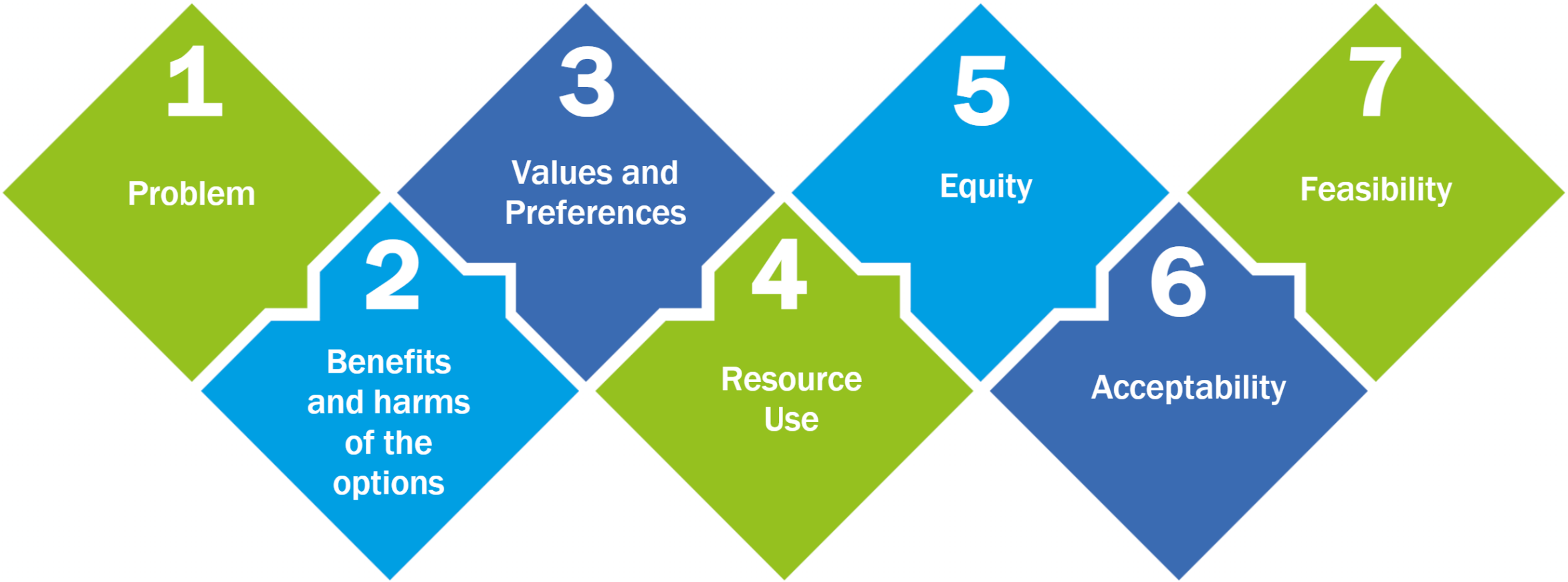
Mpox Outbreak Vaccine Rollout
Evidence to Recommendations (EtR) Process for NITAGs

- Resources to support NITAGs
  - Developing PICO Question(s)
  - Developing Evidence Tables – PICO Specific
    - 7 Criteria Domains
    - Examples developed in consultation with WHO, US CDC experts
    - Domain 1 – Problem
    - Domain 2 – Benefits and Harms
    - Domains 3-7 – in resource materials
  - Additional Information
    - Vaccines available – General characteristics, Safety/Efficacy, Use in different age groups
    - Worksheet for considering risk groups to vaccinate
  - All EtR resource materials available - to be updated as appropriate

  - Primary Source - WHO Position Paper – Smallpox and Mpox (Orthopoxviruses) - August 2024 Immunization, Vaccines and Biologicals (who.int)

Evidence to Recommendations
Seven Criteria Domains



Evidence to Recommendations Criteria Table
Domain 1: Problem

Element	Categories of Evidence
1.1 Burden of disease	• Incidence of morbidity & mortality • Age-specific morbidity and mortality • Risk groups • Serotype distribution • Disease occurrence over time • Changes in epidemiology over time
1.2 Clinical characteristics of the disease	• Signs and symptoms of disease • Severe forms • Long-term complications of disease • Medical management of disease
1.3 Use and Costs of Health Care	• Primary/secondary/tertiary care implications • Short- and long-term use of healthcare (e.g., treatments, hospitalization)
1.4 Alternative preventive and control measures	• Alternative preventive and control measures (e.g., health education, hygiene) and their effectiveness, costs, practicality
1.5 Regional and international considerations	• Existence of regional and global recommendations • Disease potential for international spread and pandemic risk

PICO-Specific Evidence Table

Example - Mpox

Policy Question: Should country X recommend mpox vaccines for populations in the community at high risk* of mpox during the current outbreak?

PICO Question: In persons at high risk of mpox in the community during an mpox outbreak, what is the evidence that mpox vaccine is safe and can reduce the incidence of infection, hospitalization, and death?

Domain 1: Problem

Element	Categories of Evidence	PICO-Specific Evidence to Collect	Priority	Sources of Evidence
1.1 Burden of disease	☐ Incidence of morbidity & mortality ☐ Age-specific morbidity and mortality ☐ Risk groups ☐ Serotype distribution ☐ Disease occurrence over time ☐ Changes in epidemiology over time			
1.2 Clinical characteristics of the disease	☐ Signs and symptoms of disease ☐ Severe forms ☐ Long-term complications of disease ☐ Medical management of disease			
1.3 Use and Costs of Health Care	☐ Primary/secondary/tertiary care implications ☐ Short- and long-term use of healthcare (e.g., treatments, hospitalization)			
1.4 Alternative preventive and control measures	☐ Alternative preventive and control measures (e.g., health education, hygiene) and their effectiveness, costs, practicality			
1.5 Regional and international considerations	☐ Existence of regional and global recommendations ☐ Disease potential for international spread and pandemic risk			

PICO-Specific Evidence Table

Example - Mpox

PICO Question: In persons at high risk of mpox in the community during an mpox outbreak, what is the evidence that mpox vaccine is safe and can reduce the incidence of infection, hospitalization, and death?

Domain 1: Problem

Element	Categories of Evidence	PICO-Specific Evidence to Collect	Priority	Sources of Evidence
1.1 Burden of disease	☒ Incidence of morbidity & mortality	Incidence, hospitalizations and deaths due to mpox before and during outbreak	Critical	Surveillance (country), AFR CDC, WHO AFRO Rapid review (NISH/UCT)
	☒ Age-specific morbidity and mortality	Age specific incidence, hospitalizations, mortality		
	☒ Risk groups	Risk groups (severe disease) – immunocompromised, pregnant and breast-feeding women, young children Persons at risk during outbreaks – laboratory staff and clinical persons treating disease, key populations (commercial sex workers, MSM, persons with multiple casual sex partners, transgender), outbreak response team and frontline workers, congregate settings (prisons, etc)		Persons at risk during outbreaks to be defined by country MOH/govt
	☒ Serotype distribution	Mpox virus clade, genomic sequences		
	☒ Disease occurrence over time	Incidence prior to outbreak and time course during outbreak		
	☒ Changes in epidemiology over time			
1.2 Clinical characteristics of the disease	☒ Signs and symptoms of disease	Skin rash (systemic, genital), fever, lymphadenopathy, headaches, etc	Critical	WHO SAGE, Mpox Website; AFR CDC; country information
	☒ Severe forms	Severe systemic rash, secondary sin lesions, encephalitis, hepatitis, pneumonitis, hospitalization, death		
	☒ Long-term complications of disease	? Skin scarring, corneal and facial scarring impaired vision/blindness, sexual impairment		
	☒ Medical management of disease	Prevention secondary infection, ? other; ? antivirals		

PICO-Specific Evidence Table

Example - Mpox

PICO Question: In persons at high risk of mpox in the community during an mpox outbreak, what is the evidence that mpox vaccine is safe and can reduce the incidence of infection, hospitalization, and death?

Domain 1: Problem (continued)

Element	Categories of Evidence	PICO-Specific Evidence to Collect	Priority	Sources of Evidence
1.3 Use and Costs of Health Care	☒ Primary/secondary/tertiary care implications ☒ Short- and long-term use of healthcare (e.g., treatments, hospitalization)	Clinic care, hospital care, ? ICU	Critical Important	Country information
1.4 Alternative preventive and control measures	☒ Alternative preventive and control measures (e.g., health education, hygiene) and their effectiveness, costs, practicality	Infection prevention/control – isolation, handwashing, gloving/gowning, clinical care; surveillance, contact tracing, self monitoring; health education, hygiene, ? other	Critical	Country information
1.5 Regional and international considerations	☒ Existence of regional and global recommendations ☒ Disease potential for international spread and pandemic risk	WHO SAGE, RITAG recommendations, emergency committee, EPR/TAG statements Substantial risk of cross border transmission – neighboring countries, distant travel (IHR, Africa CDC)	Critical	WHO SAGE, AFR CDC, WHO AFR

PICO-Specific Evidence Table

Example - Mpox

PICO Question: In persons at high risk of mpox in the community during an mpox outbreak, what is the evidence that mpox vaccine is safe and can reduce the incidence of infection, hospitalization, and death?

Domain 2: Benefits and Harms

Element	Categories of Evidence	PICO-Specific Evidence to Collect	Priority	Sources of Evidence
2.1 Vaccine characteristics	☒ Vaccine presentation, formulation, dosage, and route of administration ☒ Administration schedule and possibility of co-administration with other vaccines and drugs ☒ Flexibility of vaccination schedule ☒ Cold chain and logistic requirements	MVA-BN (non-replicating)(2 dose –SQ or ID , 4 weeks apart); LC-16 (minimally replicating)(1 dose, percutaneous with bifurcated needle) ACAM-2000 (replicating, 1 dose, bifurcated needle) # doses/vial No data re. Co-administration with other vaccines MVA-BN – 18+ yrs; <18 EUA; LC-16 – all ages; unsuitable for immunocompromised, pregnant, proliferative skin diseases ACAM2000 – immunocompetent adults: unsuitable for immunocompromised, pregnant, proliferative skin diseases, infants < 1yr Liquid frozen (MVA-BN) or freeze dried (MVA-BN, LC-16)	Important	WHO SAGE August 2024 Vaccine Product package inserts
2.2 Safety	☒Type, consequences and frequency of short and long-term adverse events following vaccination ☒ Risk groups or risk factors for adverse events ☒ Contraindications or precautions	Type, consequences and frequency of adverse events following vaccination during clinical trials - Local or muscle pain, redness, swelling, headache, fatigue No serious AEFI identified for MVA-BN, LC-16; ACAM2000-Myopericarditis – 20.1/100000 doses LC-16, ACAM2000 - immunocompromised, pregnant persons, proliferative skin diseases ACAM2000 – infants < 1 yr	Critical	WHO SAGE Meta-analyses 2022, 2024 Vaccine package inserts Country information

PICO-Specific Evidence Table

Example - Mpox

PICO Question: In persons at high risk of mpox in the community during an mpox outbreak, what is the evidence that mpox vaccine is safe and can reduce the incidence of infection, hospitalization, and death?

Domain 2: Benefits and Harms (continued)

Element	Categories of Evidence	PICO-Specific Evidence to Collect	Priority	Sources of Evidence
2.3 Efficacy and effectiveness	☒ Vaccine efficacy/effectiveness and types of specific protection ☒ Critical determinants of the immune response associated with protection ☒ Duration of protection and waning of immunity in general and risk groups ☒ Interference regarding protection or immunity with other vaccines	MVM-BN , ACAM2000 , LC16 efficacy, effectiveness for primary preventive vaccination for high-risk population of exposure (by age, previous vaccination with Small pox vaccine) Determinants of vaccine efficacy and effectiveness in populations with underlying conditions such as immunocompromised, malnutrition, pregnant women ...] Efficacy and effectiveness when co-administrated with other vaccines (YF, MR, DPT booster) Duration of protection and waning of protection in high risk population Efficacy only shown for 12 + months; neutralizing antibodies persist many years Booster doses q. 2-5 yrs depending on exposure.	Critical	WHO SAGE recommendations Meta-analyses for SAGE MVA-BN – pre-exposure – 76 % (1 dose), 82% (2 doses); post-exposure – 20% Immunocompromise – 51-70% efficacy LC-16, ACAM2000 – protective in non-human primates; neutralizing antibody in 95% (naïve, 80-95% previously vaccinated
2.4 Vaccine indirect effects	☐ Herd immunity/protection ☐ Potential negative population impact of emergence of non-vaccine serotypes	No information available		

Mpox Vaccines - General Information

PICO Question: In persons at high risk of mpox in the community during an mpox outbreak, what is the evidence that mpox vaccine is safe and can reduce the incidence of infection, hospitalization, and death?

Product	Description	Dosing	Administration	Presentation	Indicated Age Groups	Where Licensed
MVA-BN	Non-replicating vaccinia-based vaccine, 3rd generation	Two doses four weeks apart	Needle and syringe (subcutaneous or intradermal administration)	Liquid frozen or freeze-dried ? Single dose vial	18+ yrs; < 18 yrs EUA (US)[1]	Canada, EU, USA, UK, Switzerland
LC-16	Minimally replicating vaccinia-based vaccine, 3rd generation	Single dose	Bifurcated needle, percutaneous route/administration	Freeze-dried Multidose vials	No limitations	Japan
ACAM2000	Replicating vaccinia-based vaccine, 2nd generation	Single dose	Bifurcated needle, percutaneous route/administration	Freeze-dried Multidose vial	16 + yrs	USA (Emergency investigational new drug), Australia, Singapore

1. EUA - Emergency Use Authorization (United States)

Source: WHO Position Paper – Smallpox and Mpox (Orthopoxviruses)(August 2024) Immunization, Vaccines and Biologicals (who.int)

Mpox Vaccines - Safety and Efficacy

PICO Question: In persons at high risk of mpox in the community during an mpox outbreak, what is the evidence that mpox vaccine is safe and can reduce the incidence of infection, hospitalization, and death?

Product	Description	Adverse reactions	Serious Adverse Reactions	Efficacy	Immunogenicity	Duration	Source:
MVA-BN	Non-replicating	Frequent minor local and systemic AEFI	? myocarditis 4.77/million doses (not higher than background)	Pre-exposure 1 dose – 76% (64%-88%) 2 dose – 82% (72%-92%) Post-exposure 20% (-24%-64%)	>= 98%	Not studied; Booster 2-5 yrs	WHO SAGE 2024
LC-16	Minimally replicating vaccinia based	Frequent minor local and systemic AEFI	None identified	No human data 100% Protective against lethal challenge – mice, rabbits, monkeys	90-100% take rate 100% seroconversion (naïve) 60% previously vaccinated	Not studied	WHO SAGE 2024
ACAM2000	Replicating vaccinia-based vaccine	Frequent minor local and systemic AEFI	Myopericarditis – 20.1 per 100,000 doses Generalized vaccinia (<1 per 100,000 doses)	No human data 100% Protective against lethal challenge in animals	~100% take rate (healthy 18-29 yrs) 97% seroconversion (naïve) 76% in previously vaccinated	Not studied	WHO SAGE 2024

Source: WHO Position Paper – Smallpox and Mpox (Orthopoxviruses))(August 2024) [Immunization, Vaccines and Biologicals (who.int)]

Mpox Vaccines - Choice of Mpox Vaccines For Different At-Risk Populations (WHO SAGE 2024)

PICO Question: In persons at high risk of mpox in the community during an mpox outbreak, what is the evidence that mpox vaccine is safe and can reduce the incidence of infection, hospitalization, and death?

Product	Description	Adult (> 18 yrs) Immunocompetent	Infant, child, adolescent < 18 yrs	Pregnant women	Immunocompromised (including persons living with HIV)	Other – Atopic Dermatitis
MVA-BN	Non-replicating	++	++ (US EUA)[1]	+ (off label use)	++	++
LC-16	Minimally replicating vaccinia based	++	++	Contraindicated	Contraindicated	Contraindicated
ACAM2000	Replicating vaccinia-based vaccine	++	- Contraindicated < 1 yr	Contraindicated	Contraindicated	Contraindicated

Source: WHO Position Paper – Smallpox and Mpox (Orthopoxviruses))(August 2024) [Immunization, Vaccines and Biologicals (who.int)]

Considerations for Mpox Vaccine Recommendations
(Domain 1 – Problem/Disease Burden) – Worksheet (Draft)

PICO Question: In persons at high risk of mpox in the community during an mpox outbreak, what is the evidence that mpox vaccine is safe and can reduce the incidence of infection, hospitalization, and death?

Outbreak Situation	Risk Group	Notes	Geographic considerations	Estimated Risk	Risk complications	Vaccination Strategy
		Risk defined per national/local epidemiology	Risk defined per national/local incidence, epidemiology	Risk defined per national/local epidemiology		Primary Prevention vs. Post-Exposure
Non-Outbreak	Laboratory workers	Exposure to orthopox viruses				
	Outbreak response team	Potential exposure to orthopox viruses				
Prevention – Outbreak	Contacts of cases					Post-exposure
	Health workers involved in outbreak	HW, laboratorians, persons with clinical contact with cases; lab laboratory specimens, contaminated materials				
	First responders/ frontline workers involved in outbreak	Potential contact with cases, contaminated materials				
	Sexually active with casual partners (e.g.	MSM, sex commercial workers, heterosexuals with multiple casual partners				
	Children	<5 yrs			++	
		5-18 yrs				
	Immunocompromised				+++	
	Congregate settings	Eg. prisons, boarding schools, etc				
	Pregnant women				++	

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Questions ?

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