46 | VARIOLA VIRUS

46.1 | Disease agent

- Variola virus

46.2 | Disease agent characteristics

- Family: *Poxviridae*; Subfamily: *Chordopoxvirinae*; Genus: *Orthopoxvirus*; Species: Variola
- Virion morphology and size: Enveloped, biconcave core with two lateral bodies, brick-shaped to pleomorphic virions, 360 × 270 × 250 nm in size
- Nucleic acid: Nonsegmented, linear, covalently closed, double-stranded DNA, ~18.6 kb in length
- Physicochemical properties: Stable in dried condition (survives at room temperature in crusts for over a year and for ~3 months in the dark and over a month in the light when dried on slides); killed by heating at 60°C for 10 min when moist, but can withstand 100°C for 5–10 min when dry; sensitive to UV light (sunlight); inactivated by sodium hypochlorite or by formaldehyde at a concentration of 0.2% in 24 h at room temperature; resistant to 1% phenol for weeks at 4°C but inactivated within 24 h at 37°C; may retain infectivity for several hours even if aerosolized

46.3 | Disease name

- Smallpox (variola major and variola minor or variola alastrim)

46.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical.
- Public perception and/or regulatory concern regarding blood safety: Absent; Variola has been eradicated in nature. There is no risk to the blood supply in the absence of accidental or intentional release of variola, or a threat of bioterrorism sufficient to require a significant and widespread reintroduction of smallpox immunization.
- Public concern regarding disease agent: Very low; natural variola has been eradicated, and risk remains low but not absent because of the risks of a bioterrorism event or accidental release of the virus from remaining stocks in the former Soviet Union or the US.

46.5 | Background

- The last naturally occurring case of smallpox occurred in Somalia in 1977 and the World Health Organization has considered the disease eradicated since 1979.
- The last occurrence of the disease in the United States was in 1949.
- Classified among the highest priority for bioterrorism agents by the CDC (Category A). There are two WHO-designated sites where stocks of variola virus are stored and used for research: US CDC, and the former Soviet Union.

46.6 | Common human exposure routes

- Inhalation of large airborne respiratory droplets usually through direct or prolonged face-to-face close contact.
- Lower transmissibility from fomites or contact with infectious material in scabs.

46.7 | Likelihood of secondary transmission

- A person with smallpox is sometimes contagious with onset of fever, but the person becomes most contagious when the rash appears. Once the rash appears the person is usually very sick and not able to move around in the community. The infected person is contagious until the last smallpox scab falls off.
- Significant by direct contact or inhalation (58% in unvaccinated close or household contacts or 3.8% in previously vaccinated close contacts). Scabs are much less infectious than respiratory secretions, presumably due to binding of the virions in the fibrin matrix of the scab.
- Parenteral transmission has not been recognized.

46.8 | At-risk populations

- All unimmunized people and those with waning immunity from prior vaccination in the event of reintroduction of the virus
- A threat as a bioterrorist weapon for populations not previously considered being at risk

46.9 | Vector/reservoir involved

- None

46.10 | Blood phase

- By the third or fourth day after infection, virus-infected macrophages enter regional lymph nodes and possibly the bloodstream. This is before prodromal symptoms develop at 7–17 days after infection.
- Secondary viremia (which is also largely cell-associated) occurs with the onset of symptoms.

46.11 | Survival/persistence in blood products

- Unknown

46.12 | Transmission by blood transfusion

- None observed or documented

46.13 | Cases/frequency in population

- Zero at this time

46.14 | Incubation period

- 7–17 days after exposure (average incubation period from 12 to 14 days)

46.15 | Likelihood of clinical disease

- High; may be even higher (greater mortality) with engineered bioterriorism strains

46.16 | Primary disease symptoms

- Initial onset of symptoms is 7–17 days after exposure. Starts with 3-day viral prodrome: fever (38.3–40°C up to 3 days before the rash), prostration, headache, backache, vomiting.
- Toxemic phase including a rash that typically begins centrally and spreads peripherally to the extremities (primarily upper) and face. Typically, by 14 days after infection, the characteristic progression of skin lesions is observed: macules, papules, vesicles, pustules, umbilication (classic and characteristic), and crusting
- All lesions are in a single stage of development.

46.17 | Severity of clinical disease

- Severity of disease is correlated with rash burden; it is more severe in children or pregnant women.

46.18 | Mortality

- Variola major: Up to 30% in those with no immunity; variola minor: <1%; could be higher with engineered bioterrorism strains

46.19 | Chronic carriage

- None

46.20 | Treatment available/efficacious

- Two antiviral agents for treatment of clinical smallpox, tecovirimat (in 2018) and brincidofovir (in 2021), have been approved in the United States for use in the event of an outbreak.
  - They are included in US Strategic National Stockpile.
  - The approvals were made using data accrued under the FDA's Animal Rule, since natural disease in humans has been eradicated.
- Antibiotics may be used for coincident secondary infections, and vaccinia immune globulin may modify the disease course.

46.21 | Agent-specific screening question(s)

- No specific question is in use.
- Not indicated because transfusion transmission has not been demonstrated.
- No sensitive or specific question is feasible.
- Under circumstances of accidental or deliberate release, the need for, and potential effectiveness of, specific donor screening questions would need to be addressed.
- Recent receipt of live attenuated, replication-competent vaccinia vaccines by essential personnel in support of bioterrorism preparedness or for mpox prevention requires deferral for a minimum of 21 days or until the vaccination site has healed.
- The JYNNEOS live, non-replicating smallpox/mpox vaccine has been widely used for prevention of mpox during the 2022–2023 global epidemic but does not require deferral.

46.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Serology, NAT, and virus isolation are available, but primarily in specialized labs, and there are no assays currently suitable for high throughput screening. Generic *Orthopoxvirus* PCR and negative stain electron microscopy (EM) identification of a pox virus in a clinical specimen are suggestive of an *Orthopoxvirus* infection but not diagnostic for smallpox.
- Laboratory diagnostic testing for variola virus should be conducted in a CDC Laboratory Response Network facility capable of high-level containment using approved PCR tests.

46.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.
- Not applicable as there is no likelihood of exposure in the absence of an accidental or deliberate release of virus.
- Guidance concerning blood donors, and retrieval and quarantine of blood collected from exposed or infected donors, will likely be issued should disease activity become recognized.

46.24 | Impact on blood availability

- Agent-specific screening question(s): Not applicable; in response to an accidental or deliberate release, impact of a local deferral would be significant.
- Laboratory test(s) available: Not applicable.

46.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable; unknown impact in response to an accidental or deliberate release
- Laboratory test(s) available: Not applicable

46.26 | Leukoreduction efficacy

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

46.27 | Pathogen reduction efficacy for plasma derivatives

- Inactivation of the closely related vaccinia virus below the limit of detection was demonstrated in one study (that used 6 logs of virus) with pasteurization, caprylate, and solvent-detergent treatments. Filtration of plasma reduced titers approximately 4 logs in one study. Efficacy for variola virus is expected to be similar to vaccinia.

46.28 | Other prevention measures

- Smallpox (vaccinia) vaccination for at-risk persons

SUGGESTED READING

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