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and drift must be taken into account when strains are being incubation period from exposure to illness averages 2–3 days. Viruses results in a pandemic, or worldwide epidemic, with the potential to cause millions of influenza-related deaths. Introduction of a new HA into human influenza viruses and belongs to the family Orthomyxoviridae. There are three virus types within this family: influenza A, B, and C. Influenza A and B viruses are the types that predominantly infect humans, and A viruses are responsible for pandemic outbreaks of influenza and annual epidemics. The virus contains three important envelope glycoproteins: hemagglutinin (HA), neuraminidase (NA), and matrix proteins (M1 and M2). HA is the viral attachment protein responsible for entry of the virus into cells; it is an important surface antigen to which virus-neutralizing antibodies are directed. NA is an enzyme whose main function is to facilitate the cell-to-cell spread of virus; it is the target for the antiviral drugs zanamivir and oseltamivir. Antibody against HA is very protective against infection and illness, and antibody against NA can reduce illness severity. The matrix protein 2 (M2) is a structural protein linking the viral envelope with the virus core and is integral to the infectivity of the influenza virion. Influenza viruses have a segmented genome, containing eight strands of RNA. This property enables gene reassortment to occur among different subtypes of influenza, allowing new subtypes to form. Variation in the structure of HA and NA between influenza virions is the basis of the subtype H and N classification nomenclature (e.g. influenza A H1N1) (Fig. 27.1). Influenza viruses have developed ways to evade the body’s immune response using an antigenic variation known as antigenic shift and drift. Antigenic shift is seen only with influenza A viruses and results from the replacement of HA (or occasionally NA) with novel subtypes from other nonhuman influenza viruses. Introduction of a new HA into human viruses results in a pandemic, or worldwide epidemic, with the potential to cause millions of influenza-related deaths. Antigenic drift results from the accumulation of mutations within the antibody-binding sites in HA, NA, or both. These mutations prevent antibodies against previous strains from being effective against the current strain, enabling spread throughout a partially immune population. Antigenic drift occurs in both influenza A and B viruses. Antigenic shift and drift must be taken into account when strains are being considered for inclusion in annual influenza vaccines.

**Epidemiology**

Human-to-human transmission of influenza occurs through small-particle aerosols or droplets, which enter the environment from an infected individual. The virus then binds to epithelial cells of the upper and lower respiratory tract. The incubation period from exposure to illness averages 2–3 days but can be as rapid as 18 hours or as long as 5 or more days. Healthy adults will shed influenza virus for 3–7 days, and young children may shed for 10 days or longer with generally higher viral titers.

Influenza occurs each year in winter through early spring and is associated with significant morbidity and mortality in certain high-risk populations (Table 27.1). In the United States up to 36,000 deaths per year are attributable to influenza, with people above 65 years of age accounting for more than 90% of deaths. Influenza is responsible for 5%–15% of upper respiratory tract infections in children.

Healthy children aged 6–23 months are at substantially increased risk of influenza-related hospitalizations, and children aged 24–59 months remain at increased risk of influenza-related clinic and emergency department visits and hospitalizations but less so than younger children.

**Pathology/Pathogenesis**

Influenza virus infection begins with the attachment of viral HA to terminal sialic acids on the surface of target host cells. In the lungs, the target cells of the influenza virus are typically ciliated columnar epithelial or alveolar epithelial cells (AECs), with each HA subtype displaying a unique tropism. Attachment of the influenza virus triggers receptor-mediated endocytosis by host cells and thus entry into the cell. To effectively release influenza RNA into the cytosol, viral M2 forms ion channels in the viral envelope. Liberated viral RNA then travels to the nucleus of the infected cell, where messenger RNA (mRNA) and viral RNA are synthesized. Assembly and budding of daughter virions occurs at the cell surface, where NA facilitates virion release by cleavage of sialic acid attachments to viral HA. Without this cleavage, influenza virions aggregate at the cell surface and are not released, which is the mechanism by which NA inhibitors are effective.

Ultimately, viral infection leads to apoptosis of the infected epithelial cells, which denudes the airways, resulting in acute tracheobronchitis. When type I AECs are damaged, the tight junctions of the alveolar capillary membrane allow a transudate of fluid and proteins to enter the alveolar spaces, producing acute alveolar damage with the potential of progressing to acute respiratory distress syndrome (ARDS). Viral HA and M2 also inhibit the resorption of alveolar fluid by the epithelial sodium channel, further promoting alveolar edema. Influenza infection and resultant cytokine induction can also activate the endothelial pole of the alveolar capillary barrier, facilitating neutrophil influx and further disruption of barrier function.

The host immune response to influenza infection is complex and redundant, incorporating both innate and adaptive processes (see Chapter 8 for details of innate and adaptive
ABSTRACT

Influenza A and B viruses are orthomyxoviruses with three important envelope glycoproteins: hemagglutinin (HA), neuraminidase (NA), and matrix proteins. Influenza viruses have developed ways to evade the body’s immune response using an antigenic variation known as antigenic shift (replacement of HA and NA antigens with novel subtypes from non-influenza viruses) and drift (mutations within antibody-binding sites in HA and or NA). Because of new influenza viruses constantly emerging from antigenic shift and drift, new influenza vaccines are required each year. Human-to-human transmission of influenza occurs each winter and early spring through small-particle aerosols or droplets. The influenza virus attacks epithelial cells of the upper and lower respiratory tract, with the potential for secondary bacterial infection and acute respiratory distress syndrome (ARDS). The symptoms of influenza infection include fever, headache, cough, sore throat, myalgia, and nasal congestion. Lower respiratory tract manifestations such as pneumonia and bronchiolitis are virtually indistinguishable from other viral infections. Children with certain comorbidities, such as chronic lung disease and severe neurologic impairment, are at higher risk of influenza-related complications. The most reliable test for influenza is reverse transcription polymerase chain reaction (RT-PCR). Rapid antigen tests have lower sensitivity and specificity and are not reliable during periods of low influenza activity. Antiviral treatment with NA inhibitors can shorten the duration of fever, symptoms, and hospitalization, especially when started within 48 hours of influenza illness onset. Prevention of influenza through annual influenza vaccination is recommended for all children 6 months of age and older. The vaccines contain three or four influenza subtypes, chosen depending on the circulating strains. The two formulations approved for children are the inactivated influenza vaccine (IIV) and live-attenuated influenza vaccine (LAIV).

KEYWORDS

influenza
respiratory virus
respiratory tract illness
Influenza

AN INFLUENZA VIRUS

Influenza virus

Hemagglutinin

Neuraminidase

M2 ion channel

Ribonucleoprotein

Fig. 27.1 Graphic representation of an influenza virion showing its structure and important components. RNP, Ribonucleoprotein. (From http://www.cdc.gov/flu/images.htm.)

Clinical Features

SYMPTOMS

There is great overlap in the symptomatology of influenza and other respiratory pathogens. The influenza syndrome usually has a sudden onset, associated with fever, headache, cough, sore throat, myalgia, nasal congestion, weakness, and loss of appetite. In a retrospective study of adolescents and young adults with influenza-like illness, the best predictors of influenza infections were cough and fever, with a positive predictive value of 79%. Young children, however, have a less classic presentation compared with adults and tend to have higher fevers, less prominent respiratory symptoms, and more gastrointestinal symptoms such as abdominal pain, vomiting, diarrhea, and decreased appetite. Influenza infection is also an important cause of febrile seizures.

Lower respiratory tract manifestations in young children are virtually indistinguishable from those due to other viral infections. Influenza, similar to other respiratory viruses, may cause bronchiolitis, interstitial pneumonia, laryngotracheitis (croup), bronchitis, exacerbations of asthma, wheezing, and pneumonia. Extrapulmonary manifestations include myocarditis, hepatitis, encephalitis, myositis, renal insufficiency, Guillain-Barré syndrome, rhabdomyolysis, and multiorgan system failure.

PHYSICAL FINDINGS

Findings on examination include tachypnea, conjunctival erythema, nasal injection, edema, nasal discharge, and cervical adenopathy. Rash is an uncommon manifestation of influenza, but when it occurs it is usually a generalized maculopapular rash sparing the palms and soles. Other rashes associated with influenza infection have been characterized as petechial, macular, papular, reticular, or purpuric; they can be localized and pruritic or nonpruritic.

RADIOGRAPHIC FINDINGS

The chest radiographic features of influenza pneumonia are indistinguishable from those of pneumonia caused by other organisms. The most common radiographic findings are

Table 27.1 Individuals at High Risk for Influenza Complications

| Hospitalized | Severe, complicated, or progressive illness |
| Children aged <2 years* |
| Individuals <19 years receiving long-term aspirin therapy |
| Adults aged ≥65 years |
| People of all ages with: |
| chronic pulmonary (including asthma), cardiovascular, renal, hepatic, metabolic (including diabetes), hematologic, neurologic (including seizure disorders) conditions; intellectual disability (mental retardation), moderate to severe developmental delay, and neurodevelopmental conditions |
| People with immunosuppression |
| Pregnant or recently postpartum women |
| American Indians/Alaska Natives |
| People who are morbidly obese (body mass index ≥40) |
| Residents of nursing homes or chronic care facilities |

*Although all children below 5 years of age are considered at higher risk for complications from influenza, the highest risk is for those younger than 2 years, with the highest hospitalization and death rates among infants younger than 6 months.

immune responses. In response to infections, activated macrophages and neutrophils work to eliminate viral particles and damaged or apoptotic epithelial cells. Although this is a key element in viral elimination and the recovery of epithelial integrity, the inflammatory by-products—such as myeloperoxidase, neutrophil elastases, and increased nitric oxide synthase—may cause further injury to the airway. Increased risk of secondary bacterial infection may be due to delayed epithelial healing after influenza infection, excessive interferon gamma production, and type I interferons.

The majority of systemic symptoms observed in acute influenza infection are attributable to the cytokines produced and released during the host immune response. Viremia is uncommon in an immunocompetent host. Similarly, dysfunction in nonrespiratory organs—such as myocarditis, encephalopathy, encephalitis, and rhabdomyolysis—is not usually associated with viral infection in those tissues.

Viral infections can also stimulate the Th2 arm of the immune system by producing thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. TSLP stimulates dendritic cells to induce Th2 cells and predisposes the host to allergic airway inflammation and asthma. IL-25 and IL-33 stimulate type 2 cytokine–producing innate lymphoid cells (ILC-2) to synthesize IL-5 and IL-13, which are promoters of eosinophilic inflammation, excessive mucus secretion, and bronchial hyperresponsiveness. This may explain, in part, how acute influenza infection exacerbates asthma and potentiates a subsequent asthma phenotype.
bilateral, symmetric, perihilar, and peribronchial opacities, but focal opacities and asymmetric disease may also occur (Fig. 27.2). Lymph node enlargement can occur, but pleural effusions are rare. The nonspecific findings make it challenging to differentiate viral from bacterial pneumonia based on the radiographic appearance alone. Younger children with influenza pneumonia may have bilateral patchy opacities that probably reflect the retention of mucus. Progression of the pneumonia can lead to diffuse airspace disease with an ARDS picture and acute respiratory failure. Complete resolution to a normal chest radiograph should be expected following mild disease.

COMPlications

Children with chronic lung disease, asthma, airway disease, cardiovascular disease, neuromuscular disease, and immunocompromised states are at highest risk of complicated influenza infection (see Table 27.1). Severe influenza infection can present with bilateral pulmonary infiltrates and hypoxemia, leading to ARDS and death. In particular, the 2009 H1N1 pandemic influenza virus was associated with higher rates of life-threatening lower respiratory tract illness, including ARDS, which was thought to be due to an increased predilection to infection of ciliated epithelial cells of the lower respiratory tract. Pneumonia and secondary bacterial infection is a common cause of hospitalization from influenza. Although Streptococcus pneumoniae is the most common pathogen identified, Staphylococcus aureus is a commonly associated copathogen. Methicillin-resistant S. aureus (MRSA) coinfections with influenza are increasingly being identified and are a risk factor for mortality in previously healthy children and adolescents. Clinical features that support a bacterial superinfection among children with influenza include secondary fever after a period of defervescence, focal findings on pulmonary auscultation, lobar consolidation on chest imaging, and new onset of respiratory compromise occurring several days after initial symptoms.

Diagnosis and Differential Diagnosis

Testing for influenza is recommended if positive or negative results will influence clinical management or clinical practice for other patients. Testing should be considered, regardless of immunization status, during the influenza season among children with fever and acute onset of respiratory signs and symptoms, and those with acute exacerbations of underlying chronic lung disease. Infants and young children with fever and no other signs and symptoms, hospitalized children with acute respiratory symptoms who develop an acute febrile respiratory illness, and severely ill children with fever or hypothermia should also be tested. Testing should occur at any time of the year for children who are epidemiologically linked to an influenza outbreak (e.g., household and close contacts of people with suspected influenza, returned travelers from countries where influenza viruses may be circulating, participants in international mass gatherings, and cruise ship passengers). Testing 5 days or more beyond illness onset may result in false-negative test results because of decreased viral shedding; this occurs in particular among older children.

Testing modalities available include influenza-specific reverse transcription polymerase chain reaction (RT-PCR), multiplex respiratory pathogen PCR, direct fluorescent antibody (DFA) tests, and rapid influenza antigen tests. RT-PCR is the most accurate testing modality for influenza; it is useful for differentiating between influenza types and subtypes and is significantly more sensitive than rapid influenza antigen detection tests (>95% vs. 10%–70%, respectively). Rapid antigen tests have less sensitivity and specificity than RT-PCR tests. A meta-analysis of children demonstrated sensitivity of 64.6% for influenza A and 52.2% for influenza B. These and other studies indicate that rapid antigen tests are not reliable during periods of low influenza activity. Immuno-fluorescent antibody testing can distinguish between influenza A or B and other respiratory viruses. However, the test performance is dependent on the quality of the respiratory specimen and expertise of the laboratory.

Viral culture is usually unhelpful in the clinical setting because results are not available until 48–72 hours later. However, it is helpful for the confirmation of screening results, surveillance, and research. Serologic testing is also not helpful in the clinical setting because acute and convalescent (obtained 10 days later) sera are required for diagnosis. Testing platforms include hemagglutination-inhibition, enzyme-linked immunosorbent assays (ELISA) and complement fixation assays. A fourfold rise or greater in antibody titers between acute and convalescent specimens confirms the diagnosis of influenza.

The differential diagnosis of influenza infection is listed in Table 27.2.

Management and Treatment

TREATMENT

Clinical trials and observational data show that early antiviral treatment can shorten the duration of fever, influenza
Neuraminidase inhibitors (NAIs) oseltamivir and zanamivir are the antiviral medications still recommended for the treatment and chemoprophylaxis of influenza A and influenza B virus infections owing to near universal susceptibility. They inhibit the viral NA enzyme that helps progeny escape from infected cells. NAIAs may also have efficacy against the novel influenza viruses. Oseltamivir is given orally for 5 days with dose adjustments required for renal impairment and weight (Table 27.3). The most common side effects of oseltamivir are nausea and/or vomiting. Transient neuropsychiatric events (self-injury or delirium) have been reported, mainly among Japanese adolescents and adults. Zanamivir is a dry powder administered via oral inhalation. It is not FDA-approved for the treatment of children under 7 years of age. The dose is two breath-activated inhalations twice daily for 5 days. The prophylactic dose is two inhalations once daily for children 5 years of age and older. It is not recommended for children with underlying airway disease. (If zanamivir is used in patients with underlying airway disease, they should be instructed to have a short-acting bronchodilator available.) Allergic reactions including rashes and oropharyngeal or facial edema have been reported. Side effects include diarrhea, nausea, sinusitis, rhinitis, nasal congestion, bronchitis, cough, headache, dizziness, and ear/nose/throat complaints. Peramivir is an intravenous NAI indicated for the treatment of acute, uncomplicated influenza in patients 18 years of age and older who have been symptomatic for no more than 2 days; it is given as a single 600-mg administration. Matrix protein inhibitors amantadine and rimantadine target the M2 protein and are potentially effective against only influenza A owing to the lack of a M1/M2 protein channel in influenza B viruses. These antiviral medications are not currently recommended for treatment or chemoprophylaxis since most circulating influenza A strains have developed resistance to them. 

Steroids have been proposed as an adjunctive therapy for influenza pneumonia; however, several studies failed to demonstrate clinical benefit in the treatment of patients and hospitalization; it may also reduce the risk of complications from influenza (e.g., otitis media in young children, pneumonia, respiratory failure, and death). Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hours of influenza illness onset. Treatment should not wait for laboratory confirmation of influenza but should be started as soon as possible when clinically indicated.

Antiviral treatment is recommended regardless of the day of illness for any patient with confirmed or suspected influenza who is hospitalized; has severe, complicated, or progressive illness; or is an outpatient who is at higher risk for influenza complications based on age or underlying medical conditions. Clinical judgment—based on the patient’s disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms—is important in making decisions regarding antiviral treatment for high-risk outpatients. Antiviral treatment may be considered for any outpatient with confirmed or suspected influenza who is otherwise healthy if treatment can be initiated within 48 hours of illness onset.

### Table 27.2 Differential Diagnosis of Influenza Infection

| Upper Respiratory Infection | Lower Respiratory Tract Infection | Exacerbations of Wheezing/Asthma |
|-----------------------------|----------------------------------|----------------------------------|
| Rhinovirus                  | hMPV                             | RSV                              |
| hMPV                        | Adenovirus                       | hMPV                             |
| Adenovirus                  | RSV                              | Rhinovirus                       |
| RSV                         | PIV                              | hMPV                             |
| PIV                         | Coronaviruses                    | PIV                              |
| Coronaviruses               | Chlamydophila pneumonia          | hMPV                             |
| Enteroviruses               | Mycoplasma pneumonia             | Chlamydophila pneumonia          |
|                             | Bovacillus                       | pneumonia                         |
|                             | Streptococcus pneumonia          | pneumonia                         |
|                             | Staphylococcus aureus            | pneumonia                         |
|                             | Haemophilus influenzae           | pneumonia                         |
|                             | Streptococcus pyogenes           | pneumonia                         |

hMPV, Human metapneumovirus; PIV, parainfluenza virus; RSV, respiratory syncytial virus.

### Table 27.3 Treatment and Prophylactic Dosing of Oseltamivir

| Age                                      | Treatment Dose               | Prophylactic Dose |
|------------------------------------------|------------------------------|-------------------|
| 2 weeks–3 months*                        | 3 mg/kg per dose twice a day | Not recommended unless situation judged critical |
| Children 3–11 months*                    | 3 mg/kg per dose twice a day | 3 mg/kg per dose once daily |
| Children 1–12 years old and weighing     |                              |                   |
| ≤15 kg                                   | 30 mg/dose twice a day       | 30 mg once daily |
| >15–23 kg                                | 45 mg/dose twice a day       | 45 mg once daily |
| >23–40 kg                                | 60 mg/dose twice a day       | 60 mg once daily |
| >40 kg                                   | 75 mg/dose twice a day       | 75 mg once daily |
| Children ≥13 years of age and adults     | 75 mg/dose twice a day       | 75 mg once daily |

*Although not part of the US Food and Drug Administration (FDA)-approved indications, use of oral oseltamivir for treatment of influenza in infants less than 14 days old and for chemoprophylaxis in infants 3 months to 1 year of age is recommended by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics.

*The American Academy of Pediatrics recommended an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants aged 9–11 months for the 2013–14 season on the basis of data indicating that a higher dose of 3.5 mg/kg was needed to achieve the protocol-defined targeted exposure for this cohort as defined in the Capability Acquisition and Sustainment (CASG) 114 study (Kimberlin, 2013). It is unknown whether this higher dose will improve efficacy or prevent the development of antiviral resistance. However, there is no evidence that the 3.5-mg/kg dose is harmful or causes more adverse events to infants in this age group.
with severe influenza infection. Furthermore, studies indicate an increase in overall mortality, increased incidence of hospital-acquired pneumonia, and longer duration of mechanical ventilation and ICU stay in patients treated with steroids.\textsuperscript{61,62}

### Prevention

Routine annual influenza vaccination is recommended for all children 6 months of age and older. Ideally, vaccination should occur before the onset of influenza in the community and should be administered as soon as a vaccine supply is available. Vaccination should be continued as long as influenza viruses are circulating. Multiple different vaccine formulations are available, and some are licensed for specific age groups or are more appropriate for particular patient populations. Recommendations regarding influenza and vaccine dosing are updated by the CDC each year and are available via the Centers for Disease Control and Prevention (CDC) influenza website (http://www.cdc.gov/flu/); they are also published in the Morbidity and Mortality Weekly Report by the CDC.\textsuperscript{63,64} Two formulations of vaccine are approved for children: inactivated influenza vaccine (IIV) and live-attenuated influenza vaccine (LAIV). LAIV is an intranasal vaccine and is offered solely in quadrivalent form. IIV is available in trivalent or quadrivalent formulations. The Centers for Disease Control and Prevention (CDC) has recommended that LAIV should not be used until further notice due to low vaccine effectiveness against influenza A during the 2013–2014 and 2015–2016 seasons. Recombinant influenza vaccine (RIV) is available for adults with egg allergy.

Children 6 months through 8 years of age receiving vaccine for the first time require two doses of vaccine at least a month apart. Influenza vaccine contraindications are provided in Table 27.4. Data demonstrate that IIV and LAIV\textsuperscript{65} given in a single, age-appropriate dose is well tolerated by virtually all recipients who have egg allergy. Children with anaphylaxis to eggs may receive influenza vaccine by a health care provider who is familiar with the potential manifestations of egg allergy in a setting where anaphylaxis can be recognized and treated. Such children should be observed for at least 30 minutes for signs of a reaction after administration of each vaccine dose.

#### CHEMOPROPHYLAXIS

NAIs are 70%–90% effective in preventing influenza. Yet the CDC does not recommend widespread or routine use of chemoprophylaxis owing to the possibility that resistant viruses could emerge, thus limiting the usefulness of these medications for high-risk or severely ill people. Oseltamivir can be used for chemoprophylaxis of influenza among infants below 1 year of age when indicated, although, owing to limited data in this age group, children less than 3 months of age should not receive prophylaxis unless the situation is judged to be critical.

Chemoprophylaxis is not usually recommended if more than 48 hours have elapsed since the last exposure to an infected person. For effective prophylaxis, an antiviral medication must be taken each day for the duration of potential exposure to a person with influenza and continued for 7 days after the last known exposure. Postexposure prophylaxis should be considered for family members and close contacts of infected patients if they are at high risk of complications from influenza.

#### Prognosis/Outcome

With or without antiviral treatment, most children have a full and uneventful recovery after an acute, uncomplicated influenza infection. Unfortunately, some will have a fatal outcome. Death from influenza is more frequent in children with comorbidities such as asthma or severe neurologic impairment and in those who develop ARDS.\textsuperscript{66} A small proportion of children may develop asthma after experiencing an acute influenza infection, although asthma subsequent to infection seems

| Vaccine | Contraindications | Precautions |
|---------|------------------|-------------|
| Inactivated influenza vaccine (IIV\textsubscript{1} or IIV\textsubscript{2}) | Severe allergic reaction to any component of the vaccine, including egg protein, or after previous dose of any influenza vaccine. | Moderate to severe illness with or without fever; history of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine. |
| Cell culture–based IIV\textsubscript{3} | Severe allergic reaction to any component of the vaccine. | Moderate to severe illness with or without fever; history of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine. |
| High-dose IIV\textsubscript{3} | | Moderate to severe illness with or without fever. History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine. |
| Recombinant influenza Vaccine (RIV\textsubscript{3}) | Concomitant use of aspirin or aspirin-containing medications in children and adolescents. In addition, Advisory Committee on Immunization Practices recommends LAIV not be used for pregnant women, immunosuppressed people, people with egg allergy, and children aged 2–4 years who have asthma or who have had a wheezing episode noted in the medical record within the past 12 months, or for whom parents report that a health care provider stated that they had wheezing or asthma within the last 12 months. | Asthma in people 5 years of age and older. Medical conditions that might predispose to higher risk for complications attributable to influenza. |
| Live-attenuated influenza vaccine (LAIV\textsubscript{4}) | Severe allergic reaction to any component of the vaccine, including egg protein, or after previous dose of any influenza vaccine. | |
to be more common with other viral lower respiratory tract infections such as RSV or human rhinovirus.67

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