Overview of Available Vaccines against Smallpox & Monkeypox

Who R & D Blueprint team meeting:
“Monkeypox research: What are the knowledge gaps and priority research questions?”
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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 a rare disease 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

• Repeated outbreaks of monkeypox had been reported in West- and Central African countries but in May 2022, multiple clusters of monkeypox have been reported in European countries and North America

• Monkeypox is clinically less severe than smallpox
  • case fatality rate has been between 1% (West African Clade) and 10 % (Central African Clade)
# Overview of Smallpox Vaccines


<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 passaged in CEF  (^b)</td>
<td>Lister/Elstree</td>
</tr>
<tr>
<td></td>
<td>CCSV</td>
<td>NYCBH lymph-derived virus passaged 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 passaged in CEF</td>
<td>MVA571</td>
</tr>
<tr>
<td></td>
<td>DIs (^e)</td>
<td>Minute-pock-forming variant virus passaged in eggs</td>
<td>Dairen I</td>
</tr>
<tr>
<td>Fourth-generation</td>
<td>LC16m8Δ</td>
<td>Derived from LC16m8 by deleting the B3R 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>

\(^a\) New York City Board of Health; \(^b\) chicken embryo fibroblast; \(^c\) Lister Clone 16m8; \(^d\) Modified Vaccinia Ankara; \(^e\) Dairen I minute-pock variants
<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

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine</th>
<th>Doses</th>
<th>Vaccine type</th>
<th>Company</th>
<th>Date Approved</th>
<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 of age and older</td>
</tr>
<tr>
<td>Canada</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 determined to be 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>Investigational strategic reserve</td>
<td>released in 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, since 2003 Kaketsuken</td>
<td>Active immunization against smallpox</td>
</tr>
</tbody>
</table>
US licensure of ACAM2000 (2
nd
generation smallpox vaccine)

• Vaccine derived from the New York City Board of Health strain of vaccinia virus
  • derived from Dryvax, (1st 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
Licensure of future smallpox & monkeypox vaccines

• Efficacy studies using a clinical disease endpoint may still be challenging (geography, timing and extent of outbreak unpredictable)

• Data supporting licensure may be a combination of
  • Clinical safety studies
  • Clinical immunogenicity studies including evaluation of the impact of the investigational vaccine on subsequent takes with 2nd generation smallpox vaccines
  • Animal data (e.g., challenge/protection studies)

• However, demonstration of effectiveness using NI immunogenicity studies comparing the new vaccine to a licensed comparator may depend on the technology platform that is used
  • Characterization of the clinical and nonclinical immune response induced by new vaccine and comparator critical to determine whether an immunobridging approach is possible to infer effectiveness
Additional Research needs

• 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