45 | VACCINIA VIRUS

45.1 | Disease agent

- Vaccinia virus

45.2 | Disease agent characteristics

- Family: *Poxviridae*; Subfamily: *Chordopoxvirinae*; Genus: *Orthopoxvirus*.
- Virion morphology and size: Enveloped, biconcave core with two lateral bodies, brick-shaped to pleomorphic virions, ~360 × 270 × 250 nm in size.
- Nucleic acid: Non-segmented, linear, covalently closed, double-stranded DNA, 18.9–20.0 kb in length.
- Physicochemical properties: Virus is inactivated at 60° C for 8 min, but antigen can withstand 100°C; lyophilized virus maintains potency for 18 months at 4–6°C; virus may be stable when dried onto inanimate surfaces; susceptible to 1% sodium hypochlorite, 2% glutaraldehyde, and formaldehyde; disinfection of hands and environmental contamination with soap and water are effective.

45.3 | Disease name

- Progressive vaccinia (vaccinia necrosum, vaccinia gangrenosum or disseminated vaccinia)
- Generalized vaccinia
- Eczema vaccinatum
- Postvaccination encephalomyelitis
- Fetal vaccinia

45.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical.
- Public perception and/or regulatory concern regarding blood safety: Very low; the existence of any threat of vaccinia to blood safety is dependent on the occurrence of an accidental or intentional release of variola, or a threat of bioterrorism sufficient to require a significant, widespread, reintroduction of smallpox (vaccinia) immunization.
- Public concern regarding disease agent: Absent.

45.5 | Background

- While vaccinia was originally thought to originate from cowpox virus, this is not the case and the exact origins and natural hosts of strain(s) used for smallpox immunization are obscure, likely because of poor quality control during the early years of propagation of the virus stocks for vaccination.
- Currently two FDA-approved vaccines manufactured with vaccinia can be used in smallpox vaccination for individuals working with variola (smallpox) in laboratories, for some military personnel, and for the prevention of mpox.
  - ACAM2000, a live, replicating smallpox (vaccinia) vaccine. ACAM2000 is administered via scarification that produces an infectious local lesion with a maximal response at 8–11 days, which generally scabs over in 14–21 days. Accidental infections occur following transfer of replicating virus from the vaccination site to another site (autoinoculation) or to another person following physical contact with lesions or secretions.
  - JYNNEOS, a live, non-replicating smallpox and mpox vaccine is administered intradermally and does not produce a lesion at the vaccination site, minimizing risk for secondary transmission.

45.6 | Likelihood of secondary transmission

- Significant following direct contact with replication-competent vaccinia virus like ACAM2000.
- There is no evidence of secondary transmission for the live, non-replicating JYNNEOS vaccine following large-scale administration during 2022 mpox outbreak.

45.7 | Common human exposure routes

- Intentional dermal inoculation for vaccination

45.8 | At-risk populations

- Individuals receiving replication-competent vaccinia vaccination
- Individuals who come in direct contact with vaccinated persons
- Those at risk for more severe complications of infection include the following:
  - Immunocompromised persons
  - Pregnant women
  - Patients with atopic dermatitis
  - Patients with extensive exfoliative skin disease (e.g., Darier disease, other types of eczema, psoriasis)

45.9 | Vector and reservoir involved

- Vaccinia can infect multiple host species (such as bovines or rodents), although the public health significance is uncertain, whereas variola is limited to humans.

45.10 | Blood phase

- Vaccinia DNA was detected by PCR in blood samples from 6.5% of 77 military members from 1 to 3 weeks after smallpox (vaccinia) vaccination which resulted in a major skin reaction.
- In the absence of complications after immunization, recently published PCR and culture data suggest that viremia with current vaccines must be rare 3 weeks after vaccination.

45.11 | Survival/persistence in blood products

- Unknown

45.12 | Transmission by blood transfusion

- Never observed despite the coexistence of extensive immunization activity and blood donation and transfusion during much of the 20th century. However, this was not systematically investigated.
- JYNNEOS is non-replicating and should pose no risk.

45.13 | Cases/frequency in population

- There is minimal use of smallpox vaccination, absent a bioterrorism threat or individuals working with variola.
- The source of current concern is speculation about cases occurring upon implementing widespread vaccination programs using replication-competent preparations in anticipation of or response to the intentional reintroduction of smallpox into the population.

45.14 | Incubation period

- Complications of ACAM2000 immunization tend to occur 4–21 days after inoculation.
- In one study, using a replication-competent vaccine, viral DNA was infrequently detectable up to 21 days after uncomplicated immunization. However, in another study, 220 samples from 28 volunteers were processed by 3 laboratory detection methods and all were negative for the presence of vaccinia virus (confidence interval, 0%–12.3%). Viremia with vaccinia virus after smallpox vaccination appears to be an uncommon occurrence.

45.15 | Likelihood of clinical disease (using a replication-competent vaccine)

- Low, except in immunocompromised persons

45.16 | Primary disease symptoms (using a replication-competent vaccine)

- Erythema multiforme: Usually benign rash after immunization.
- Accidental skin infection or keratitis through transference or intimate skin contact.
- Generalized vaccinia: Disseminated maculopapular or vesicular rash that occurs because of lymphohematogenous spread 6–9 days following vaccination. Immunocompetent hosts usually experience a benign clinical course, whereas this can be life-threatening in immunocompromised persons.
- Progressive vaccinia: Necrotic, locally progressive virus replication in the skin and soft tissue of a vaccination site (generally seen in vaccinees or their contacts with defective cellular or humoral immunity).
- Eczema vaccinatum: Localized or generalized papular, vesicular, pustular, or erosive rash syndrome approximately 5–19 days after exposure through vaccination or close contact with a smallpox vaccinee, with substantial mortality. Lesions have a predilection for areas currently or previously affected by atopic dermatitis.
- Postvaccination encephalopathy and encephalomyelitis.
- Fetal infection (rare).
- Cardiomyopathy, myocarditis, pericarditis.
- Secondary (bacterial) infection of vaccination site.

45.17 | Severity of clinical disease (using a replication-competent vaccine)

- Certain post-vaccination manifestations carry substantial morbidity and mortality (fetal vaccinia, progressive vaccinia, postvaccination encephalomyelitis, eczema vaccinatum, heart disease), while generalized vaccinia is serious in immunocompromised hosts.

45.18 | Mortality (using a replication-competent vaccine)

- Mortality rates vary by complications that occur. It is highest in fetal or progressive vaccinia, moderate with myocarditis or encephalomyelitis (15%–25%) and <10% with eczema vaccinatum. Historically higher rates of mortality and severe morbidity have been modified with the availability of modern supportive care, vaccinia immune globulin, and antivirals (e.g., tecovirimat, cidofovir and brincidofovir).

45.19 | Chronic carriage (using a replication-competent vaccine)

- In children with immunological defects in cell-mediated immunity, vaccinia virus replicates without restriction, resulting in a sub-acute progressive primary lesion, persistent viremia, and widespread secondary viral infection of many organs. In patients with thymic dysplasia and partially or completely intact immunoglobulin-synthesizing capacity (Nezelofs syndrome), the progression is slower and less persistent, but usually results in death.
- Not recognized in immunocompetent vaccinees.

45.20 | Treatment available/efficacious (using a replication-competent vaccine)

- Uncontrolled data suggest that vaccinia immune globulin may mitigate complications of vaccination.
- Animal models and very limited human data suggest the antiviral agents such as tecovirimat, cidofovir and brincidofovir may have clinical activity.

45.21 | Agent-specific screening question(s)

- Currently required by the FDA and included in AABB's Donor History Questionnaire:
  - In the past 8 weeks, have you had any vaccinations or other shots?
  - In the past 8 weeks, have you had contact with someone who was vaccinated for smallpox in the previous 8 weeks?
- While only minimal smallpox (vaccinia) immunization is occurring, many individuals received non-replicating JYNNEOS vaccination during the 2022–2023 mpox epidemic.

45.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Antibody assays might be useful as evidence of immunity.
- Research assays exist for virus isolation, virus detection by direct fluorescent assay in lesion samples, and nucleic acid amplification. None of these are licensed in the United States nor are they immediately suitable for high-throughput applications.

45.23 | Currently recommended donor deferral period

- 21 days or until vaccination scab separates (longer of the two) for well vaccinees.
- 14 days (additional donor deferral) after resolution of all symptoms in vaccinees with complications or in vaccinee contacts with complications.
- Prospective donors who are symptomatic after contact with recipients of smallpox vaccine are deferred until complete healing and spontaneous separation of scabs from localized skin lesions, as visually verified by donor room staff. If the scab was otherwise removed, deferral is for 3 months from the vaccination of the source vaccinee. If the date of vaccination of the source is unknown but could have been within the last 3 months, deferral is for 2 months from the donor's attempt to donate.

45.24 | Impact on blood availability

- Agent-specific screening question(s): Minimal in the absence of widespread, emergent, population-based immunization initiatives. Impact will be small in conjunction with local or narrowly targeted immunization programs. Impact will be major with community-wide immunization programs and could be devastating to the blood supply during rapidly implemented, widespread regional or national immunization programs.
- Laboratory test(s) available: Not applicable.

45.25 | Impact on blood safety

- Agent-specific screening question(s): Minimal, given lack of evidence of viremia from vaccination in recent studies
- Laboratory test(s) available: Not applicable

45.26 | Leukoreduction efficacy

- Unknown.
- Cellular tropism studies using primary hematolymphoid cells suggest some viral clearance by leukoreduction can be anticipated.

45.27 | Pathogen reduction efficacy for plasma derivatives

- This enveloped virus was inactivated below the limit of detection in one study (that used 6 logs of virus) with pasteurization, caprylate, and solvent-detergent treatments.
- Sterile filtration of plasma for further manufacture reduced titers approximately 4 logs in one study.

45.28 | Other prevention measures

- None

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