confirmed if vaccine-related). [p]

Serious adverse events: adverse events requiring hospitalization

834465 (1 observational study)[q]	not serious	not serious	serious[g,r]	not serious[s]	none	⨁◯◯◯ Very low	• Adverse events requiring hospitalization may be very rare in ACAM2000 vaccinees, but the evidence is very uncertain. • 143 out of 834,465 vaccinees (17 per 100,000) were hospitalized. However, it was not specified if the hospitalizations were vaccine-related.

Immunogenicity: vaccination take rate

2268 (6 studies)[t]	very serious[b]	not serious	not serious	not serious[e]	none	⨁⨁◯◯ Low	• The proportion of ACAM2000 vaccinees with vaccination take may be high, but the evidence is uncertain. • The proportion of ACAM2000 vaccinees with a take ranged from 84% to 100%.

Immunogenicity: % of vaccinees with seroconversion

317 (4 studies)[u]	very serious[b]	not serious	serious[v]	not serious[e]	none	⨁◯◯◯ Very low	• The proportion of ACAM2000 vaccinees reaching seroconversion with MPXV neutralizing antibodies may be high, but the evidence is very uncertain. • We found no studies addressing seroconversion with MPXV neutralizing antibodies, but the proportion of ACAM2000 vaccinees that reached seroconversion (non-MPXV specific) ranged from 76% to 97%.

Clinical effectiveness/efficacy against monkeypox infection - not reported

-	-	-	-	-	-	-	• We found no clinical study assessing this outcome. • The clinical effectiveness/efficacy of primary preventive vaccination with ACAM2000 versus no vaccination against monkeypox is unknown. • ACAM2000 clinical effectiveness/efficacy against MPX is inferred from indirect evidence, such as efficacy data from animal challenge studies, immunogenicity data of ACAM2000 compared to Dryvax, and indirect surveillance data in Democratic Republic of the Congo.

Explanations

a. Six RCTs (H-400-002; H-400-003; H-400-005; H-400-009; H-400-012; POX-MVA-006); one uncontrolled trial (VA-006); one observational study (H-406-004).

b. Uncontrolled designs, lack of blinding, inconsistent measurement and reporting of outcomes, and unclear risk of selective outcome reporting.

c. We did not downgrade for inconsistency as the findings pointed consistently to a high frequency of the outcome.

d. We did not downgrade for indirectness. Although safety data from large population-based programs is limited, we consider that the safety profile captured in the included evidence can reflect the local AEs in most populations.

e. We did not downgrade for imprecision as the study samples were usually powered to detect this outcome, which was frequent.

f. Six RCTs (H-400-002; H-400-003; H-400-005; H-400-009; H-400-012; POX-MVA-006); one uncontrolled trial (VA-006) and two observational studies (H-406-004; McNeil 2014).

g. Studies were performed with selected populations in controlled contexts, such as trials with healthy subjects and military personnel. General use of the vaccine may reveal effects not observed in these situations.

h. Four RCTs (H-400-002; H-400-009; H-400-012; H-400-005); four observational studies (McNeil 2014; H-406-005; H-406-004; Engler 2015).

i. I2=99% showed substantial statistical heterogeneity.

j. Although the metanalysis pointed to a low incidence of myopericarditis, its 95% CI was wide enough to reduce the certainty of the evidence.

k. Post-vaccinial encephalitis (PVE), post-vaccinial encephalomyelitis (PVEM)

l. Two RCTs (H-400-002; H-400-005); 2 observational studies (H-406-004; McNeil 2014).

m. At least one study sample was powered to detect the outcome.

n. One RCT (H-400-005); two observational studies (McNeil 2014; H-406-004).

o. Three RCTs (H-400-005; POX-MVA-006; H-400-002); one uncontrolled trial (VA-006); two observational studies (McNeil 2014; H-406-005).

p. One subject showed myocarditis (dilated cardiomyopathy), infarction/necrosis of the liver and hemorrhage/necrosis of the right adrenal gland (McNeil 2014). The other death was attributed to rhabdomyolysis without myocarditis evidence at autopsy (H-406-005). It was not confirmed if the vaccine caused the deaths.

q. Only McNeil 2014 reported this outcome.

r. It was not specified if the hospitalizations were vaccine-related.

s. We did not downgrade for imprecision as the study sample was powered to detect this outcome.

t. Five RCTs (ACAM2000_FDA_Study1; ACAM2000_FDA_Study2; H-400-002; POX-MVA-006; H-400-005); one observational study (Pugh 2014).

u. Four RCTs (H-400-005; H-400-002; H-400-003; POX-MVA-006).

v. We found no studies demonstrating MPXV-neutralizing antibodies in vaccinated individuals.

Annex 2: Summary of findings: Primary preventive vaccination with MVA-BN compared to no vaccination for persons with a high risk of exposure to monkeypox

Certainty assessment							Summary of findings
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Impact**
Local adverse events							
5921 (6 studies)[a]	very serious[b]	not serious[c]	not serious[d]	not serious[e]	none	⨁⨁◯◯ Low	• Local adverse events may be very frequent in MVA-BN vaccines, but the evidence is uncertain. • Local adverse events commonly reported were injection site pain (up to 85%), including movement limitation, redness (up to 61%), pruritus (up to 18%), swelling (up to 52%), induration and itching (up to 43%)
Systemic adverse events							
5457 (6 studies)[f]	very serious[b]	not serious[c]	serious[g]	not serious[e]	none	⨁◯◯◯ Very low	• Systemic adverse events may be frequent in MVA-BN vaccinees, but the evidence is very uncertain. • Constitutional symptoms were frequent, such as muscle pain (up to 43%), fatigue (up to 30%), malaise (up to 17%), fever (up to 2%), chills (up to 10.4%), headache (up to 34.8%) and nausea (up to 17.3%).
Myopericarditis							
9713 (19 studies)[h]	very serious[b]	not serious[i]	serious[g]	very serious[j]	none	⨁◯◯◯ Very low	• Myopericarditis may not occur in MVA-BN vaccinees, but the evidence is very uncertain. • The included studies did not find any case of myopericarditis. • POX-MVA-013 reported that one out of its 2,798 MVA-BN vaccinees presented a potential myocarditis (but the case did not meet the CDC definition).

Serious adverse events: Neurological serious adverse events[k]

9713 (19 studies)[l]	very serious[b]	not serious[i]	serious[g]	very serious[j]	none	⨁◯◯◯ Very low	• Neurological serious adverse events may not occur in MVA-BN vaccinees, but the evidence is very uncertain. • No neurological serious adverse events were reported.

Serious adverse events: eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia

9713 (19 studies)[l]	very serious[b]	not serious[i]	serious[g]	very serious[j]	none	⨁◯◯◯ Very low	• Eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia may not occur in MVA-BN vaccinees, but the evidence is very uncertain. • No cases were reported.

Serious adverse events: autoinoculation

9713 (19 studies)[l]	very serious[b]	not serious[i]	serious[g]	very serious[j]	none	⨁◯◯◯ Very low	• Autoinoculation may not occur in MVA-BN vaccinees, but the evidence is very uncertain. • No cases of autoinoculation were described. • No case of ocular vaccinia was reported.

Serious adverse events: vaccine-related deaths

9713 (19 studies)[l]	very serious[b]	not serious[i]	serious[g]	very serious[j]	none	⨁◯◯◯ Very low	• Vaccine-related deaths may not occur in MVA-BN vaccinees, but the evidence is very uncertain. • No cases of MVA-BN vaccine-related deaths were reported.[m]

Serious adverse events: adverse events requiring hospitalization

9713 (19 studies)[l]	very serious[b]	not serious[i]	serious[g]	very serious[j]	none	⨁◯◯◯ Very low	• Adverse events requiring hospitalization may not occur in MVA-BN vaccinees, but the evidence is very uncertain. • No AEs requiring hospitalization were reported.

Immunogenicity: vaccination take rate - not reported

-	-	-	-	-	-	-	• Not applicable for MVA-BN: it is a replication-deficient vaccine, thus vaccination with MVA-BN does not produce a take.

Immunogenicity: % of vaccinees with seroconversion

1222 (8 studies)[o]	very serious[b]	not serious	serious[p]	not serious[e]	none	⨁◯◯◯ Very low	• The proportion of MVA-BN vaccinees reaching seroconversion with MPXV neutralizing antibodies may be high, but the evidence is very uncertain. • We found no studies addressing seroconversion with MPXV neutralizing antibodies, but the proportion of MVA-BN vaccinees that reached seroconversion (non-MPXV specific) was always over 98%.[q]

Clinical effectiveness/efficacy against monkeypox infection - not reported

-	-	-	-	-	-	-	• We found no peer-reviewed clinical studies assessing this outcome. • The clinical effectiveness/efficacy of primary preventive vaccination with MVA-BN versus no vaccination against monkeypox is unknown.[r]

CI: confidence interval

Explanations

a. Five RCTs (POX-MVA-006; POX-MVA-013; POX-MVA-029; POX-MVA-031; MVA_07-0042) and one uncontrolled trial (POX-MVA-03x).

b. Uncontrolled designs, lack of blinding, inconsistent measurement and reporting of outcomes, and unclear risk of selective outcome reporting.

c. We did not downgrade for inconsistency as the findings pointed consistently to a high frequency of the outcome.

d. We did not downgrade for indirectness. Although safety data from large population-based programs is limited, we consider that the safety profile captured in the included evidence can reflect the local AEs in most populations.

e. We did not downgrade for imprecision as the study samples were usually powered to detect this outcome, which was frequent.

f. Four RCTs (POX-MVA-006; POX-MVA-013; POX-MVA-031; MVA_07-0042); one non-randomized trial (POX-MVA-010); one uncontrolled trial (POX-MVA-03x).

g. Studies were performed with selected populations in controlled contexts, such as trials with healthy subjects and military personnel. General use of the vaccine may reveal effects not observed in these situations.

h. 15 RCTs (MVA_05-0010; MVA_11-0021; Vollmar 2006; POX-MVA-002; POX-MVA-004; POX-MVA-005; POX-MVA-006; POX-MVA-008; POX-MVA-009; POX-MVA-013; POX-MVA-027; POX-MVA-028; POX-MVA-029; POX-MVA-031; POX-MVA-037); 3 non-randomized trials (POX-MVA-007; POX-MVA-010; POX-MVA-011); 1 uncontrolled trial: (POX-MVA-03x).

i. All the studies presented zero cases.

j. The study samples were not powered to detect rare adverse events.

k. Post-vaccinial encephalitis (PVE), post-vaccinial encephalomyelitis (PVEM)

l. 15 RCTs: MVA_05-0010; MVA_11-0021; POX-MVA-002; POX-MVA-004; POX-MVA-005; POX-MVA-006; POX-MVA-008; POX-MVA-009; POX-MVA-013; POX-MVA-027; POX-MVA-028; POX-MVA-029; POX-MVA-031; POX-MVA-037; Vollmar 2006; 3 non-randomized trial: POX-MVA-007; POX-MVA-010; POX-MVA-011; 1 uncontrolled trial POX-MVA-03x).

m. Only three studies reported explicitly all-cause mortality. Two out 1129 vaccinees died in POX-MVA-031 (unknown cases). No death occurred among the 22 vaccinees in POX-MVA-03x and the 221 vaccinees in POX-MVA-006.

n. Five RCTs (ACAM2000_FDA_Study1; ACAM2000_FDA_Study2; H-400-002; POX-MVA-006; H-400-005); one observational study (Pugh 2014).

o. Seven RCTs (POX-MVA-008; POX-MVA-009; MVA_11-0021; POX-MVA-027; POX-MVA-028; POX-MVA-029; POX-MVA-031); one uncontrolled trial (POX-MVA-03x).

p. We found no studies demonstrating MPXV-neutralizing antibodies in vaccinated individuals.

q. One preprint (Zaeck 2022) concluded that primary MVA-BN immunization in subjects not previously exposed to MPXV or historic vaccination yielded relatively low levels of MPXV neutralizing antibodies.

r. One preprint (Arbel 2022) posted on August 22, 2022 indicated that one dose MVA-BN was effective in preventing MPX infections at the short term (vaccine effectiveness 100%; 95% CI: 100%-100%; 8,168 subjects of which 626 (7%) were vaccinated; follow-up: between 7 and 15 days from the first dose).

Annex 3: Summary of findings: Primary preventive vaccination with LC16m8 compared to no vaccination for persons with a high risk of exposure to monkeypox

Certainty assessment							Summary of findings		
							Study event rates (%)		
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no vaccination	With primary preventive vaccination with LC16m8	Impact
Local adverse events									
3614 (3 studies)[a]	very serious[b]	not serious[c]	not serious[d]	not serious[e]	none	⨁⨁◯◯ Low			• Local adverse events may be very frequent in LC16m8 vaccines, but the evidence is uncertain. • Local AEs commonly reported were rash (up to 2.4%), movement limitation (up to 12%), lymphadenopathy (up to 36.8%), local erythema (up to 78.0%) and induration (up to 100%). • Severe local AEs (such as those intense enough to prevent routine daily activities) were inconsistently reported. Rash of severe onset in the extremities to trunk, or trunk only was not frequent (up to 0.1%) in one cohort study (n = 3221 vaccinees; Saito 2009).
Systemic adverse events									

Annex 3: Summary of findings: Primary preventive vaccination with LC16m8 compared to no vaccination for persons with a high risk of exposure to monkeypox

Certainty assessment							Summary of findings
3614 (3 studies)[a]	very serious[b]	not serious[c]	serious[f]	not serious[e]	none	⨁◯◯◯ Very low	• Systemic adverse events may be frequent in LC16m8 vaccinees, but the evidence is very uncertain. • Systemic adverse events reported included constitutional symptoms such as fatigue (up to 0.7%) and fever (up to 7%) among LC16m8 vaccinees (one cohort study: n = 268 vaccinees; Nishiyama 2015). • Another study reported that at least one instance of systemic reactogenicity was present in 75% of vaccinees participating, but the range of events included in this category was unclear (n = 125; VAX012). • Information on common systemic adverse in other studies such as headache, malaise, chills, nausea and muscle pain for the overall populations examined in the included studies was not provided.

Myopericarditis

3346 (2 studies)[g]	very serious[b]	not serious[h]	serious[f]	very serious[i]	none	⨁◯◯◯ Very low	• Myopericarditis may not occur in LC16m8 vaccinees, but the evidence is very uncertain. • Studies reporting on cardiac events found no symptomatic myocarditis, pericarditis or myopericarditis among LC16m8 vaccinees.

Serious adverse events: Neurological serious adverse events[j]

3488 (2 studies)[k]	very serious[b]	not serious[h]	serious[f]	very serious[i]	none	⨁◯◯◯ Very low	• Neurological serious adverse events may not occur in LC16m8 vaccinees, but the evidence is very uncertain. • No neurological serious adverse events were reported.

Annex 3: Summary of findings: Primary preventive vaccination with LC16m8 compared to no vaccination for persons with a high risk of exposure to monkeypox

Certainty assessment							Summary of findings
Serious adverse events: eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia							
3614 (3 studies)[a]	very serious[b]	not serious[h]	serious[f]	very serious[i]	none	⨁◯◯◯ Very low	• Eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia may not occur in LC16m8 vaccinees, but the evidence is very uncertain. • No cases were reported.
Serious adverse events: autoinoculation							
3489 (2 studies)[k]	very serious[b]	not serious[h]	serious[f]	very serious[i]	none	⨁◯◯◯ Very low	• Autoinoculation may be rare in LC16m8 vaccinees, but the evidence is very uncertain. • Autoinoculation was not frequent (up to 0.4%) among LC16m8 vaccinees. • No case of ocular vaccinia was reported.
Serious adverse events: vaccine-related deaths							
268 (1 studies)[l]	very serious[m]	not serious[h]	serious[f]	very serious[i]	none	⨁◯◯◯ Very low	• Vaccine-related deaths may not occur in LC16m8 vaccinees, but the evidence is very uncertain. • No cases of LC16m8 vaccine-related deaths were reported.
Serious adverse events: adverse events requiring hospitalization							
3221 (1 study)[n]	very serious[o]	not serious	serious[f]	very serious[i]	none	⨁◯◯◯ Very low	• AEs requiring hospitalization may be very rare in LC16m8 vaccinees, but the evidence is very uncertain. • One study reported one case (0.03%) requiring hospitalisation due to a vaccine-related adverse event. The hospitalisation took place during the study twenty days after immunisation due to a rash onset (at day three postvaccination) that spread to the patient's extremities and trunk (Saito 2009).

Immunogenicity: vaccination take rate

3614 (3 studies)[a]	very serious[b]	not serious	not serious	not serious[e]	none	⨁⨁◯◯ Low	• The proportion of LC16m8 vaccinees with vaccination take may be high, but the evidence is uncertain. • The proportion of vaccinees with a take ranged from 90% to 100%.

Immunogenicity: % of vaccinees with seroconversion

331 (3 Studies)[a]	very serious[b]	not serious	serious[p,q]	serious[r]	none	⨁◯◯◯ Very low	• The proportion of LC16m8 vaccinees reaching seroconversion with MPXV neutralizing antibodies may be high, but the evidence is very uncertain. • We found no studies addressing seroconversion with MPXV neutralizing antibodies, but the proportion of LC16m8 vaccinees that reached seroconversion (non-MPXV specific) ranged from 60% to 100%.

Clinical effectiveness/efficacy against monkeypox infection - not reported

-	-	-	-	-	-	-	• We found no clinical studies addressing this outcome. • The clinical effectiveness/efficacy of primary preventive vaccination with LC16m8 versus no vaccination against monkeypox is unknown.

CI: confidence interval

Explanations

a. One RCT (VAX012) and two observational cohort studies (Nishiyama 2015; Saito 2009)

b. Uncontrolled designs, lack of blinding, inconsistent measurement and reporting of outcomes, and unclear risk of selective outcome reporting.

c. We did not downgrade for inconsistency as the findings pointed consistently to a high frequency of the outcome.

d. We did not downgrade for indirectness. Although safety data from large population-based programs is limited, we consider that the safety profile captured in the included evidence can reflect the local AEs in most populations.

e. We did not downgrade for imprecision as the study samples were usually powered to detect this outcome, which was frequent.

f. Studies were performed with selected populations in controlled contexts, such as trials with healthy subjects and military personnel. General use of the vaccine may reveal effects not observed in these situations.

g. One uncontrolled trial (VAX012) and one cohort study (Saito 2009).

h. All the studies presented zero cases.

i. The study samples were not powered to detect rare adverse events.

j. Post-vaccinial encephalitis (PVE), post-vaccinial encephalomyelitis (PVEM)

k. Two observational cohort studies (Nishiyama 2015; Saito 2009)

l. One cohort study (Nishiyama 2015).

m. Uncontrolled design.

n. One cohort study (Saito 2009).

o. Uncontrolled design.

p. We found no studies demonstrating MPXV-neutralizing antibodies in vaccinated individuals.

q. Analysed subsamples of vaccinees in some cases significantly younger than the overall population.

r. Serum samples from small subsamples of vaccinees

Annex 4: Summary of findings: Primary preventive vaccination with MVA-BN compared to vaccination with ACAM2000 for persons with a high risk of exposure to monkeypox

Certainty assessment							Summary of findings		
							Study event rates (%)		
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With vaccination with ACAM2000	With primary preventive vaccination with MVA-BN	Impact
Local adverse events									
412 (1 study)	serious[a]	not serious	not serious[b]	not serious[c]	none	⨁⨁⨁◯ Moderate			• MVA-BN compared to ACAM2000 probably results in fewer local AEs. • All solicited local adverse events (pain, erythema, swelling, induration, and pruritus) were more frequent in the ACAM2000-only group (P<0.001). • Certain grade 3 local adverse events were less frequent in the MVA group, particularly injection site pain (RR 0.11, 95% CI 0.04 to 0.32) and injection site pruritus (RR 0.10, 95% CI 0.02 to 0.45). • The results were inconclusive for the remainder grade 3 local AEs (injection site erythema and swelling): their CI 95% were compatible with increased benefit and increased harm.

Systemic adverse events

412 (1 study)	serious[a]	not serious	serious[d]	not serious[c]	none	⨁⨁◯◯ Low	• MVA-BN compared to ACAM2000 may result in fewer systemic AEs, but the evidence is uncertain. • All solicited systemic adverse events (headache, myalgia, chills, nausea, fatigue, and malaise) occurred more frequently in the ACAM2000 group, except pyrexia, which occurred equally in MVA period 1 and the ACAM2000. • There were also fewer grade 3 systemic adverse events in the MVA group: myalgia (RR 0.12, 95% CI 0.01 to 0.93) and fatigue (RR 0.21, 95% CI 0.05 to 0.96). • The results were inconclusive for the remainder grade 3 systemic adverse events: pirexia, chills, nausea, and malaise.

Myopericarditis

412 (1 study)	serious[a]	not serious	serious[d]	very serious[e]	none	⨁◯◯◯ Very low	• Analysis based on one RCT (POX-MVA-006) found no evidence of differences in the frequency myocarditis between MVA-BN and ACAM2000 vaccinees, but the evidence is very uncertain. • The included study did not find any case of myopericarditis. • There were no cases with clinically significant abnormal ECG results or troponin I values.

Serious adverse events: Neurological serious adverse events[f]

412 (1 study)	serious[a]	not serious	serious[g]	very serious[e]	none	⨁◯◯◯ Very low	• Analysis based on one RCT (POX-MVA-006) found no evidence of differences in serious neurological AEs between MVA-BN and ACAM2000 vaccinees, but the evidence is very uncertain. • No cases were reported.

Serious adverse events: eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia

412 (1 study)	serious[a]	not serious	serious[g]	very serious[e]	none	⨁◯◯◯ Very low	• Analysis based on one RCT (POX-MVA-006) found no evidence of differences in eczema vaccinatum or erythema multiforme, progressive vaccinia or generalized vaccinia between MVA-BN and ACAM2000 vaccinees, but the evidence is very uncertain. • No cases were reported.

Serious adverse events: autoinoculation

412 (1 study)	serious[a]	not serious	serious[g]	very serious[e]	none	⨁◯◯◯ Very low	• Analysis based on one RCT (POX-MVA-006) found no evidence of differences in this autoinoculation between MVA-BN and ACAM2000 vaccinees, but the evidence is very uncertain. • No cases of autoinoculation were described. • No case of ocular vaccinia was reported.

Serious adverse events: vaccine-related deaths

412 (1 study)	serious[a]	not serious	serious[g]	very serious[e]	none	⨁◯◯◯ Very low	• Analysis based on one RCT (POX-MVA-006) found no evidence of differences in vaccine-related deaths between MVA-BN and ACAM2000 vaccinees, but the evidence is very uncertain. • No cases of MVA-BN vaccine-related deaths were reported. [h]

Serious adverse events: adverse events requiring hospitalization

412 (1 study)	serious[a]	not serious	serious[g]	very serious[e]	none	⨁◯◯◯ Very low	• Analysis based on one RCT (POX-MVA-006) found no evidence of differences in adverse events requiring hospitalization between MVA-BN and ACAM2000 vaccinees, but the evidence is very uncertain. • No adverse events requiring hospitalization were reported.

Immunogenicity: vaccination take rate - not reported

-	-	-	-	-	-	-	• Not applicable for MVA-BN: it is a replication-deficient vaccine, thus vaccination with MVA-BN does not produce a take.

Immunogenicity: % of vaccinees with seroconversion

412 (1 study)	serious[a]	not serious	serious[l]	not serious	none	⨁⨁◯◯ Low	• We found no studies addressing seroconversion with MPXV neutralizing antibodies. • Analysis based on one RCT found that MVA-BN may associate a small increase in the seroconversion rate at peak visit measured with plaque reduction neutralization test compared to ACAM2000 (RR 1.03, 95% CI 1.00 to 1.05; 1 study; n=433 participants). [m]

Clinical effectiveness/efficacy against monkeypox infection - not reported

-	-	-	-	-	-	-	• We found no peer-reviewed clinical studies assessing this outcome.[n]

CI: confidence interval

Explanations

a. Some concerns with attrition bias and selective outcome reporting.

b. We did not downgrade for indirectness. Although safety data from large population-based programs is limited, we consider that the safety profile captured in the included evidence can reflect the local AEs in most populations.

c. We did not downgrade for imprecision as the study sample was powered to detect this outcome, which was frequent.

d. The study was performed with selected populations in controlled contexts, particularly with healthy subjects and military personnel, so broad use of the vaccine could reveal systemic AEs not observed in these situations.

e. The study sample was not powered to detect this outcome, which was rare.

f. Post-vaccinial encephalitis (PVE), post-vaccinial encephalomyelitis (PVEM)

g. Studies were performed with selected populations in controlled contexts, such as trials with healthy subjects and military personnel. General use of the vaccine may reveal effects not observed in these situations.

h. Only three studies reported explicitly all-cause mortality. Two out 1129 vaccinees died in POX-MVA-031 (unknown cases). No death occurred among the 22 vaccinees in POX-MVA-03x and the 221 vaccinees in POX-MVA-006.

i. Five RCTs (ACAM2000_FDA_Study1; ACAM2000_FDA_Study2; H-400-002; POX-MVA-006; H-400-005); one observational study (Pugh 2014).

j. Uncontrolled designs, lack of blinding, inconsistent measurement and reporting of outcomes, and unclear risk of selective outcome reporting.

k. We did not downgrade for imprecision as the study samples were usually powered to detect this outcome, which was frequent.

l. We found no studies demonstrating MPXV-neutralizing antibodies in vaccinated individuals.

m. One preprint (Zaeck 2022) concluded that primary MVA-BN immunization in subjects not previously exposed to MPXV or historic vaccination yielded relatively low levels of MPXV neutralizing antibodies.

n. Animal studies suggested that immunological response to MVA-BN and ACAM2000 may be similar against monkeypox (Jynneos Info 2019). In one study, three groups of macaques were vaccinated with 1 dose of ACAM2000, 1 dose of MVA-BN or 2 doses of MVA-BN. After challenge with a lethal dose of monkeypox virus at 28 days following the last vaccine dose, vaccine efficacy against death compared to an unvaccinated control group was 100% for the ACAM2000 and 2-dose MVA-BN groups, and 67% for the 1-dose MVA-BN group.

Strategic Advisory Group of Experts (SAGE) on Immunization Evidence to recommendations framework[i]

Annex 5: Evidence to recommendation framework: ACAM2000 for primary preventive vaccination

Question: Should ACAM2000 be used in immunocompetent populations with high risk of exposure to monkeypox as a primary preventive measure to prevent monkeypox disease?
Population: Immunocompetent adult gay or bisexual men who have sex with men (MSM), others with multiple sex partners, health workers at high risk of exposure, laboratory personnel working with orthopoxviruses
Intervention: Primary preventive (pre-exposure) vaccination with one dose of ACAM2000
Comparison(s): Placebo, no intervention
Outcome: Monkeypox disease, adverse events, serious adverse events

Background: Monkeypox is an infectious disease caused by the monkeypox virus. This double-stranded DNA virus is a member of the Orthopoxvirus genus in the Poxviridae family, related to the virus which caused smallpox (eradicated in 1980). Within the current multi-country outbreak, most cases reported are in men who have sex with men (MSM) with multiple intimate partners in connected social and sexual networks. Three vaccines (ACAM2000, MVA-BN and LC16), of which two (MVA-BN and LC16) have been approved in several jurisdictions for prevention of monkeypox, are currently used to respond to the outbreak.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	More than 65,000 monkeypox cases have been confirmed and 26 deaths. Cases have been found in 105 different countries or territories. On 23 July 2022, the Director-general of the World Health Organization declared the multi-country outbreak of monkeypox to be a public health emergency of international concern (PHEIC).	The epidemiological situation can be found here: 2022 Monkeypox Outbreak: Global Trends (shinyapps.io)
BENEFITS & HARMS OF THE OPTION	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	There are no peer-reviewed randomized controlled trials evaluating the clinical efficacy of primary preventive vaccination with ACAM2000 versus no vaccination against monkeypox.	In a macaque model, 1 dose of ACAM2000 has been shown to induce 100% protection against a lethal challenge of monkeypox.

					The effectiveness of vaccines against monkeypox is further inferred from indirect evidence and animal studies. Indirect surveillance data in the Democratic Republic of the Congo (2005–2007) indicated that among individuals born before 1980 (end of the official national mass smallpox vaccination program), people vaccinated against smallpox with first generation vaccines had a 5.2-fold lower risk of monkeypox than those unvaccinated (0.78 vs. 4.05 per 10,000), which represented a smallpox pre-exposure vaccine effectiveness against monkeypox of 80.7% (95% CI: 68.2–88.4%)	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☒	*Un-certain* ☐	*Yes* ☐	*Varies* ☐	Information regarding the safety of ACAM2000 has been derived from clinical trial experience and observational studies including military personnel. ACAM2000 safety data from large population-based programs is limited A rapid review undertaken by WHO identified 39 studies that evaluated the safety of 3 currently used smallpox vaccines against monkeypox in subjects with high exposure to monkeypox virus. Local and systemic AE in ACAM2000 vaccinated subjects were very frequently reported in up to 99% of the vaccinated subjects. Although AE were generally mild to moderate, ACAM2000 can be associated	

			with rare but serious AE, such as myopericarditis. The rapid review reported a total of 269 cases of myocarditis across 8 studies (n=1,743,620 vaccinees). Five cases of generalized vaccinia, one case of eczema vaccinatum and one case of progressive vaccinia and five cases of autoinoculation were reported in four studies (n=843,744)	
	Balance between benefits and harms	*Favours inter-vention* ☐ *Favours com-parison* ☐ *Favours both* ☐ *Favours neither* ☐ Unclear ☒	There are no RCTs evaluating vaccine effectiveness of ACAM2000 in preventing monkeypox. Safety data suggest potential harm following administration of a single dose of ACAM2000	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *Very low* ☒ *Low* ☐ *Mod-erate* ☐ *High* ☐ Safety of the intervention *No included studies* ☐ *Very low* ☒ *Low* ☐ *Mod-erate* ☐ *High* ☐	Please see the related GRADE tables	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☒ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☐ *No known undesirable outcomes* ☐	Available scientific evidence on the relative importance of the intervention is limited. The relative weights that the target population attributes to the desirable (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals) varies.	

RESOURCE USE			Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ *Varies* ☐	It is uncertain if the target population assigns more weight to the desirable effects than to the undesirable effects related to vaccination. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	Targeted studies should assess this aspect
	Are the resources required small?	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	Monkeypox vaccines cannot be administered through routine immunization programmes as vaccination is targeting a limited number of individuals in specific populations. Therefore, some resources are needed to ensure the implementation of a monkeypox vaccination programme. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, communications, and immunization safety surveillance.	
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	Formal global cost–effectiveness analyses have not been conducted. Cost–effectiveness analyses should be conducted at country level; cost–effectiveness of monkeypox vaccination may vary by country depending on the	

					monkeypox burden and local cost–effectiveness thresholds used	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☒	*Re-duced* ☐	*Varies* ☐	In assessing eligibility for primary preventive (pre-exposure) vaccination, national authorities should consider who may be at high risk of exposure for infection and the possible nature of the exposure. As the level of risk varies between the different high-risk groups, vaccination strategies could prioritize groups for vaccination as determined by the local epidemiological context of monkeypox. In case of limited vaccine supply, close contacts of monkeypox cases at risk of developing severe disease, such as children, pregnant women and immunocompromised people, including those on immunosuppressive therapy or living with poorly controlled HIV, should be prioritized for receipt of vaccine following analysis of risks and benefits on a case-by-case basis If distributed fairly and to individuals at high risk of exposure, monkeypox vaccines may reduce health inequities.	

ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☒ | *Com-parison* ☐ | *Both* ☐ | *Neither* ☐ | *Un-clear* ☐	Vaccination is one of the tools to prevent human-to-human transmission of monkeypox. It is assumed that key stakeholders, in particular ministries of health and immunization managers are in favour of it.	
	Which option is acceptable to target group?	*Inter-vention* ☐ | *Com-parison* ☐ | *Both* ☐ | *Neither* ☐ | *Un-clear* ☐	Monkeypox vaccine acceptability may vary between population groups and may be correlated with the perceived risk posed by the disease and the safety profile of the vaccine. A pre-print study reported that 55.4% of health workers, responded that they would probably get the vaccine if it was recommended.	https://www.medrxiv.org/content/10.1101/2022.08.25.222792025v1
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | *Varies* ☒	Existing resources could be leveraged to implement monkeypox vaccination (e.g. STI clinics). ACAM2000 is administered with the use of a bifurcated needle. Correct use and administration of ACAM2000 may be challenging and instructions should be provided to health workers regarding administration of ACAM2000. Vaccinees should also be instructed to follow special	

			care for the vaccination site as ACAM2000 consist of live vaccinia virus. Reaching high-risk groups for exposure to monkeypox for administration of the vaccine may pose a challenge in certain countries and settings. Current limited supply of the vaccine also poses challenges.		
Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☒	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

Recommendation (text)	Please see interim recommendations
Implementation considerations	Please see interim recommendations
Monitoring and evaluation	Please see interim recommendations
Research priorities	Please see interim recommendations

[i]This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework

Annex 6: Evidence to recommendation framework: LC16m8 for primary preventive vaccination

Question: Should LC16m8 be used in immunocompetent populations with high risk of exposure to monkeypox as a primary preventive measure to prevent monkeypox disease?
Population: Immunocompetent adult gay or bisexual men who have sex with men (MSM), others with multiple sex partners, health workers at high risk of exposure, laboratory personnel working with orthopoxviruses
Intervention: Primary preventive (pre-exposure) vaccination with one dose of LC16m8
Comparison(s): Placebo, no intervention
Outcome: Monkeypox disease, adverse events, serious adverse events

Background: Monkeypox is an infectious disease caused by the monkeypox virus. This double-stranded DNA virus is a member of the Orthopoxvirus genus in the Poxviridae family, related to the virus which caused smallpox (eradicated in 1980). Within the current multi-country outbreak, most cases reported are in men who have sex with men (MSM) with multiple intimate partners in connected social and sexual networks. Three vaccines (ACAM2000, MVA-BN and LC16), of which two (MVA-BN and LC16) have been approved in several jurisdictions for prevention of monkeypox, are currently used to respond to the outbreak.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	More than 65,000 monkeypox cases have been confirmed and 26 deaths. Cases have been found in 105 different countries or territories. On 23 July 2022, the Director-general of the World Health Organization declared the multi-country outbreak of monkeypox to be a public health emergency of international concern (PHEIC).	The epidemiological situation can be found here: 2022 Monkeypox Outbreak: Global Trends (shinyapps.io)
BENEFITS	Benefits of the intervention	*No*	*Un-certain*	*Yes*	*Varies*	There are no peer-reviewed randomized controlled trials evaluating the clinical	

	Are the desirable anticipated effects large?	☐	☒	☐	☐	efficacy of primary preventive vaccination with LC16m8 versus no vaccination against monkeypox. The effectiveness of vaccines against monkeypox is further inferred from indirect evidence and animal studies. A rapid review performed by WHO did not find studies measuring immunogenicity of LC16m8 against monkeypox. However, three studies described LC16 take rates and the proportion of adult vaccinees reaching non MPXV specific seroconversion. The proportion of vaccinees with a take ranged from 90% to 100% between 6- and 14-days following immunization and the proportion of LC16m8 vaccinees that reached seroconversion (non-MPXV specific) ranged from 60% to 100% at 30 days from vaccination.	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	A rapid review undertaken by WHO identified 39 studies that evaluated the safety of 3 currently used smallpox vaccines against monkeypox in subjects with high exposure to monkeypox virus. Local and systemic AE in LC16m8 vaccinees were very frequent (reported in up to 99% of the vaccinees) but mild to moderate. Myopericarditis, pericarditis or myopericarditis were not detected while serious vaccine-related AE were very rare	

		or not present. However, this is based on very limited data.	
	Balance between benefits and harms *Favours intervention* ☐ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ Unclear ☒	There are no RCTs evaluating vaccine effectiveness of LC16m8 in preventing monkeypox. Safety data suggest no serious harm following administration of LC16m8. However, this is based on very limited data. Further data are needed as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes? Effectiveness of the intervention *No included studies* ☐ *Very low* ☒ *Low* ☐ *Moderate* ☐ *High* ☐ Safety of the intervention *No included studies* ☐ *Very low* ☒ *Low* ☐ *Moderate* ☐ *High* ☐	Please see the related GRADE tables	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes? *Important uncertainty or variability* ☒ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☐ *No known undesirable outcomes* ☐	Available scientific evidence on the relative importance of the intervention is limited. The relative weights that the target population attributes to the desirable (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals) varies. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	

RESOURCE USE	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects? *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	It is expected that the target population assigns more weight to the desirable effects than to the undesirable effects related to vaccination.	Targeted studies should assess this aspect
	Are the resources required small? *No* ☒ *Un-certain* ☐ *Yes* ☐ *Varies* ☐	Monkeypox vaccines cannot be administered through routine immunization programmes as vaccination is targeting a limited number of individuals in specific populations. Therefore, some resources are needed to ensure the implementation of a monkeypox vaccination programme. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, communications, and immunization safety surveillance.	
	No *Un-certain* *Yes* *Varies*		

	Cost-effectiveness	☐	☒	☐	☐	Formal global cost–effectiveness analyses have not been conducted. Cost–effectiveness analyses should be conducted at country level; cost–effectiveness of monkeypox vaccination may vary by country depending on the monkeypox burden and local cost–effectiveness thresholds used	
EQUITY		*Increa-sed*	*Un-certain*	*Re-duced*	*Varies*		

	What would be the impact on health inequities?	☐	☒	☐	☐		In assessing eligibility for primary preventive (pre-exposure) vaccination, national authorities should consider who may be at high risk of exposure for infection and the possible nature of the exposure. As the level of risk varies between the different high-risk groups, vaccination strategies could prioritize groups for vaccination as determined by the local epidemiological context of monkeypox. In case of limited vaccine supply, close contacts of monkeypox cases at risk of developing severe disease, such as children, pregnant women and immunocompromised people, including those on immunosuppressive therapy or living with poorly controlled HIV, should be prioritized for receipt of vaccine following analysis of risks and benefits on a case-by-case basis If distributed fairly and to individuals at high risk of exposure, monkeypox vaccines may reduce health inequities.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health,	*Inter-vention*	*Com parison*	*Both*	*Neither*	*Un-clear*	Vaccination is one of the tools to prevent human-to-human transmission of monkeypox. It is assumed that key stakeholders, in particular ministries of health and immunization managers are in favour of it.	

FEASIBILITY	Immunization Managers)?	☒ ☐ ☐ ☐ ☐		
	Which option is acceptable to target group?	*Inter-vention* *Comparison* *Both* *Neither* *Un-clear* ☒ ☐ ☐ ☐ ☐	Monkeypox vaccine acceptability may vary between population groups and may be correlated with the perceived risk posed by the disease. A pre-print study reported that 55.4% of health workers, responded that they would probably get the vaccine if it was recommended.	https://www.medrxiv.org/content/10.1101/2022.08.25.222792025v1
	Is the intervention feasible to implement?	*No* *Probably No* *Uncertain* *Probably Yes* *Yes* *Varies* ☐ ☐ ☐ ☐ ☐ ☒	Existing resources could be leveraged to implement monkeypox vaccination (e.g. STI clinics). LC16m8 is administered with the use of a bifurcated needle. Correct use and administration of LC16m8 may be challenging and instructions should be provided to health workers regarding administration of LC16m8. Reaching high-risk groups for exposure to monkeypox for administration of the vaccine may pose a challenge in certain countries and settings. Current limited supply of the vaccine also poses challenges.	

<table>
<tr><td>Balance of consequences</td><td>Undesirable consequences clearly outweigh desirable consequences in most settings
☐</td><td>Undesirable consequences probably outweigh desirable consequences in most settings
☐</td><td>The balance between desirable and undesirable consequences is closely balanced or uncertain
☐</td><td>Desirable consequences probably outweigh undesirable consequences in most settings
☒</td><td>Desirable consequences clearly outweigh undesirable consequences in most settings
☐</td></tr>
<tr><td>Type of recommendation</td><td>We recommend the intervention
☐</td><td colspan="2">We suggest considering recommendation of the intervention
☐ Only in the context of rigorous research
☒ Only with targeted monitoring and evaluation
☒ Only in specific contexts or specific (sub)populations</td><td>We recommend the comparison
☐</td><td>We recommend against the intervention and the comparison
☐</td></tr>
<tr><td>Recommendation (text)</td><td colspan="4">Please see interim recommendations</td></tr>
<tr><td>Implementation considerations</td><td colspan="4">Please see interim recommendations</td></tr>
</table>

Monitoring and evaluation	Please see interim recommendations
Research priorities	Please see interim recommendations

Annex 7: Evidence to recommendation framework: MVA-BN for primary preventive vaccination

Question: Should MVA-BN be used in populations with high risk of exposure to monkeypox as a primary preventive measure to prevent monkeypox disease? **Population:** Immunocompetent adult gay or bisexual men who have sex with men (MSM), others with multiple sex partners, health workers at high risk of exposure, laboratory personnel working with orthopoxviruses **Intervention:** Primary preventive (pre-exposure) vaccination with two doses of MVA-BN, 28 days apart **Comparison(s):** Placebo, no intervention, other smallpox vaccine **Outcome:** Monkeypox disease
Background: Monkeypox is an infectious disease caused by the monkeypox virus. This double-stranded DNA virus is a member of the Orthopoxvirus genus in the Poxviridae family, related to the virus which caused smallpox (eradicated in 1980). Within the current multi-country outbreak, most cases reported are in men who have sex with men (MSM) with multiple intimate partners in connected social and sexual networks. Three vaccines (ACAM2000, MVA-BN and LC16), of which two (MVA-BN and LC16) have been approved in several jurisdictions for prevention of monkeypox, are currently used to respond to the outbreak.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	More than 65,000 monkeypox cases have been confirmed and 26 deaths. Cases have been found in 105 different countries or territories. On 23 July 2022, the Director-general of the World Health Organization declared the multi-country outbreak of monkeypox to be a public health emergency of international concern (PHEIC).	The epidemiological situation can be found here: 2022 Monkeypox Outbreak: Global Trends (shinyapps.io)
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	While there are no peer-reviewed randomized controlled trials evaluating the clinical efficacy of primary preventive vaccination with MVA-BN versus no vaccination against monkeypox, a recent observational study, published as a preprint on 23 September 2022, indicated that one dose of MVA-BN was effective in preventing monkeypox symptomatic disease. VE of one dose was estimated at 79% (95% CI: 24%-94%). The effectiveness of vaccines against monkeypox is further inferred from indirect evidence and animal studies.	In a macaque model, 2 doses of MVA-BN have been shown to induce 100% protection against a lethal challenge of monkeypox.
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	A rapid review undertaken by WHO identified 39 studies that evaluated the safety of 3 currently used smallpox vaccines against monkeypox in subjects with high exposure to monkeypox virus.	From April 2022 up until the 26th of August 2022, Vigibase, which is the global database of the WHO programme for international drug monitoring reported 360 adverse events after the use of the MVA-BN

				Local and systemic adverse events (AE) were frequently reported in MVA-BN vaccinees (up to 99%). However, there were no cases of myopericarditis or serious adverse events (SAE) requiring hospitalization reported among 9713 MVA-BN vaccinees from 19 clinical studies.	vaccine. The majority of events reported were from the US followed by the UK and France. Main events reported were incorrect route of administration and local injection site reactions such as pain, erythema ,swelling and itching. Twenty-three serious events were reported. Details about these serious adverse events were not available and it was not yet assessed if they were related to the vaccine.
	Balance between benefits and harms	*Favours inter-vention* ☒ / *Favours com-parison* ☐ / *Favours both* ☐ / *Favours neither* ☐ / Unclear ☐		Preliminary data suggest vaccine effectiveness of MVA-BN in preventing monkeypox. Safety data suggest no serious harm following administration of a first or second dose of MVA-BN. Further data are needed as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ / *Very low* ☒ / *Low* ☐ / *Mod-erate* ☐ / *High* ☐ Safety of the intervention *No included studies* / *Very low* / *Low* / *Mod-erate* / *High*		Please see the related GRADE tables	

		☐	☒	☐	☐	☐		
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability*	*Possibly important uncertainty or variability*	*Probably no important uncertainty or variability*	*No important uncertainty or variability*	*No known undesirable outcomes*	Available scientific evidence on the relative importance of the intervention is limited. The relative weights that the target population attributes to the desirable (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals) varies. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
		☒	☐	☐	☐	☐		
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No*	*Probably No*	*Uncertain*	*Probably Yes*	*Yes*	It is expected that the target population assigns more weight to the desirable effects than to the undesirable effects related to vaccination.	Targeted studies should assess this aspect
		☐	☐	☐	☒	☐		
RESOURCE USE	Are the resources required small?	*No*	*Un-certain*	*Yes*	*Varies*		Monkeypox vaccines cannot be administered through routine immunization programmes as vaccination is targeting a limited number of individuals in specific populations. Therefore, some resources are	
		☒	☐	☐	☐			

						needed to ensure the implementation of a monkeypox vaccination programme. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, communications, and immunization safety surveillance.	
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☐	Formal global cost–effectiveness analyses have not been conducted. Cost–effectiveness analyses should be conducted at country level; cost–effectiveness of monkeypox vaccination may vary by country depending on the monkeypox burden and local cost–effectiveness thresholds used	
EQUITY		*Increa-sed*	*Un-certain*	*Re-duced*	*Varies*		

	What would be the impact on health inequities?	☐	☒	☐	☐	In assessing eligibility for primary preventive (pre-exposure) vaccination, national authorities should consider who may be at high risk of exposure for infection and the possible nature of the exposure. As the level of risk varies between the different high-risk groups, vaccination strategies could prioritize groups for vaccination as determined by the local epidemiological context of monkeypox. In case of limited vaccine supply, close contacts of monkeypox cases at risk of developing severe disease, such as children, pregnant women and immunocompromised people, including those on immunosuppressive therapy or living with poorly controlled HIV, should be prioritized for receipt of vaccine following analysis of risks and benefits on a case-by-case basis If distributed fairly and to individuals at high risk of exposure, monkeypox vaccines may reduce health inequities.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health,	*Inter-vention*	*Com parison*	*Both*	*Neither*	*Un-clear*	Vaccination is one of the tools to prevent human-to-human transmission of monkeypox. It is assumed that key stakeholders, in particular ministries of health and immunization managers are in favour of it.	

FEASIBILITY	Immunization Managers)?	☒ ☐ ☐ ☐ ☐		
	Which option is acceptable to target group?	*Inter-vention* ☒ / *Comparison* ☐ / *Both* ☐ / *Neither* ☐ / *Un-clear* ☐	Monkeypox vaccine acceptability may vary between population groups and may be correlated with the perceived risk posed by the disease. A pre-print study reported that 55.4% of health workers, responded that they would probably get the vaccine if it was recommended.	https://www.medrxiv.org/content/10.1101/2022.08.25.222792005v1
	Is the intervention feasible to implement?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☐ / *Varies* ☒	Existing resources could be leveraged to implement monkeypox vaccination (e.g. STI clinics). Reaching high-risk groups for exposure to monkeypox for administration of the vaccine may pose a challenge in certain countries and settings. Current limited supply of the vaccine also poses challenges.	

Balance of consequences				
Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings

Type of recommendation	☐	☐	☐	☒	☐
	We recommend the intervention	We suggest considering recommendation of the intervention		We recommend the comparison	We recommend against the intervention and the comparison
	☐	☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations		☐	☐
Recommendation (text)	Please see interim recommendations				
Implementation considerations	Please see interim recommendations				
Monitoring and evaluation	Please see interim recommendations				
Research priorities	Please see interim recommendations				

Annex 8: Evidence to recommendation framework: ACAM2000, IL16m8 or MVA-BN for post-exposure preventive vaccination

Question: Should MVA-BN, lC16 or ACAM2000 be used in immunocompetent populations as a post-exposure preventive measure to prevent monkeypox disease?
Population: Close contacts of monkeypox cases
Intervention: Post-exposure preventive vaccination with MVA-BN, LC16m8 or ACAM2000
Comparison(s): Placebo, no intervention
Outcome: Monkeypox disease, adverse events, serious adverse events

Background: Monkeypox is an infectious disease caused by the monkeypox virus. This double-stranded DNA virus is a member of the Orthopoxvirus genus in the Poxviridae family, related to the virus which caused smallpox (eradicated in 1980). Within the current multi-country outbreak, most cases reported are in men who have sex with men (MSM) with multiple intimate partners in connected social and sexual networks. Three vaccines (ACAM2000, MVA-BN and LC16), of which two (MVA-BN and LC16) have been approved in several jurisdictions for prevention of monkeypox, are currently used to respond to the outbreak.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	More than 65,000 monkeypox cases have been confirmed and 26 deaths. Cases have been found in 105 different countries or territories. On 23 July 2022, the Director-general of the World Health Organization declared the multi-country outbreak of monkeypox to be a public health emergency of international concern (PHEIC).	The epidemiological situation can be found here: 2022 Monkeypox Outbreak: Global Trends (shinyapps.io)
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	No peer-reviewed data of clinical studies evaluating the effects of post-exposure vaccination of close contacts of MPX cases is available. A preprint was posted on 4 August 2022, describing 276 individuals who received one dose of MVA-BN after	A study in prairie dogs investigated whether post-exposure vaccination with ACAM2000 and MVA-BN vaccines was protective against monkeypox disease in different

	anticipated effects large?				exposure with a PCR-confirmed monkeypox patient. Most of the patients were men (91%, n=250) and men who have sex with men (88%, n=233). Among the 276 vaccinated individuals, 12 (4%) had a confirmed monkeypox breakthrough infection with no severe infection. Ten out of 12 patients developed a monkeypox infection in the five days following vaccination and two had a breakthrough infection at day 22 and 25.	exposure scenarios. Animals were infected with a low (104 pfu (2× LD50)) and high (106 pfu (170× LD50) dose of monkeypox virus and vaccinated with MVA-BN or ACAM2000 either 1 or 3 days after challenge. The results indicated that post-exposure vaccination protected the animals to some degree from the low, but not the high viral challenge. In the low viral challenge, it was observed that administration of vaccine at 1 day was more effective than administration at 3 days post-exposure for both vaccines.
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	A rapid review undertaken by WHO identified 39 studies that evaluated the safety of 3 currently used smallpox vaccines against monkeypox in subjects with high exposure to monkeypox virus. Local and systemic adverse events (AE) were frequently reported in MVA-BN and LC16m8 vaccinees (up to 99%). However, there were no cases of myopericarditis or serious adverse events (SAE). Local and systemic AE in ACAM2000 vaccinated subjects were very frequently reported in up to 99% of the vaccinated subjects. Although AE were generally mild to moderate, ACAM2000 can be associated	From April 2022 up until the 26th of August 2022, Vigibase, which is the global database of the WHO programme for international drug monitoring reported 360 adverse events after the use of the MVA-BN vaccine. The majority of events reported were from the US followed by the UK and France. Main events reported were incorrect route of administration and local injection site reactions such as pain, erythema ,swelling and itching. Twenty-three serious events were reported. Details about these serious

			with rare but serious AE, such as myopericarditis. The rapid review reported a total of 269 cases of myocarditis across 8 studies (n=1,743,620 vaccinees). Five cases of generalized vaccinia, one case of eczema vaccinatum and one case of progressive vaccinia and five cases of autoinoculation were reported in four studies (n=843,744)	adverse events were not available and it was not yet assessed if they were related to the vaccine.
	Balance between benefits and harms	*Favours inter-vention* ☒ / *Favours com-parison* ☐ / *Favours both* ☐ / *Favours neither* ☐ / Unclear ☐	Preliminary data suggest vaccine efficacy of MVA-BN in preventing monkeypox after one of dose of MVA-BN. Safety data suggest no serious harm following administration of MVA-BN or LC16m8. However, the safety profile of ACAM2000 is less favorable. Further data are needed.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention: *No included studies* ☐ / *Very low* ☐ / *Low* ☐ / *Mod-erate* ☐ / *High* ☐ Safety of the intervention: *No included studies* ☐ / *Very low* ☐ / *Low* ☐ / *Mod-erate* ☐ / *High* ☐	The rapid review found no peer-reviewed data of clinical studies evaluating the effects of post-exposure vaccination. Therefore, the GRADE tables were not developed.	
VALUES & PREFERE	How certain is the relative importance of	*Importa nt uncertai nty or variabilit y* / *Possibly importa nt uncertai nty or* / *Probabl y no importa nt uncertai nty or* / *No importa nt uncertai nty or* / *No known undesira ble outcome s*	Available scientific evidence on the relative importance of the intervention is limited. The relative weights that the target	

	the desirable and undesirable outcomes?	*variability* ☐ *variability* ☐ *variability* ☐ ☐ ☒ ☐ ☐ ☐	population attributes to the desirable (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals) varies. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* *Probably No* *Uncertain* *Probably Yes* *Yes* *Varies* ☐ ☐ ☐ ☒ ☐ ☐	It is expected that the target population assigns more weight to the desirable effects than to the undesirable effects related to vaccination.	Targeted studies should assess this aspect
RESOURCE USE	Are the resources required small?	*No* *Un-certain* *Yes* *Varies* ☒ ☐ ☒ ☐	Monkeypox vaccines cannot be administered through routine immunization programmes as vaccination is targeting a limited number of individuals in specific populations. Therefore, some resources are needed to ensure the implementation of a monkeypox vaccination programme. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, communications, and immunization safety surveillance.	
		No *Un-certain* *Yes* *Varies*		

	Cost-effectiveness	☐	☒	☐	☐	Formal global cost–effectiveness analyses have not been conducted. Cost–effectiveness analyses should be conducted at country level; cost–effectiveness of monkeypox vaccination may vary by country depending on the monkeypox burden and local cost–effectiveness thresholds used	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☒	*Re-duced* ☐	*Varies* ☐	In case of limited vaccine supply, close contacts of monkeypox cases at risk of developing severe disease, such as children, pregnant women and immunocompromised people, including those on immunosuppressive therapy or living with poorly controlled HIV, should be prioritized for receipt of vaccine following analysis of risks and benefits on a case-by-case basis If distributed fairly and to individuals at high risk of exposure, monkeypox vaccines may reduce health inequities.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health,	*Inter-vention*	*Com-parison*	*Both*	*Neither*	*Un-clear*	Vaccination is one of the tools to prevent human-to-human transmission of monkeypox. It is assumed that key stakeholders, in particular ministries of health and immunization managers are in favour of it.	

	Immunization Managers)?	☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Inter-vention*	*Com parison*	*Both*	*Neither*	*Un-clear*	Monkeypox vaccine acceptability may vary between population groups and may be correlated with the perceived risk posed by the disease. A pre-print study reported that 55.4% of health workers, responded that they would probably get the vaccine if it was recommended.	https://www.medrxiv.org/content/10.1101/2022.08.25.22279205v1
		☒	☐	☐	☐	☐		

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☐ / *Varies* ☒	Existing resources could be leveraged to implement monkeypox vaccination (e.g. STI clinics). Challenges with implementing post-exposure preventive vaccination of close contacts of monkeypox cases have been reported, resulting in unused doses of vaccines. Challenges include unknown contacts of cases, tracing contacts within a 2-week period to be eligible for PEPV and limited resources. ACAM2000 and LC16m8 are administered with the use of a bifurcated needle. Correct use and administration of ACAM2000 and LC16m8 may be challenging and instructions should be provided to health workers regarding administration of ACAM2000 and LC16m8. Current limited supply of the vaccine also poses challenges.	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☒	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	Please see interim recommendations			
Implementation considerations	Please see interim recommendations			
Monitoring and evaluation	Please see interim recommendations			
Research priorities	Please see interim recommendations			

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