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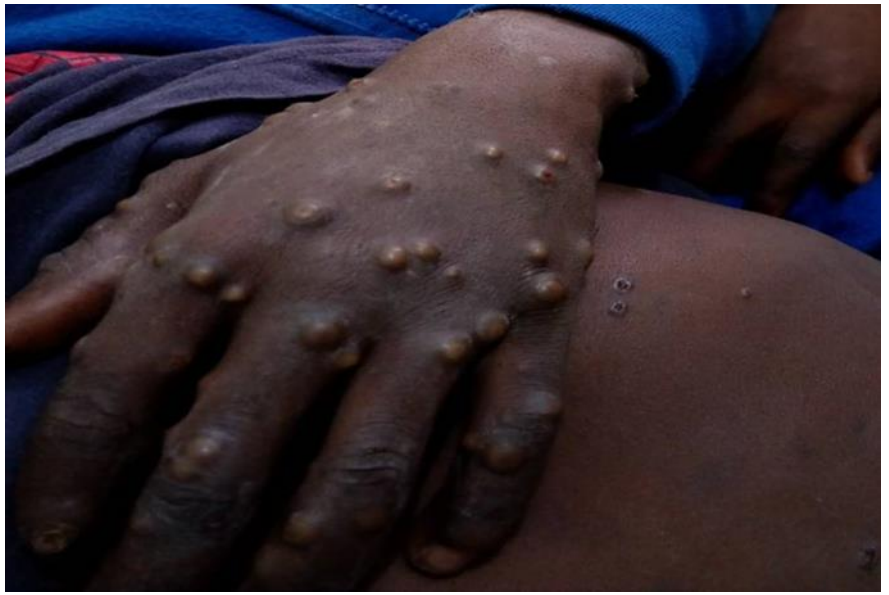
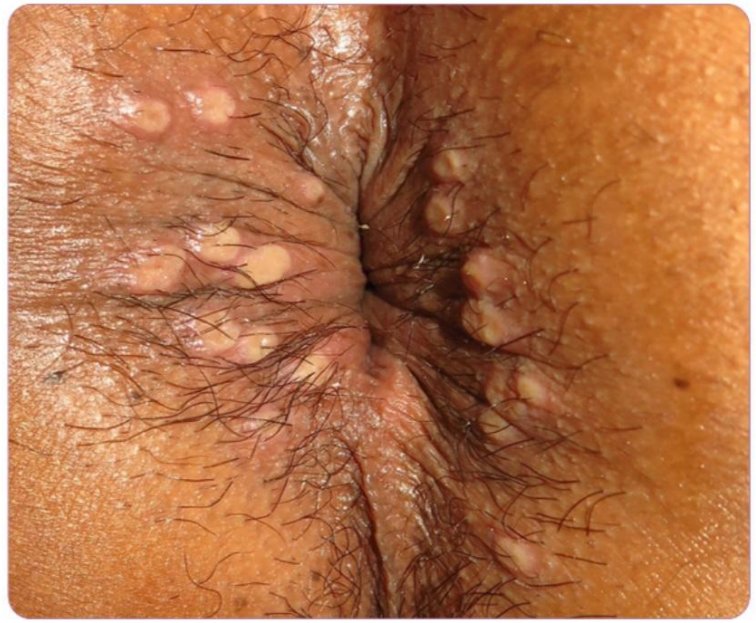
Outline

- Background
- Smallpox vaccine and eradication
- Mpox/orthopox vaccines - characteristic and immunogenicity.
- Vaccine safety and efficacy
- Mpox breakthrough infections
- Challenges and research questions
- Conclusion

Background and Epidemiology

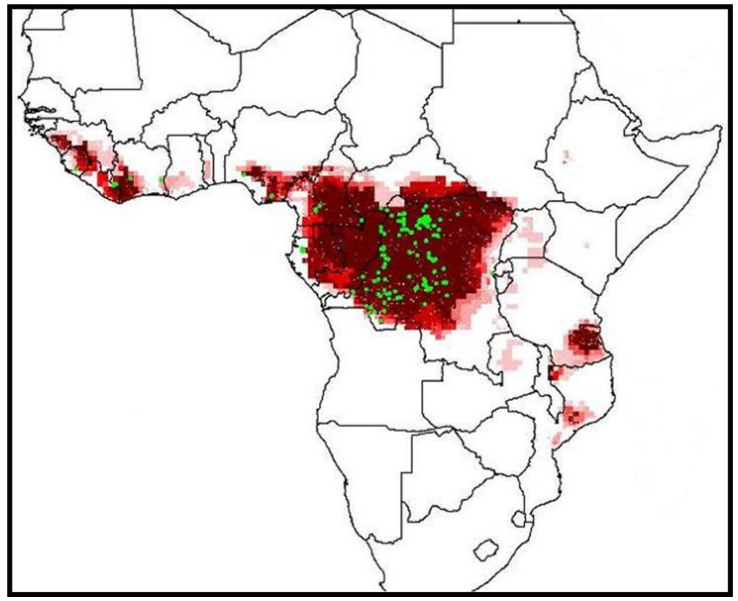
- Mpox is an infectious rash illness caused by monkeypox virus (MPXV), an o*rthopoxvirus* of the *Poxviridae family*
- Other *Orthopox viruses:* variola virus (smallpox), vaccinia virus , cowpox virus, Buffalopox (India), Bovine vaccinia (Brazil), Akhmeta virus (Georgia 2013), Alaskapox (Alaska, 2015, 2020)
- Mpox is similar to smallpox in clinical presentation
- Common symptoms are rash, headache, myalgia, lymphadenopathy
- Can be associated complications including death
- Discovered in 1958 in colonies of monkeys kept for research in Denmark
- First human case recorded in 1970 in DRC during smallpox elimination campaign in a 9month old boy in a region
- Emerged as the most important orthopoxvirus of public health importance





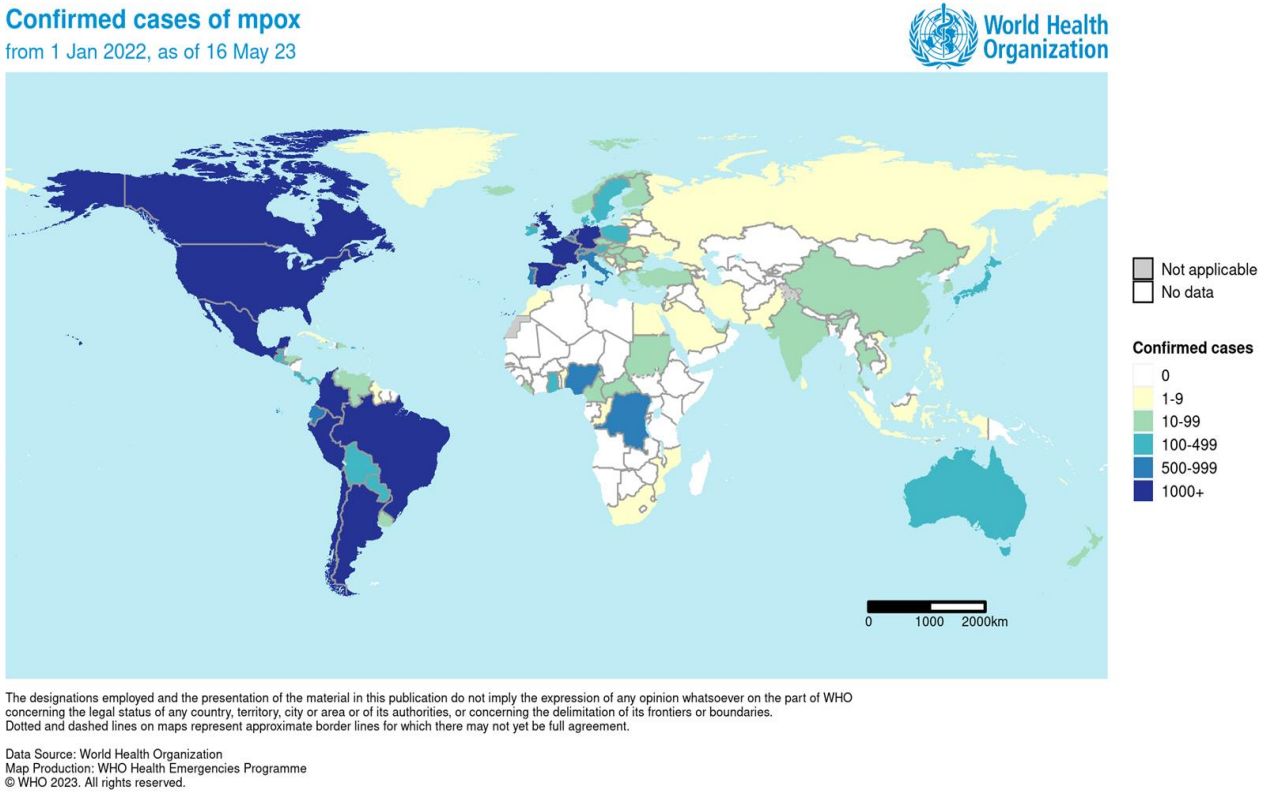
Epidemiology

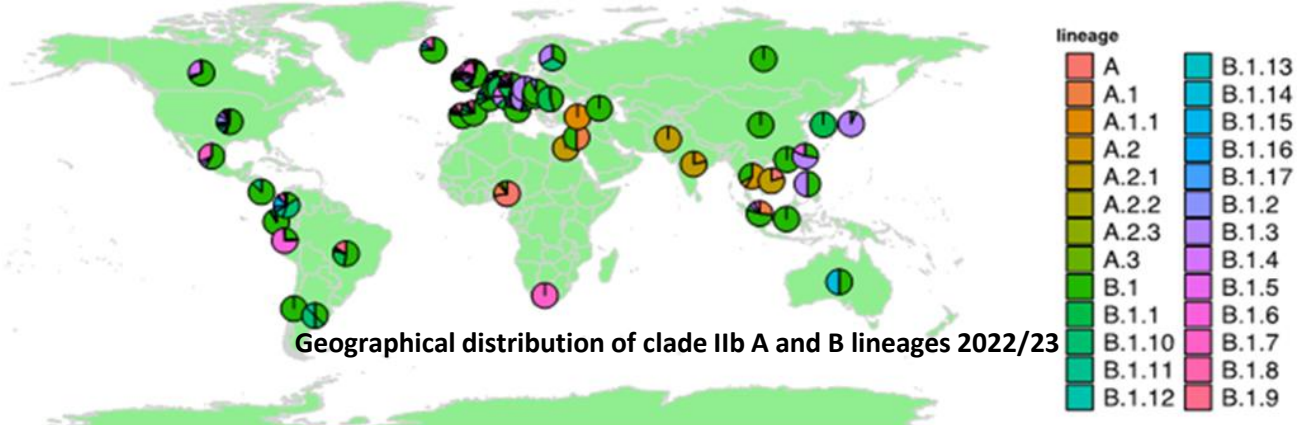
- A tropical disease
- Endemic in some countries in Central and West Africa
- Increasingly became a global problem – multi-country outbreak in 2022
- There are two clades of the monkeypox virus,
  - Clade I (formerly Congo basin clade)
  - Clade II (formerly west Africa clade)
    - phylogenetically distinct subclades IIa and IIb
    - Clade IIb has two lineages (Lineage A and B)
- Major outbreak occurred 1996-97 in the DRC
- Subsequent sporadic cases in other central and western African countries
  - Largest clade II outbreak in Nigeria in 2017 approximately
- The 2003 US outbreak was as a result of close contact with infected prairie dogs



Multi-country outbreak, 2022-2023

- May 2022 - an outbreak of mpox (clade IIb monkeypox virus)
- Rapidly spread across Europe, the Americas and then all six WHO regions
- Previously unaffected countries in Africa were also affected
- As of 15 May 2023:
  - 111 WHO Member States / territories across all 6 WHO regions
  - 87,479 confirmed cases
  - 140 deaths
- The genomic tree supports the notion of a single origin of the lineage B outbreak
- PHEIC was declared by WHO (July 2022 – May 2023)





Geographical distribution of clade IIb A and B lineages 2022/23

Mode of transmission

- Primary zoonotic disease
- Secondary h**uman-to-human** spread – characterise 2022 outbreak
- Animal reservoir is poorly understood (rodents and small mammals may play role in transmission)
- Human-to-human transmission of mpox can occur through contact with infectious skin or mucocutaneous lesions
- **Sexual behaviours and related events** play a major role in the global spread
  - >98% identified as men who have sex with men

- Mode of transmission less understood in Africa
  - Central Africa - Children and young adult
  - West Africa - men and more affected
  - Sexual (heterosexual) and household contact documented
  - Very few cases reported among MSM
  - Virus believed to be enzootic with some evidence

High risk group – human to human transmission

- men who have sex with men
- people with multiple sex partners
- sex workers
- health workers at risk of exposure

Smallpox eradication and mpox

- Smallpox vaccine from Vaccinia virus (orthopox virus)
  - highly effective against smallpox infection and other orthopox viruses
- Smallpox eradication (1980) – One of the greatest achievement in human history
- Vaccine associated with associated with mild to life-threatening side effects
- US-CDC and the Research Institute of Viral Preparations in Moscow remain WHO collaborating centre for smallpox research
  - Research safer smallpox vaccines and therapeutics for smallpox
- Four generations of these vaccines are known
- Smallpox vaccine provides protection against mpox

Mpox vaccination

- In April 2022, an Ad-hoc Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on smallpox and mpox vaccines was established
- Third generation vaccines were deployed in the ongoing mpox outbreak in some countries
- About 70 countries have access to MVA vaccine
- Ongoing effort to answer research question as related to:
  - Clinical efficacy / effectiveness
  - Schedule
  - Administration
  - Different population groups
  - Deployment strategies

Smallpox and orthopoxvirus vaccines

- **First generation vaccines: -** Used for smallpox eradication
  - Stockpiled by WHO and some countries, since 1980s
  - Examples – (APSV, Dryvax, Lancy Vaxina, Lister, Elstree, Pourquier)
  - Not recommended for mpox vaccination
- **Second generation**
  - ACAM2000 – Emergent Biosolutions (France/USA)
  - Microgen – Microgen (Russian Federation)
- **Third generation**
  - LC16 – KM Biologics (Japan)
  - MVA-BN (Denmark)
  - MVA NYC
- **Fourth generation**
  - OrthopoxVac (Russia Federation)

First generation vaccines

- Live, **replicating** vaccinia virus
- Protective efficacy against smallpox – (eradication of smallpox)
- Provides **full protection of 3-10 years** (followed wanning)
- Associated with high rate of **adverse events (AEs)**
- **Not recommended for use in mpox control**

Adverse events:

- Local - pruritus, erythema, induration, pain, swelling,
- Systemic – Fatigue, myalgia, Headache, malaise, dyspnea
- Serious AEs (Erythema multiforme, pericarditis, progressive vaccinia, encephalitis, death, etc)

Contra-indications - Vaccinee and their contact

- Children < 12 months of age
- Congenital or acquired immunodeficiencies
- Immunosuppressive treatment
- History of eczema or other exfoliative skin conditions
- Pregnancy
- Women who are breastfeeding
- Allergy to a vaccine component
- Active conjunctiva or cornea disease

Second generation vaccines

- Live, replication competent vaccinia virus
- Clonal isolates of 1st generation vaccine viruses
- Immunity similar to 1st generation vaccines
- Has reduced neurovirulence/enhanced safety profile
- High rate of adverse events as 1st the generation vaccines
- Contraindications as in 1st generation vaccines
- Example – ACAM2000 stockpiled but not currently in used for mpox control

Third generation vaccines

- Live, attenuated strains of vaccinia virus
- Do not replicate in mammalian cells
- Good safety profile
- Multiple doses may be required to generate full and long term immunity
- Protection may not last as long as with 1st gen. vaccines
- Examples:**, LC-16m8, MVA-BN** (e.g IMVAMUNE,IMVANEX, MVA-BN, **JYNEOS**)**,** MVA-TBC, NYVAC (Sanofi Pasteur)
- Some have been **licenced** and in use for protection **against mpox**
- Administration route: Subcutaneous or intradermal (bifurcation needle required)

Fourth generation vaccines

- Subunit, DNA, plant-based vaccines
- Have not been widely studied in human populations
- Some elicit protective immunity against lethal poxvirus challenge in animal models
- Many still in early stages of Research & Development
- Example- Orthopoxvac licenced in 2022 for use against MPXV by The Russia federation

Vaccines licenced for mpox outbreak response

1. **MVA-BN** (3rd gen vaccine)
   (Bavarian Nordic)
2. **LC16** (Minimally replicating 3rd gen vaccine)
   (KM Biologics - Japan)
3. **OrthopoxVac** (4th gen vaccine)

   (Russian Federation)

4. ACAM200 is licenced and stockpiled in the USA but not currently in use

- Licenced by National and regional authorities for smallpox and Mpox based on
  - human safety and
  - animal efficacy data as well
  - non-inferiority immunogenicity studies with other smallpox vaccines
- No pre-qualified vaccine
- Other vaccines in pipeline and undergoing trials

Vaccine safety

Systematic review by WHO:

- Vaccine **safety** profiles vary by product and need consideration when deciding on the choice of vaccine
- **Local and systemic** adverse events (AE) were frequently reported in MVA-BN and LC16 vaccinees (up to 99%)
  - Pruritus
- **Serious adverse events** (SAE) are rare or not reported for MVA-BN and LC16

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Letters

RESEARCHLETTER

Short-termAdverse Events Following Immunization With Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN)Vaccinefor Mpox

In response to a global shortage of modified vaccinia Ankara-BavarianNordic(MVA-BN)vaccines,Australiaadoptedadose-sparing schedule for the recent mpox outbreak, with 0.1-mL intradermal MVA-BN vaccine recommended for preexposure and 0.5-mL subcutaneous Supplemental content vaccine for postexposure prophylaxis, 2 doses given 4 weeks apart.[1] To understand the adverse events profile of MVA-BN vaccine

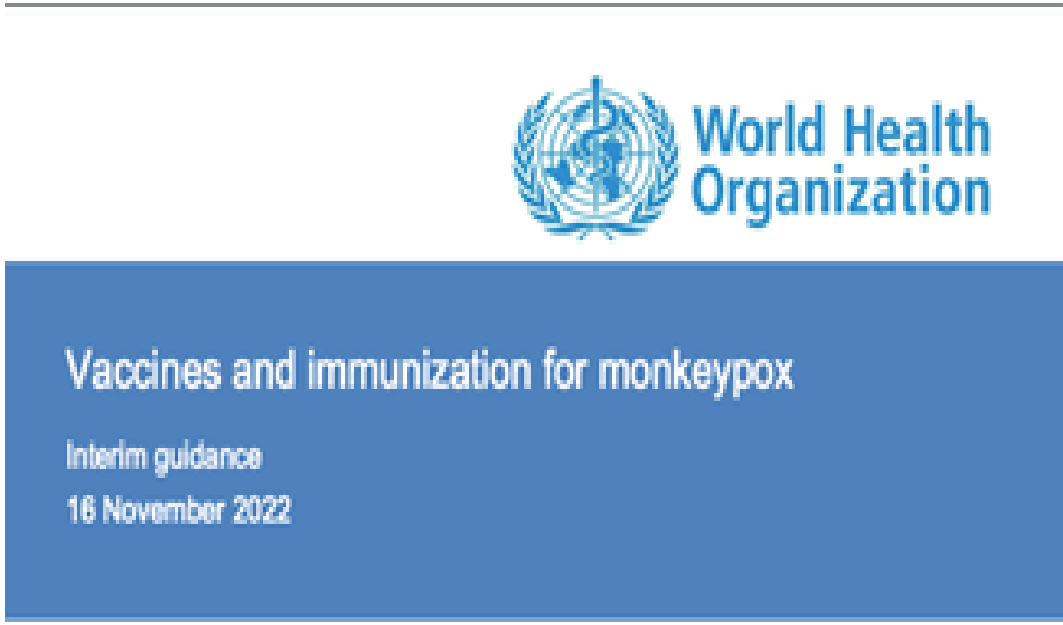
“Mpox Vaccine” performance

A rapid review undertaken by WHO identified 39 studies that evaluated the safety, immunogenicity and effectiveness of smallpox vaccines (MVA-BN, LC16 and ACAM2000) against mpox (Reported as unpublished)

- Peer-reviewed clinical trials are scarce
- Rapid reviews and observational studies
- DRC (2005-2007) - smallpox pre-exposure vaccine effectiveness against mpox of 80.7% (95% CI: 68.2–88.4%)
- Current vaccine effectiveness estimates for MVA-BN vaccine against mpox range from 36% to 86% for vaccination with a single dose and 66% to 89% for vaccination with two doses (WHO)

WHO interim recommendation for mpox vaccinationses

- Two mpox vaccination strategies are recommended in combination with other public health measures:
- **Primary (pre-exposure) preventive vaccination (PPV) is recommended for persons at high risk of exposure:**
  - gay, bisexual or men who have sex with men,
  - others persons with multiple casual sex partners
  - sex workers
  - health workers, clinical laboratory personnel working on MPXV/orthopoxviruses
  - Others who may be at high risk of severe disease
- **Non-replicating** vaccines are recommended for post-exposure preventive vaccination in **children**
- National adaption according to access
- **Post-exposure vaccination (PEPV) is recommended for close contacts of cases**
- **Mass vaccination is not recommended for mpox – irrespective of access and supply**



Current Access options for mpox vaccine

- Direct procurement by countries
- Pooled procurement e.g Global/regional access and allocation initiatives (EU, PAHO)
- Bilateral donation between countries
- Donation through a 3rd party (WHO, GAVI, ECDC)

Breakthrough infections

- Mpox reported in persons who:
  - Vaccinated with third generation vaccines
  - Persons who had smallpox vaccination in childhood
- Possible causes:
  - High vaccination coverage among high-risk groups can present with a relatively high breakthrough infection rate.
  - The timing of post exposure vaccination (Ideally within 4 days of exposure)
  - Secondary vaccine failure - ?duration of immunity (associated with milder disease)
  - Primary vaccine failure
  - Continued exposure to monkeypox virus following vaccination puts vaccinated persons at risk.

Some mpox vaccines and immunization challenges

- Limited supply
- High cost
- Access - Low and middle income countries yet to have access
- Stigmatization of affected
- Limited skills in the use of bi-furcation needles by health care workers

Mpox vaccine research areas

- Clinical efficacy / effectiveness
- Duration of immunity
- Schedule (effectiveness of single / multiple doses)
- Administration(subcut/intradermal route)
- Different population groups (children, pregnancy, immunosuppression)
- Role HIV in infection
- Deployment strategies (pre-exposure/post exposure; ring vaccination)

Next steps /Conclusion

- Eliminating human to human transmission and limiting zoonotic transmission of monkeypox virus are the strategic goals of mpox control.
- Investment in smallpox vaccine development provided the tool for mpox countermeasure
- More Research needed – qualitative and quantitative
- Mpox control involve strategic combination of effective vaccination with other public measure.
- Achieving mpox elimination is justice for the global smallpox eradication effort

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Acknowledgement

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- WHO Mpox IMST team
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World Health Organization

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THANK YOU