

UPDATED 01/14/25

17 | **INFLUENZA A AND B VIRUSES**

17.1 | Disease agents

- Influenza A and B viruses

17.2 | Disease agent characteristics

- Family: *Orthomyxoviridae*; Genera: *Alphainfluenza-virus* and *Betainfluenzavirus*
- Virion morphology and size: Enveloped, helical nucleocapsid, spherical to pleomorphic virions, 80–120 nm in diameter
- Nucleic acid: Linear, segmented, negative-sense, single-stranded RNA, ~13.6 kb in length for influenza A and ~14.6 kb in length for influenza B
- Physicochemical properties: Virions are sensitive to treatment with heat, lipid solvents, nonionic detergents, formaldehyde, oxidizing agents; infectivity reduced after exposure to radiation.

17.3 | Disease name

- Influenza

17.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical
- Public perception and/or regulatory concern regarding blood safety: Very low
- Public concern regarding disease agent: Moderate

17.5 | Background

- Seasonal epidemics are characteristic of influenza A and B. These are primarily in the late fall and winter in temperate climates.
- When major changes (antigenic shift) occur in influenza A antigens, pandemics occur with high attack rates and variable morbidity and mortality.
- Influenza B does not undergo shifts but evolves by antigenic drift and is not associated with severe pandemics.
- Depending on vaccine efficacy and other factors associated with epidemic activity, epidemics occur annually

and pandemics every few decades.

- Influenza A viruses infect avian species, humans, and several other mammalian species (especially swine). Influenza B infects only humans.
- Highly pathogenic influenza A viruses, avian-derived; for example, H5N1 (HPAI)
 - Transmission of HPAI to humans from domestic fowl was first described in Southeast Asia in 1997 with high mortality among both birds and humans.
 - Transmission to humans is inefficient, human disease is rare after more than 20 years of avian-human exposures, and evidence of person-to-person spread is absent.
 - Since 1997, more than 880 human cases have been reported from 21 countries with substantial mortality, but very few cases have been identified worldwide since 2016.
- A panzootic of HPAI A(H5N1-2.3.4.4b) began in 2022 and has affected a wide range of avian species, terrestrial and marine mammals. The virus has been detected in wild birds in 50 states or territories as of mid-December 2024, and in mammals in 20 states, especially dairy herds in 15. Wild birds and poultry are infected with genotype D1.1 and bovines with B3.13.
 - Human infections with the current H5N1 HPAI were first detected in March 2024 after dairy herd exposure, and 60 cases had been recognized by mid-December. These infections have been mild in almost all cases, and human-to-human transmission has not been documented.
 - On-going surveillance for all highly pathogenic strains should occur. If circulating strains adapt for human-to-human transmission, an influenza pandemic is possible. CDC currently considers this to be a low-risk scenario but is monitoring H5 flu activity in both people and animals.

17.6 | Common human exposure routes

- Person-to-person spread of transmissible human influenza strains is primarily via contact with droplets expelled during coughing and sneezing
- Virions are present in high titers in nasal secretions starting about 2–3 days after exposure and just before symptoms.
- Preschool and school-age children are major contributors to transmission of influenza A viruses.
- Human HPAI infections are overwhelmingly from contact with infected birds and more recently from infected dairy cattle in domestic herds. Human-to-human spread has not been documented.

17.7 | Likelihood of secondary transmission

- Characteristic of influenza following exposure to secretions from infected persons

17.8 | At-risk populations

- Elderly individuals (>65 years).
- Infants and pregnant women.
- Those with a variety of chronic medical conditions
- During pandemics, much larger segments of the population are immunologically naïve, and susceptible to infection.

17.9 | Vector and reservoir involved

- Influenza A viruses circulate in birds and mammalian species, especially pigs, where they undergo antigenic drift and shift with eventual transmission to humans.
- Influenza B infection is confined to humans.

17.10 | Blood phase

- Animal models of influenza A demonstrate viremia after experimental infection. Influenza A (H3N2) viral RNA was identified in 1 of 28 Brazilian blood donors who were deferred because of post-donation information using metagenomics analysis in 2019. Virus isolation was not reported.
- No influenza A (H1N1) 2009 RNA was detected by PCR in plasma samples from 579 blood donors by the Japanese Red Cross. Virus isolation was not reported.
- No influenza A (H1N1) 2009 RNAemia was detected by TMA and 2 RT-PCR assays in plasma samples from 478 retrospectively collected and 1004 prospectively collected US blood donors. Virus isolation was not attempted.
- Influenza A (H1N1) 2009 viral RNA was identified in the blood of 2 patients with severe disease. Virus isolation was not reported.
- Influenza RNA in blood was detected in 9 of 79 stored serum and plasma samples from hematopoietic cell transplant recipients. Virus isolation was not reported.
- In a REDS-II study published in 2012, no viral RNA was found in 1482 US donor samples from areas with substantial risk of influenza A.
- Virus isolation at autopsy from organs outside the respiratory tract (heart, CNS, kidney, spleen, liver, fetus) is indirect evidence of dissemination during nat-

ural infection that suggests viremia.

- Viremia and influenza A “RNAemia” are described in a small series of symptomatic patients (who would have been disqualified as donors because of symptoms).
- A single case report describes influenza A H3N2 (Hong Kong) viremia in a naturally infected, asymptomatic patient, which would be most relevant to concerns about transfusion transmission.
- An RT-PCR assay in 96-sample minipools from German blood donors for influenza A H5N1 was evaluated in 10,272 blood donor samples. All were negative.
- Experimental human infections have been accompanied by viremia during the incubation period, but the relevance of the high-dose intranasal inoculation (as opposed to the natural droplet route) has been questioned. Influenza B viremia was detected in 4 of 11 pediatric patients 2–4 days after symptom onset.

17.11 | Survival/persistence in blood products

- Unknown

17.12 | Transmission by blood transfusion

- Never documented in humans.
- A small study published in 2014 found dose-dependent transmission and mortality from A(H5N1-VN.1203.04) from ferrets infected by the respiratory route to recipients of their blood.

17.13 | Cases/frequency in population

- The US CDC estimates from 2010 to 2020 that the number of illnesses from influenza were between 9 and 41 million (about 8% of the US population will get sick from influenza each year, ranging from 3% to 11%). WHO estimates up to 650,000 deaths worldwide each year.
- The incidence varies from season to season, but population attack rates during a pandemic first wave can approach 40%.
- During seasonal epidemics, incidence rates of up to 18% are seen (higher in children) and up to 70% in confined or selected populations. Up to 10% of weekly mortality attributable to influenza during outbreaks
- In March 2009, a new influenza A (H1N1) virus emerged in the United States and spread quickly across the US and the world causing the first Influenza A

pandemic in 40 years.

- This virus was characterized by a combination of influenza genes not previously isolated from animals or people and designated as influenza A (H1N1) pdm09 virus. Phylogenetic analyses suggested that the virus was derived from one or multiple reassortments between influenza A virus circulating in swine in Eurasia and in North America (H1N1, H1N2 and H3N2).
- From April 2009 to April 2010, there were an estimated 60.8 million cases (range: 43.3–89.3 million), 274,304 hospitalizations (range: 195,086–402,719), and 12,469 deaths (range: 8868–18,306) in the United States. due to the (H1N1) pdm09 virus according to CDC. Worldwide mortality was estimated at 151,700–575,400.
- The US, including the blood community, mounted a complex, multi-faceted response to the pandemic.
- Human infections with the current panzootic HPAs were first detected in March 2024 after dairy herd exposure, and 60 cases had been recognized by mid-December. These infections have been mild in almost all cases (mainly conjunctivitis consistent with the route of exposure to bovine mammary infections), and no human-to-human transmission has been documented. Two severe cases, one in Canada and a second in Louisiana, were with the “avian” D1.1 genotype.

17.14 | Incubation period

- About 2 days ranging from 1 to 5 days (longer for influenza B virus); infectivity is highest 3–4 days after illness begins.

17.15 | Likelihood of clinical disease

- Based on experimental infection, most influenza A cases are symptomatic, with high fever in 60%–90% of subjects.
- While some authorities suggest that influenza B is milder than A, most believe they closely resemble each other.
- Children younger than 18 are more than twice as likely to develop a symptomatic flu virus infection than adults 65 and older (9.3% vs. 3.9%).

17.16 | Primary disease symptoms

- Abrupt onset of fever of 38–40°C but can reach 41°C when symptoms first develop; usually continuous but may come and go; may be lower in older adults than

in children and young adults.

- Myalgias, commonly occurring in the back, arm, or legs.
- Headache, chills, dry cough.
- Retroorbital pain, conjunctivitis.
- Fatigue, malaise, anorexia.
- Tracheobronchitis with rhinorrhea; cough can persist for 1 or 2 additional weeks after fever and upper respiratory tract symptoms resolve.

17.17 | Severity of clinical disease

- WHO estimates about 3–5 million cases of severe illness each year.
- Symptoms can be severe and associated with increased hospitalizations during epidemics (1/2900 infected for 1–44-year-old group and 1/270 infected for those older than 65 years).

17.18 | Mortality

- WHO estimates up to 650,000 deaths worldwide each year.
- Influenza is the cause of excess mortality each year, especially in persons >65 years (1/2200 infected increasing to 1 in 300 infected during a pandemic) in industrialized countries. Over 99% of deaths in children <5 years old related to influenza-related lower respiratory tract infections occur in the developing world.
- During pandemics mortality is generally highest at the extremes of age; however, during the 1918 pandemic, there was a mortality peak in young adults.

17.19 | Chronic carriage

- No

17.20 | Treatment available/efficacious

- Several antiviral drugs (amantadine and rimantadine) and neuraminidase inhibitors (zanamivir, oseltamivir) are available that have both prophylactic and clinical efficacy, although resistance, including transmission of primary resistant strains, is a major concern.

17.21 | Agent-specific screening question(s)

- No specific question is in use, but symptomatic donors are excluded by current donor criteria (“Are you feeling well and healthy today?”).
- No question is feasible for exposure to influenza A or B during a community outbreak.

17.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Antemortem diagnosis confirmed by viral isolation, experimental nucleic acid testing for virus-specific RNA, and the less sensitive antigen-detection tests.
- All tests have been validated for sputum/pharyngeal secretions but not for blood or blood fractions. Isolation may be higher from pharyngeal samples (at a median of 5.5 days).

17.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.
- Prudent practice would be to defer donor until signs and symptoms are gone.

17.24 | Impact on blood availability

- Agent-specific screening question(s):
 - Symptomatic infection is already a cause for deferral.
 - If there is a concern about asymptomatic viremia and a deferral for contact with influenza is considered during a seasonal outbreak or pandemic, the impact could be major.
- Laboratory test(s) available: No screening test is currently available; if screening for viremia by NAT were implemented, additional impact on availability is unknown.

17.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

17.26 | Leukoreduction efficacy

- Unknown, but thought to be minimal because of hemagglutinin moiety of influenza and high levels of virus in plasma and RBC fractions in experimental models

17.27 | Pathogen reduction efficacy for plasma derivatives

- Virus inactivation steps used to manufacture derivatives (including pasteurization for albumin, solvent/detergent treatment for intravenous immunoglobulin, vapor heating for factor VIII inhibitor bypassing activity, and incubation at low pH for intravenous immunoglobulin) were effective in one study using a reassorted strain of H5N1 influenza A.

17.28 | Other prevention measures

- Vaccines developed annually have moderate impact on tempering seasonal epidemics.

SUGGESTED READING

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