Currently Available Evidence on Monkeypox Vaccines

WHO Global Consultation – Monkeypox vaccine study designs

“Monkeypox Research: What study designs can be used to address the remaining knowledge gaps for monkeypox vaccines”

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Smallpox disease and eradication efforts

• Smallpox disease is caused by the variola virus, genus *Orthopoxvirus*
  • Spreads through person-to-person contact and saliva droplets
  • Case fatality rate up to 30%

• Smallpox was officially declared eradicated in 1980 attributable to a WHO-led global vaccination program with the last known natural case of the disease occurring in 1977 in Somalia

• Routine vaccination against smallpox was discontinued, leading to a growing majority of the world’s population lacking immunity to smallpox

• Vaccine used in the eradication campaign contained *vaccinia* virus, closely related to *variola* virus

• 2nd and 3rd generation smallpox vaccines using the *vaccinia* strain were subsequently developed
Monkeypox disease

- Monkeypox is caused by infection with the monkeypox virus, genus *Orthopoxvirus*
- Monkeypox virus was discovered in 1958 in monkey research colonies, first human case recorded in 1970 in DRC
- From January 1st through July 22nd, 2022, 16,016 laboratory confirmed cases of monkeypox and 5 deaths have been reported to WHO from 75 countries/territories/areas in all six WHO Regions
- Males between 18-44 years of age continue to be disproportionately affected by this outbreak accounting for 77% of cases.
- WHO (July 23, 2022) declared outbreak of Monkeypox a public health emergency of international concern
  - WHO external situation report (July 25, 2022)
# Overview of Smallpox Vaccines

**Kidokoro M., Shida H.,** Vaccines, 2014, 2, 755-771

## Table 1. Smallpox vaccines and candidate vaccines classified according to generation.

<table>
<thead>
<tr>
<th>Generation</th>
<th>Product</th>
<th>Platform</th>
<th>Parental Strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation</td>
<td>Lister/Elstree</td>
<td>Lymph-derived</td>
<td>Lister/Elstree</td>
</tr>
<tr>
<td></td>
<td>Dryvax</td>
<td>Lymph-derived</td>
<td>NYCBH a</td>
</tr>
<tr>
<td></td>
<td>Ikeda</td>
<td>Lymph-derived</td>
<td>Ikeda</td>
</tr>
<tr>
<td></td>
<td>Dairen I</td>
<td>Lymph-derived</td>
<td>Dairen I</td>
</tr>
<tr>
<td>Second-generation</td>
<td>ACAM1000</td>
<td>Clonal virus grown in MRC-5 cells</td>
<td>Dryvax</td>
</tr>
<tr>
<td></td>
<td>ACAM2000</td>
<td>Clonal virus grown in Vero cells</td>
<td>ACAM1000</td>
</tr>
<tr>
<td></td>
<td>Elstree-BN</td>
<td>Lister/Elstree lymph-derived virus passed in CEF b</td>
<td>Lister/Elstree</td>
</tr>
<tr>
<td></td>
<td>CCSV</td>
<td>NYCBH lymph-derived virus passed in MRC-5 cells</td>
<td>NYCBH</td>
</tr>
<tr>
<td>Third-generation</td>
<td>LC16m8 c</td>
<td>Minute-pock-forming, temperature-sensitive variant virus</td>
<td>Lister/Elstree</td>
</tr>
<tr>
<td></td>
<td>IMVAMUNE (MVA) d</td>
<td>MVA571 additionally passed in CEF</td>
<td>MVA571</td>
</tr>
<tr>
<td></td>
<td>DIa</td>
<td>Minute-pock-forming variant virus passed in eggs</td>
<td>Dairen I</td>
</tr>
<tr>
<td>Fourth-generation</td>
<td>LC16m8Δ</td>
<td>Derived from LC16m8 by deleting the B5R gene</td>
<td>LC16m8</td>
</tr>
<tr>
<td></td>
<td>NYVAC</td>
<td>Attenuated clonal Copenhagen strain generated by deleting 18 non-essential genes</td>
<td>Copenhagen</td>
</tr>
</tbody>
</table>

*New York City Board of Health; b chicken embryo fibroblast; c Lister Clone 16m8; d Modified Vaccinia Ankara; e Dairen I minute-pock variants.*
## Available smallpox & monkeypox vaccines

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine</th>
<th>Schedule</th>
<th>Vaccine type</th>
<th>Company</th>
<th>Date Approved</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>ACAM2000</td>
<td>1 dose, percutaneous route (scarification), booster every 3 years</td>
<td>Live replicating vaccinia virus, derived from NY City Board of health strain of vaccinia</td>
<td>Emergent</td>
<td>8/2007</td>
<td>Active immunization against smallpox disease for persons determined to be at high risk for smallpox infection</td>
</tr>
<tr>
<td>USA</td>
<td>Jynneos</td>
<td>2 doses, s.c., primary series - booster in previously vaccinated</td>
<td>Live vaccine produced from Modified Vaccinia Ankara, attenuated (MVA), non-replicating</td>
<td>Bavarian Nordic</td>
<td>9/2019</td>
<td>Prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection</td>
</tr>
<tr>
<td>USA</td>
<td>APSV: Aventis Pasteur smallpox vaccine</td>
<td>1 dose scarification</td>
<td>Live replicating vaccinia virus, derived from NY City Board of health strain of vaccinia</td>
<td>SP</td>
<td></td>
<td>Strategic National Stockpile- Used in smallpox emergency</td>
</tr>
</tbody>
</table>
## Available smallpox & monkeypox vaccines

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<thead>
<tr>
<th>Country</th>
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<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>IMVANEX</td>
<td>2 doses, s.c. -booster in previously vaccinated</td>
<td>Live vaccine produced from Modified Vaccinia Ankara, attenuated (MVA), non-replicating</td>
<td>Bavarian Nordic A/S</td>
<td>7/2013</td>
<td>Active immunization against smallpox disease for persons ≥18 years; protection of adults from monkeypox &amp; disease caused by vaccinia virus</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imvamune</td>
<td>2 doses, s.c. -booster in previously vaccinated</td>
<td>Live vaccine produced from Modified Vaccinia Ankara, attenuated (MVA), non-replicating</td>
<td>Bavarian Nordic A/S</td>
<td>2013, extended to include monkeypox in 2020</td>
<td>Active immunization against smallpox, monkeypox and related orthopoxvirus infection &amp; disease in adults ≥ 18 years at high risk for exposure</td>
</tr>
<tr>
<td>Canada</td>
<td>Smallpox vaccine (dried and frozen liquid formulation)</td>
<td>Single dose, scarification</td>
<td>Live vaccinia virus, derived from NYCBH</td>
<td>SP</td>
<td>strategic reserve</td>
<td>emergency situation for active immunization against smallpox</td>
</tr>
<tr>
<td>Japan</td>
<td>LC16m8</td>
<td>Single dose, scarification</td>
<td>Live, replicating attenuated vaccine (derived from Lister (Elstree) strain)</td>
<td>Chemo-Sero-Therapeutic Institute (Kaketsuken)</td>
<td>1975: Chiba Serum Institute, 2003: Kaketsuken</td>
<td>Active immunization against smallpox</td>
</tr>
</tbody>
</table>
US licensure of ACAM2000
(2\textsuperscript{nd} generation smallpox vaccine)

- Vaccine derived from the New York City Board of Health strain of vaccinia virus
  - derived from Dryvax, (1\textsuperscript{st} generation smallpox vaccine)

- The effectiveness of ACAM2000 was demonstrated in a multi-center randomized controlled study in naïve (18 – 30 years old) and previously vaccinated (31 - 84 years old) individuals comparing the “take rates” (cutaneous reaction) induced by ACAM2000 and Dryvax
  - “Take rates” were deemed comparable and thus, effectiveness of ACAM2000 was inferred
  - ACAM2000 was found to be acceptable as a booster dose in previously vaccinated individuals
US licensure of ACAM 2000 (cont.)

- Limited to use in individuals at high risk for smallpox disease because of severe side effects
  - E.g., progressive vaccinia in less severely immunocompromised individuals for whom the vaccine is not contraindicated, eczema vaccinatum in individuals with atopic dermatitis, myopericarditis in smallpox naive individuals, fetal vaccina in pregnant women
- Contraindicated in severely immunocompromised individuals
- ACAM2000 is the first vaccine licensed with a Medication Guide approved by FDA (21 CFR Part 208)
- Package insert contains a boxed warning
US Licensure of Jynneos
(3rd generation smallpox vaccine)

- Vaccine is based on the modified Vaccinia Virus Ankara- Bavarian Nordic (MVA-BN), highly attenuated vaccinia virus derived from strain MVA-572, non-replicating in human cells

- Twenty-two clinical trials were submitted to support the effectiveness and safety of the vaccine including:
  - Phase 3 NI trial comparing MVA-BN with ACAM2000 in naïve individuals using a primary endpoint of non inferior vaccinia specific neutralizing antibody titers (pre-specified NI margin 0.5)
    - Co-primary endpoint: attenuation of ACAM2000 take reaction in persons previously vaccinated with MVA-BN compared to smallpox vaccine naive individuals
  - Phase 3 placebo-controlled lot consistency trial
  - Four (4) phase 2 trials to support use in individuals with atopic dermatitis, HIV-infection, vaccinia experienced individuals and individuals 65 years and older
US Licensure of Jynneos (cont.)

• Vaccine antigens and replication competence differ for MVA-BN and ACAM2000
• Neutralizing antibody response predicting protection not established
• Therefore, demonstration of vaccine effectiveness in NHPs (monkeypox challenge) was necessary in addition to the clinical immunologic non-inferiority comparison to enable vaccine licensure
US Licensure of Jynneos: Rationale for monkeypox indication

- Bavarian Nordic (BN) did not propose an indication against protection of monkeypox
- FDA received several inquiries from USG and external stakeholders whether data for MVA-BN would support an indication for monkeypox
- FDA granted a monkeypox indication because
  - Variola, vaccinia and monkeypox viruses are orthopoxviruses belonging to the poxviridae family & vaccines induce x-protection
  - Effectiveness of Jynneos for the prevention of monkeypox is inferred from the antibody responses in clinical study participants and studies in NHPs demonstrating that prior vaccination with Jynneos protected animals from lethal monkeypox challenge
  - 2nd indication (i.e., prevention from monkeypox) addresses an important public health need
LC16m8 – Japanese smallpox vaccine

- Generated by Chiba Serum Institute, Japan (Dr. Hashizume) in the 1970’s
  - Passage of the Lister strain in primary rabbit kidney (PRK) cells at 30° Celsius
  - Isolation of LC16m8 from intermediate strains, i.e., LC16 and LC16 mO (clone that forms medium sized pocks and isolated from LC16)
  - LC16m8 (final attenuated clone, forms small sized pocks) is directly derived from LC16mO
  - Neurovirulence of LC16m8 markedly reduced in rabbits and cynomolgus monkeys compared to parent Lister strain & Dryvax
  - LC16m8 exhibited markedly diminished dermal reaction in rabbits and humans
  - Vaccine protective effectiveness of LC16m8 extrapolated from studies in rabbits measuring HI and PRNT and compared favorably with responses to original Lister strain

LC16m8 – Japanese smallpox vaccine

In 1974 LC16m8 was used to vaccinate 50,000 children (2-5 year olds)

- LC16m8 produced take rates comparable to other vaccines used in Japan
- Local and systemic reactions significantly less than that observed using Lister


Animal challenge protection studies

- Protective efficacy of LC16m8 demonstrated in rabbits using lethal rabbitpox virus (RPXV) and in mice using aerosolized ectromelia virus (ECTV)

*Empig C. et al, 2006, Vaccine 24: 3686-3694*

- Immunization of monkeys with LC16m8 protects animals from lethal monkeypox

*Masayuki, S. et al 2006, J. Virol, 80(11): 5179-5188*
LC16m8 – Japanese smallpox vaccine

Clinical safety and immunogenicity data

• Randomized, multicenter, double-blind comparative Phase 1/2 study of the LC16m8 and Dryvax smallpox vaccines conducted in healthy vaccinia-naive adult volunteers at 5 sites in the United States

• Local and systemic reactogenicity after vaccination with LC16m8 similar to Dryvax.

• No clinically significant abnormalities consistent with cardiac toxicity were seen for either vaccine

• Both vaccines achieved antivaccinia, antivariola, and antimonkeypox neutralizing antibody titers >1:40, although the mean plaque reduction neutralization titer of LC16m8 at day 30 after vaccination was lower than for Dryvax

• LC16m8 produced robust cellular immune responses that trended higher than Dryvax for lymphoproliferation but lower for IFN-γ ELISPOT

Kennedy, J.S., et al 2011 Safety and Immunogenicity of LC16m8, an attenuated smallpox vaccine in vaccina-naïve adults, J. Infect. Dis; 204(9): 1395-1402
2\textsuperscript{nd} and 3\textsuperscript{rd} Generation Smallpox Vaccines - Knowledge Gaps

- Effectiveness against smallpox and monkeypox inferred from challenge/protection studies in animal models & vaccine-induced immune response in humans
  - No direct evidence of efficacy against smallpox and monkeypox
- Correlate of protection not established – neutralizing antibody ?!
  - Additional studies evaluating humoral and cellular immune response
- Duration of immunity induced by 2\textsuperscript{nd} and 3\textsuperscript{rd} generation smallpox vaccines
• Consider post-approval effectiveness study using licensed 3rd generation vaccines, e.g., accrual of real-world evidence in an outbreak situation
• Additional clinical safety studies
• Characterization of immune response of candidate smallpox vaccines compared to currently licensed vaccines to potentially identify biomarkers predictive of protection