Influenza A and B Viruses (Other Than H5N1)

Disease Agents:
- Influenza A and B viruses

Disease Agent Characteristics:
- Family: Orthomyxoviridae; Genera: Influenzavirus A or Influenzavirus B
- 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, \( \sim 13.6 \text{ kb} \) in length for influenza A and \( \sim 14.6 \text{ kb} \) 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.

Disease Name:
- Influenza

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

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.

Common Human Exposure Routes:
- Person-to-person spread 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.

Likelihood of Secondary Transmission:
- Characteristic of influenza following exposure to secretions from infected persons

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.

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.

Blood Phase:
- Animal models of influenza A demonstrate viremia after experimental infection.
- Virus isolation at autopsy from organs outside the respiratory tract (heart, CNS, kidney, spleen, liver, fetus) is indirect evidence of dissemination during natural infection that suggests viremia.
- Viremia and influenza A “RNA-emia” 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.
- 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.

Survival/Persistence in Blood Products:
- Unknown

Transmission by Blood Transfusion:
- Never documented

Cases/Frequency in Population:
- The incidence varies from season to season, but population attack rates during a pandemic first wave can approach 40%. During seasonal epidemics, rates of up to 18% are seen (higher in children) and up to 70% in confined or selected populations.
Worldwide prevalence: Up to 10\% of weekly mortality attributable to influenza during outbreaks

In March-April 2009, a new strain of influenza A H1N1 was isolated in Mexico and then rapidly worldwide. The spread of the virus and disease soon qualified as a level 5 of 6 (the highest indicating a pandemic) using the WHO influenza pandemic definitions. Although formally achieving the existing WHO criteria for level 6, by community spread of the new H1N1 virus in a second region by the end of May, the WHO did not raise the pandemic alert to level 6 until June 11, 2009. This is the organization’s first flu pandemic declaration in more than 40 years. Raising the alert to level 6 does not indicate the disease is more fatal or riskier than at level 5, but that it has spread to an increasing number of countries. As of June 11, 2009:

- 74 countries reported 28,774 cases including 144 deaths
- 94\% of global cases are from the Americas with most from Mexico
- Cases of disease have been milder than expected based on initial reports from cases in Mexico

Phylogenetic cluster analyses using the new H1N1 strain and its closest relatives support the fact that the 2009 worldwide H1N1 virus derived from one or multiple reassortments between influenza A viruses circulating in swine in Eurasia and in North America (H1N1, H1N2 and H3N2).

Receipt of recent (2005-2009) seasonal influenza vaccines is unlikely to elicit a protective antibody response to the novel H1N1 virus

- 2-fold increase in cross-reactive antibody in those aged 18-64 (compared to a 12- to 19-fold for the seasonal H1N1 influenza strain)

Incubation Period:
- 1-5 days (longer for influenza B virus)

Likelihood of Clinical Disease:

Based on experimental infection, most influenza A cases are symptomatic, with high fever in 60-90\% of subjects.

Asymptomatic influenza A infection does occur and was documented in 4 of 34 infected prisoners.

While some authorities suggest that influenza B is milder than A, most believe they closely resemble each other.

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 younger adults
- Myalgias, commonly occurring in the back, arm, or legs
- Headache, chills, dry cough
- Retro-orbital 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.

Severity of Clinical Disease:

- Symptoms can be severe and associated with increased hospitalizations during epidemics (1/2900 infected for 1- to 44-year-old group and 1/270 infected for those older than 65 years).
- During the past four influenza seasons, the peak percentage of patient visits for influenza-like illness ranged from 4.0 to 7.6%.

Mortality:

- 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)
- During pandemics mortality is generally highest at the extremes of age; however, during the 1918 pandemic, there was a mortality peak in young adults.

Chronic Carriage:
- No

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.

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.

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).
An RT-PCR assay in minipools for the associated influenza A H5N1 subtype has been evaluated in 10,272 blood donor samples. All were negative.

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.

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.

Impact on Blood Safety:
- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

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

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 reassortant strain of H5N1 influenza A.

Other Prevention Measures:
- Vaccines developed annually have moderate impact on tempering seasonal epidemics.

Suggested Reading: