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Christopher P. Conlon 8.5.24 HIV in low- and middle-income countries 933 Alison D. Grant and Kevin M. De Cock 8.5.25 HTLV-1, HTLV-2, and associated diseases 941 Kristien Verdonck and Eduardo Gotuzzo 8.5.26 Viruses and cancer 945 Robin A. Weiss 8.5.27 Orf and Milker’s nodule 947 Emma Aarons and David A. Warrell 8.5.28 Molluscum contagiosum 949 David A. Warrell and Christopher P. Conlon 8.5.29 Newly discovered viruses 951 Susannah J.A. Froude and Harriet C. Hughes 8.5.1 Respiratory tract viruses Malik Peiris ESSENTIALS Viral respiratory infections, including rhinovirus, coronavirus, adeno- virus, respiratory syncytial virus, human metapneumovirus, para- influenza viruses, and influenza viruses, are a substantial cause of morbidity worldwide. Transmission occurs through direct contact, contaminated fomites, and large airborne droplets, with long-range

724 section 8 Infectious diseases transmission by small particle aerosols reported in at least some in- stances of influenza and severe acute respiratory syndrome. Clinical syndromes affect the upper and/or lower respiratory tract, including coryza, pharyngitis, croup, bronchiolitis, and pneumonia. Each syndrome can potentially be caused by several viruses, and each respiratory virus can be associated with different clinical syn- dromes. Measles is a major cause of lower respiratory tract infections and fatality in tropical countries. Diagnosis—nasopharyngeal aspirates, washes, and swabs are su- perior to throat and nose swabs for diagnosis, with virus detected by culture or detection of antigen or nucleic acid (e.g. polymerase chain reaction-based methods). Sputum is a useful specimen for viruses predominantly affecting the lower respiratory tract (e.g. Middle East respiratory syndrome). New respiratory viruses con- tinue to be discovered, but some acute respiratory infections have no identifiable aetiology, and some patients have multiple respira- tory viruses detectable in the respiratory tract in association with their disease—whether these have a synergistic role in pathogenesis remains unclear. Particular respiratory tract viruses Influenza—types A and B are clinically important causes of human disease; the viral envelope contains two glycoproteins, haemagglu- tinin (H) and neuraminidase (N), which are critical in host immunity and used to designate viral subtype (e.g. H1N1). Potential to cause pandemics makes influenza type A an unique challenge for global public health. Typically causes an illness associated with fever, chills, headache, sore throat, coryza, nonproductive cough, myalgia, and sometimes prostration. It can cause pneumonia directly or by sec- ondary bacterial infections. Oseltamivir and zanamivir result in a re- duction of 1–2 days in the time to alleviation of symptoms when administered within the first 48 h of illness, but even later com- mencement of therapy might still confer clinical benefit in severe influenza illness. Disease can be prevented by influenza vaccine, which contains antigens from the two subtypes of human influenza A (H3N2 and H1N1) and the Victoria and Yamagata lineages of influ- enza B viruses, but the composition of the vaccine must be updated on an annual basis to keep abreast of change in the surface antigens of the virus, and annual reimmunization is required. Synergic inter- action with Streptococcus pneumoniae enhances pathogenesis, and pneumococcal conjugate vaccine reduces hospitalization associated with respiratory viruses. Respiratory syncytial virus—a major cause of bronchiolitis and pneumonia in infants. Infection in adults is often mild, but during the respiratory syncytial virus season (winter months in temperate regions) it is an important cause of lower respiratory tract disease in older people. It may be lethal (as can other respiratory viruses) in patients immunocompromised following organ or blood and marrow transplants (but is not a significant problem in patients with AIDS). Severe acute respiratory syndrome—this novel coronavirus of ani- mals adapted to efficient human transmission and spread world- wide, causing a global outbreak in 2003 of an illness characterized by lower respiratory tract manifestations, severe respiratory failure, and death in about 10% of cases. Public health interventions interrupted viral transmission and it is no longer transmitting within humans, but the precursor virus remains in the animal reservoir (bats, Rhinolophus spp.) and could readapt to cause human disease in the future. Middle East respiratory syndrome coronavirus is endemic in drom- edary camels and causes zoonotic disease in the Arabian peninsula and the Middle East, sometimes leading to outbreaks associated with transmission between humans, especially within healthcare facilities. Travel-associated cases have been reported in other countries. While the virus can infect all ages, severe clinical disease predominantly manifests in older people or in those with comorbidities. Introduction Viral respiratory infections are amongst the most common afflic- tions of humankind. They are the most frequent reasons for med- ical consultations, are believed to account for 30% of work absences and school absenteeism, and are a major reason for antibiotic pre- scriptions. Longitudinal family

studies suggest that a person has, on average, 2.4 respiratory viral infections per year, a quarter of them leading to a medical consultation. The synergistic interactions between viruses and bacteria in pathogenesis are being increas- ingly recognized, for example that between influenza virus and Streptococcus pneumoniae or Staphylococcus aureus. With the excep- tion of influenza in elderly people, these viral infections are not a major cause of mortality in otherwise healthy people in the devel- oped world, but it is estimated that they contribute to over 1 million deaths annually in the developing world. The term ‘respiratory virus’ for the purpose of this discussion will include those that have the respiratory tract as their primary site of clinically relevant pathology. Taxonomically, they belong to six virus families (Table 8.5.1.1) and are global in distribution. Other viruses cause systemic disease with respiratory tract involvement as part of an overall disseminated disease process in patients who are im- munocompetent (e.g. measles, Hantavirus pulmonary syndrome) or immunocompromised (e.g. cytomegalovirus). These are dealt with elsewhere. A respiratory virus may cause a range of clinical syndromes. Conversely, a respiratory syndrome may be caused by more than one virus. The major viral respiratory syndromes and their common aetiological agents are shown in Table 8.5.1.2. Although season- ality may differ, the patterns of disease seen in tropical countries are similar; but a notable difference is the role of measles as a major cause of lower respiratory tract infections and fatality in the tropics. The anatomical demarcation between upper and lower respira- tory tract infections is the larynx. Influenza, respiratory syncytial virus, parainfluenza virus and adenoviruses are well-recognized causes of lower respiratory tract infection in adults as well as in children, although many other respiratory viruses might do so occasionally. Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and zoonotic avian influenza (e.g. H5N1, H5N6, H7N9) are unusual in that lower respiratory manifestations predominate over the involvement of the upper respiratory tract. With newer molecular-based approaches to pathogen discovery, new respiratory viruses continue to be recognized. Some recently recognized viruses have been long endemic in humans (e.g. human metapneumovirus, coronaviruses NL-63 and HKU1, bocavirus) while others are novel pathogens, newly emergent as causes of human infections such as SARS, MERS, and avian influenza.

8.5.1 Respiratory tract viruses 725 Transmission The routes of respiratory virus transmission are through direct contact, contaminated fomites, and large airborne droplets (mean diameter >5 μm, range of transmission <1 m). There remains con- troversy over the potential for the spread of viruses such as influ- enza over longer distances by small particle aerosol (mean diameter <5 μm), but even here, large droplets, direct contact, and fomites are Table 8.5.1.1 Respiratory tract viruses: summary of classification, incubation period, duration of infectivity, and diagnostic options Virus Classification (virus family) and composition of virus Subgroups, serotypes, and subtypes Incubation period (days) Duration of virus shedding in immunocompetent patients (days) Options for laboratory diagnosisa Rhinovirus Picornaviridae Nonenveloped RNA viruses

> “ 150 serotypes phylo-genetically divided into three groups: A, B, and C 1–2 days 5–6 days by culture; 50% remain positive by RT-PCR for 2 weeks or longer RT-PCR (viral culture is less sensitive and only possible with some rhinoviruses) Enterovirus Picornaviridae Nonenveloped RNA viruses 112 serotypes distributed in groups A–D Few days Up to 2 weeks from respiratory tract, much longer in faeces RT-PCR. Viral culture less sensitive and not possible for some types

unless animal inoculation is used. Coronavirus Coronaviridae. Enveloped RNA viruses 6 types (OC43, 229E, NL-63, HKU-1, SARS-CoV, MERS-CoV) 4–5 days 5–8 days. SARS-CoV and MERS-CoV can be detectable by RT-PCR for many weeks. RT-PCR Respiratory syncytial virus (RSV) Paramyxoviridae Enveloped RNA virus Subgroup A and B 5 days 6–7 days Culture Rapid antigen detection,a RT-PCR Serology: useful in adults but less so in infants Human metapneumovirus Paramyxoviridae Enveloped RNA virus Serotypes A and B ND ND RT-PCR Viral antigen detection (not readily available) Parainfluenza Paramyxoviridae Enveloped RNA virus Type 1, 2, 3, 4a, 4b 3–6 days 7 days Culture Rapid antigen detection,a RT-PCR Serology: useful in adults but less so in infants Influenza Orthomyxoviridae Enveloped RNA virus Types A, B, C Human influenza A subtypes currently in circulation are H1N1 and H3N2 Average 2–3 (range 1–7) c. 5 days in adults c. 7 days in children Culture Rapid antigen detectiona, RT-PCR Serology Adenovirus Adenoviridae Nonenveloped DNA virus Subgroups A–G Types 1–54 Average 10 (range 2–15) Days–weeks (from respiratory tract), weeks–months (in faeces) Culture Rapid antigen detection,a RT-PCR, Serology Bocavirus Parvoviridae Nonenveloped DNA virus Four species, bocavirus (BCoV) types 1–4 ND Prolonged virus shedding for weeks or months RT-PCR ND, not defined. a Best sensitivity from nasopharyngeal aspirates or nasopharyngeal swabs (in that order). Throat swabs give lower sensitivity. Table 8.5.1.2 Viral aetiology of common respiratory syndromes Virus Coryza Pharyngitis Croup Bronchiolitis Pneumonia Rhinovirus +++a ++

-
Rare Coronavirus ++ +

- (NL-63) SARS-CoV, HKU-1, MERS-CoV Adenoviruses (+) ++ ++ ++ ++ (all ages) RSV ++
-
++ +++ +++ (children);

- (elderly) Human metapneumovirus
-
++ ++ (children) Parainfluenza 1 + ++ +++ + Parainfluenza 2 + ++ ++ + Parainfluenza 3 + ++ ++ ++ ++ (children) Influenza A/B + ++ ++ + ++ (more severre in children and elderly) a Frequency of cases caused by the virus: +++ the major cause (>25%); ++ a common cause (5–25%); + an occasional cause; blank, rare cause or not reported. Data adapted from Treanor 2009.

726 section 8 Infectious diseases probably more important. Occasionally, SARS-CoV and MERS- CoV appear to have spread by small particle aerosols, although droplets and fomites probably contributed to the major part of the transmission of these diseases. Adenoviruses are transmitted by the faeco-oral route as well as by direct contact and large droplets. Factors increasing transmission of respiratory viruses include the time of exposure, close contact (e.g. spouse, mother), crowding, family size, and lack of pre-existing immunity (including lack of breastfeeding). School-age children often introduce an infection into the family and the beginning of school term

might affect transmis- sion patterns in the community. Infected children shed higher titres of viruses than adults. The duration of virus excretion is shown in Table 8.5.1.1. Infectivity usually precedes the onset of clinical symp- toms. Immunocompromised patients shed virus for a longer time. Seasonality Some respiratory viruses have a predictable seasonality, which varies regionally. For example, influenza A is a typically winter disease in temperate regions, a spring/summer disease in the subtropics (e.g. Hong Kong) and occurs all year round (e.g. Singapore) or predom- inantly in the rainy season (e.g. Thailand) in the tropics. The basis for such seasonality is unclear, but climatic factors such as high hu- midity and temperature may help virus survival in small particle aerosols or droplets, and on contaminated surfaces. Factors affecting population congregation such as commencement of school term and seasonal effects on social behaviour might also play a role. Laboratory diagnosis A well-collected specimen is the first and often most important deter- minant in successful laboratory diagnosis. Nasopharyngeal aspirates (secretions aspirated from the back of the nose into a mucus trap), nasopharyngeal washes, and nasopharyngeal swabs are superior to throat and nose swabs for the diagnosis of many respiratory viruses. They offer the advantage that rapid ('same day') diagnosis for sev- eral viruses is possible provided the appropriate methods are avail- able. Swabs for viral culture are placed in viral transport medium immediately upon collection and kept cool (around 4°C) until pro- cessed. Sputum appears to be a useful specimen for viruses that pre- dominantly cause lower respiratory disease (e.g. MERS-CoV, avian influenza H7N9). More invasive specimens such as endotracheal aspirates, bronchoalveolar lavage, or lung biopsy, when available, usually provide better information. For example, in patients with influenza pneumonia during the 2009 pandemic, endotracheal as- pirate specimens sometimes provided positive results even when the upper respiratory tract specimens were negative. However, the likely site of pathology must be kept in mind—the more invasive specimen is not always better. Laboratory methods used for detecting a virus in clinical spe- cimen/s are viral culture, antigen detection, and nucleic acid de- tection (e.g. polymerase chain reaction (PCR)-based methods). The widespread use of molecular methods for viral detection has led to recognition that some viruses that are difficult to culture (e.g. coronaviruses and some rhinoviruses and enteroviruses) are found more often in patients with acute respiratory disease than previously recognized. Similarly, these methods have allowed the discovery of novel viruses associated with respiratory disease (e.g. coronaviruses NL-63, HKU1, bocavirus). They have also revealed that infection with multiple viruses is relatively common. These findings neces- sitate a reassessment of the clinical relevance of positive PCR re- sults. Relevant questions include how commonly these viruses are detectable by these methods in age-matched healthy controls and how long viruses remain detectable after infection. It is important to understand the relevance of detection of multiple pathogens in a respiratory specimen. Are these viruses synergistic in pathogenesis or is one more important than another? Many of these questions re- main to be resolved. Demonstration of rising antibody titres in paired sera is used to diagnose some respiratory virus diseases, but serology is imprac- ticable for others such as rhinoviruses where the large number of antigenically distinct serotypes have no common immunodominant antigen(s). However, adenoviruses and influenza viruses, though having many antigenic types or variants, have common antigen(s) and a single antigen can detect serological responses to many of them. IgM assays are not routinely available for diagnosis of respira- tory viral diseases. Serology is also helpful in assessing the clinical relevance of a virus detected in a respiratory specimen (see earlier) by helping differentiating recent infection from more remote events. 'Near patient testing' is becoming a reality for some viruses (e.g. influenza, respiratory syncytial virus or RSV) with availability of tests that can be performed in a general practice setting.

These be- come more relevant with the greater availability of antiviral drugs. Rhinoviruses Rhinoviruses belong to the Picornavirus family and are adapted to replicate at temperatures of 33–35°C, as found in the external air- ways. Until recently, more than 150 serotypes of rhinoviruses were recognized phylogenetically clustered into groups A, B, and C; group C viruses are noncultivable and recently discovered by mo- lecular methods. Several rhinovirus types will circulate in a region at any given time. Epidemiology Rhinoviruses remain one of the most common infections of hu- mans: 0.5 infections per person per year is a conservative estimate. Secondary attack rates in families can be around 50% overall and 70% in those who are antibody negative. They were thought to cause mainly mild community infections, but are being recognized increas- ingly as the commonest viral agent detected by RT-PCR in children hospitalized with acute respiratory illness. Many of these represent coinfections with other potential respiratory pathogens. As rhino- viruses are often detectable by RT-PCR for weeks after initial infec- tion (50% remain positive at 2 weeks), the aetiological significance of this finding is unresolved and more studies with relevant control populations are needed. Rhinoviruses are important triggers of ex- acerbation of asthma and chronic obstructive pulmonary disease. Immunity In experimental challenges, immunity is serotype specific. Homologous type specific protection lasts for at least 1 year and correlates with serum IgA, IgG, and secretory IgA antibody levels.

8.5.1 Respiratory tract viruses 727 Pathogenesis Viral replication occurs predominantly in the ciliated epithelial cells of the nasopharynx. The structure of the epithelium is preserved. Mucosal secretions associated with coryza appear to be due to the release of inflammatory mediators and neurogenic reflexes. It was thought that the preference of the virus for a lower tem- perature for replication restricted it to the upper respiratory tract. However, this is not strictly true. The virus has been isolated from the lower respiratory tract (including bronchial brushings) and viral RNA has been demonstrated by in situ hybridization in bronchial epithelial cells. Rarely, the virus has been isolated post-mortem from lungs of immunocompromised patients. Clinical manifestations Rhinorrhoea, nasal obstruction, pharyngitis, and a cough are common features of rhinovirus infections. Fever and systemic symptoms are rare, but more common in older people in whom disease can be more severe. Rhinoviruses are a major cause of exacerbations of asthma and chronic obstructive respiratory disease in adults. Lower respira- tory tract symptoms are uncommon in healthy young adults, but may occur in children (bronchiolitis), the immunocompromised, and older people. Rhinovirus infections associated with wheezing in the first 3 years of life is predictive of asthma in later childhood. Treatment and prevention There are no established antiviral drugs for treatment and manage- ment is symptomatic. Topical interferon-α prevents symptoms if given before onset of disease, but cannot be used for prophylaxis over prolonged periods because of side effects. Inhaled interferon-β is currently in clinical trials in adult asthmatics on inhaled cortico- steroids with a history of clinical deterioration following upper re- spiratory infections. Pleconaril is a viral capsid-binding agent that blocks viral attachment and uncoating and has had modest benefit in clinical trials, but concerns over drug interactions have prevented its licensing. Vapendavir is a drug with similar action that is cur- rently in clinical trials for rhinovirus infections. Antibiotics are ineffective in preventing bacterial complications of the common cold. Mucopurulent discharges are part of the natural course of the common cold and are not an indication for antimicrobial treatment, unless it persists (e.g. >10 days). Given the considerable number of rhinovirus serotypes, vaccination is not an option. Enteroviruses Enteroviruses and rhinoviruses (see earlier) are genera within the family Picornaviridae. Enteroviruses have long been known as causes of central nervous system infections, myocarditis,

or exan- thema rather than as a respiratory pathogen, the latter role being assigned to rhinoviruses. As many enteroviruses fail to replicate in cell culture, the wider use of molecular diagnosis has revealed an increased role of enteroviruses in acute respiratory infections. Clinically, patients present with rhinitis, cough, fever, sore throat, or otitis media. There remains a need for studies of age-matched controls to better establish the clinical relevance of these molecular tests. In comparative studies done on the duration of shedding of enteroviruses and rhinoviruses, fewer enterovirus infected children continue to shed virus for longer than 2 weeks while 50% of rhino- virus infections do. This suggests that a positive enterovirus RT-PCR result in the respiratory tract is probably more likely to be clinically relevant than one for rhinovirus. Recently there have been outbreaks of acute respiratory illness, predominantly in children, caused by en- terovirus 68, manifesting as cough, wheezing, and hypoxemia some patients requiring hospitalization and intensive care. This virus may also cause flaccid paralysis. Coronaviruses Six human coronaviruses are currently known, four of them being new viruses discovered since the SARS outbreak in 2003. Coronaviruses are taxonomically subdivided into four groups; the human coronaviruses 229E and NL-63 are alphacoronaviruses while OC43, HKU1, SARS-CoV, and MERS-CoV are β-coronaviruses. There are no known human γ- or deltacoronaviruses yet recognized. Human coronaviruses OC43 and 229E have long been recognized as important causes of the common cold but coronaviruses cause a range of respiratory illnesses. SARS-CoV and MERS-CoV area newly emerged pathogens of zoonotic origin. Human coronaviruses are difficult to culture from clinical specimens and laboratory diag- nosis largely relies on molecular methods. Epidemiology Infection with OC43 and 229E occur in early childhood and 85 to 100% of adults have antibody to both virus types. NL-63 has a similar epidemiology but less is presently known of HKU1. SARS- CoV emerged from an animal reservoir, adapted to human trans- mission, and caused a global outbreak in 2003 that affected 29 countries across five continents. Determined public health inter- ventions interrupted transmission of this virus and it is no longer transmitting within humans. However, the precursor virus remains in the animal reservoir (bats, Rhinolophus spp.) and these could, at some future date, readapt to cause human disease. MERS-CoV was first recognized in a patient with fatal pneumonia in Saudi Arabia in 2012 but the virus has been endemic in dromedary camels for many decades. Zoonotic human infection has so far been confined to the Arabian Peninsula or the Middle East and might sometimes be mild and not recognized. Severe disease occurs mainly in older people on in those with underlying comorbidities. Clusters of human trans- mission have occurred within healthcare facilities. Patients who acquired infection in the Middle East and travelled elsewhere have sometimes caused outbreaks in other parts of the world. Immunity Volunteer reinfection studies with 229E show that 1 year after ini- tial infection, protection from reinfection and illness following a challenge from the homologous virus is incomplete. Comparable data are not available for the newly recognized NL-63, HKU1, or SARS-CoV. Pathogenesis In common with rhinoviruses, coronaviruses 229E induce little or no damage to the respiratory mucosa. The mucosal discharge is caused by the release of mediators from affected host cells. SARS-CoV and MERS-CoV have a predilection to infect alveolar pneumocytes in

 the lower respiratory tract and consequently caused a severe viral pneumonia. Disease severity of SARS was markedly age related. Children had mild disease whereas those over 50 years had a poor prognosis. The basis for this age-related pathogenesis is unknown. The virus receptor for 229E is CD13, both SARS-CoV and NL-63 utilize the human ACE-2 molecule for virus entry while MERS-CoV binds to human DPP4 (CD26). Clinical findings Coronaviruses 229E and OC43 typically cause upper respiratory tract infection and the common

cold but also cause a range of other respiratory manifestations and are significant pathogens in elderly people. NL-63 and HKU1 cause both upper and lower respiratory disease. NL-63 appears to be an important cause of croup, bronchio- litis, and pneumonia. HKU1 appears to be an important pathogen particularly in those with underlying respiratory complications. SARS typically presented with lower respiratory tract manifest- ations and radiological changes with minimum involvement of the upper respiratory tract. Many patients had diarrhoea resulting from viral replication in the gastrointestinal tract. Overall case fatality was 9.6%. Terminal events were severe respiratory failure associated with acute respiratory distress syndrome and multiple organ failure. Age, comorbidities, and viral load in the nasopharynx and serum during the first 5 days of illness correlated with an adverse prognosis. Clinical features of MERS are broadly similar to those of SARS; fever, chills, or rigors, cough (dry or productive), and shortness of breath being the common presenting symptoms. Diarrhoea or vomiting were reported by around one-third of patients. Upper respiratory symptoms are uncommon. Chest radiographic abnor- malities can include unilateral or bilateral hilar infiltrates, patchy in- filtrates, segmented or lobar opacities or ground glass opacities, with the lower lobes being generally more affected than the upper lobes, early in the illness. Lymphopenia, thrombocytopenia and high lac- tate dehydrogenase levels are seen in around one-third of patients. Reported case fatality ranges from 30 to 40%, but this is probably because milder cases are not being recognized. Treatment and prevention There are presently no clinically validated antiviral treatments for human coronaviruses disease, although several drugs have been documented to have in vitro activity against SARS-CoV and MERS- CoV and some (ribavirin, interferon, HIV protease inhibitors) have been used in uncontrolled settings with inconclusive results. Passive immunotherapy is currently being explored for treatment of MERS. Several experimental vaccines were developed for SARS, but with its disappearance from the human population, the incentive to take these forward to human clinical trials and licensing has waned. Vaccines for MERS-CoV for humans and for camels are in preclin- ical trials. Adenoviruses Currently there are 54 adenovirus types classified in six groups (A–F). Adenoviruses in subgroups A to D cause respiratory, ocular, hepatic, genitourinary, or gastrointestinal system disease in immunocompe- tent or immunocompromised individuals. Only respiratory diseases are considered here. Productive replication and excretion of infectious virus can occur for a prolonged period (see next). In addition, adenoviruses can es- tablish chronic persistence or ‘latency’, the virological basis and clin- ical significance of which is poorly understood. Epidemiology Adenovirus infections are common during childhood (usually sero- types 1, 2, 5 in early childhood, 3 and 7 during school years or later), but continue to occur throughout life. Reinfection with the same serotype occurs but is usually asymptomatic. Serotypes 1, 2, 5, and 6 are typically endemic, types 4 and 7 more typically associated with outbreaks, and type 3 can occur in either situation. Recently, adeno- virus 14p1 (previously designated 14a) has been spreading in the United States of America and elsewhere and is associated with more severe disease especially within military facilities. Clinical features Adenovirus respiratory illness often leads to upper respiratory tract infection with coryza and sore throat. Fever may last up to 2 weeks. The sore throat may be exudative and clinically difficult to differ- entiate from streptococcal infection. Adenoviral infection may pre- sent as pharyngoconjunctival fever. Otitis media is a complication in children. Unlike other respiratory viral infections, adenoviruses may be associated with elevated white blood cell counts (exceeding 15 × 109/litre), C-reactive protein, or erythrocyte sedimentation rate, and thus more easily confused with bacterial diseases. Though uncommon, pneumonia can occur sporadically or in epi- demics (e.g. caused by serotypes 4 and 7), particularly in closed com- munities such as the military where stress and physical exertion may predispose to lower

respiratory tract involvement. Community out- breaks of adenoviral pneumonia have been reported. Radiological appearance varies from diffuse to patchy interstitial infiltrates and pleural effusion may be present. Adenovirus type 7 pneumonia can lead to permanent lung damage, including bronchiectasis, bron- chiolitis obliterans, and unilateral hyperlucent lung syndrome. Adenoviral infection may disseminate and present as ‘septic shock’ in neonates. Manifestations in immunocompromised pa- tients include hepatitis (especially in liver transplant recipients), colitis and haemorrhagic cystitis (in stem cell and organ transplant recipients) in addition to pneumonia. The serotypes associated with disease in these patients may differ from those typically found in the immunocompetent patient, and include the subgroup B2 serotypes 11, 34, and 35. With improving control of other common viral dis- eases of immunocompromised patients (e.g. cytomegalovirus), the role of adenovirus infections is being increasingly appreciated. Isolation or PCR detection of an adenovirus from a clinical spe- cimen presents a challenge in interpretation. Adenoviruses are ex- creted for a prolonged period after initial infection, especially, but not exclusively, from faeces. In children, one-third of patients shed viruses for longer than 1 month and 14% longer than 1 year. The clinical significance of a positive result depends on the specimen, the method, and the serotype. Isolation of viruses from the respiratory tract carries greater significance than that from faeces. Patients who have symptomatic adenoviral diseases have higher viral loads than those with asymptomatic carriage. Thus, a rapidly growing virus, a positive antigen detection test from a respiratory specimen (both re- flecting higher virus load), or a detectable serological response all point to greater clinical significance.

8.5.1 Respiratory tract viruses 729 Immunocompromised patients might be infected with unusual serotypes. The detection of the virus in the peripheral blood or in multiple body sites suggests greater clinical significance and is an indication that therapeutic intervention needs to be considered. Treatment and prevention Most adenoviral infections in immunocompetent patients are self- limited and require no specific therapy; however, some infections, especially but not exclusively in immunocompromised patients, are severe and life-sthreatening. Intravenous cidofovir has been used for treatment of adenoviral infections in the immunocompromised, but nephrotoxicity and neutropenia limit its use. Orally administered brincidofovir (lipid ester derivative of cidofovir) appears to provide better clinical outcome with fewer side effects, but clinical trials are ongoing. Live attenuated oral vaccines containing serotypes 4 and 7 (associ- ated with outbreaks in military conscripts) are now used for military personnel in the United States and are safe and effective, but not li- censed for general use. Respiratory syncytial virus Respiratory syncytial virus (RSV) infects human and nonhuman primates and was first isolated from a chimpanzee with a ‘cold’. The virus has two surface glycoproteins on its envelope (G and F) and the immune responses to them correlate with protection. Two sub- groups (A and B) are recognized on the basis of antigenic differences of the G glycoprotein. Epidemiology Over two-thirds of infants acquire RSV infection during the first year of life. Of patients hospitalized with RSV disease, 75% are younger than 5 months. The peak of morbidity occurs around 2–4 months of age, a time when passive maternal antibodies protect against most other viral infections. It is associated with significant morbidity worldwide and to between 66 000 and 200 000 deaths annually, pre- dominantly in low- and middle-income countries. Primary infec- tion does not lead to solid immunity and reinfection is common. The first reinfection can still be associated with lower respiratory tract involvement. Subsequent reinfection occurs throughout life leading to asymptomatic or upper respiratory tract infection. However, sig- nificant diseases may result in the immunocompromised or elderly. Immunity Both antibody and cell mediated immunity are important in pro- tection. Antibody to the

G protein prevents attachment of viruses to the cellular receptor, but immunity to the F protein is required to prevent cell to cell spread via fusion of virally infected cells. Cell mediated immunity is important in eliminating established viral infection. Pathogenesis The virus leads to a ballooning degeneration of the ciliated epithe- lial cells, lymphocytic infiltration, and necrosis of the epithelium. There is oedema and increased secretion from the mucous cells and the formation of plugs of mucous and cellular debris in the bronchi- oles. This results in obstruction and air trapping leading to collapse or overdistension of the distal alveoli. Cells throughout the respira- tory tract are affected but the alveoli are spared unless there is RSV pneumonia. The pathogenesis of RSV bronchiolitis still remains controversial. Severe RSV bronchiolitis is strongly associated with subsequent childhood asthma. RSV appears to promote type 1 hypersensitivity responses following subsequent exposure to unrelated antigens. Clinical features RSV infections of infants may lead to bronchiolitis and pneumonia. Bronchiolitis in infants is associated with expiratory wheeze, sub-costal recession, hyperinflation of the chest, nasal flaring, and hyp- oxia with or without cyanosis. Fever is not prominent in one-half of the patients. Complete obstruction of a small airway leads to subsegmental atelectasis. Apnoea can occur (particularly in prema- ture infants or in those <3 months of age) and might precede the de- velopment of bronchiolitis. Interstitial pneumonitis is uncommon but carries a bad prognosis. Otitis media is a common complication of RSV infection in children. Infants at highest risk from severe RSV disease are those aged under 6 months, those with pre-existing con- genital heart disease, chronic lung diseases (e.g. bronchopulmonary dysplasia), and those born premature. Infection in adults is often asymptomatic or leads to upper re- spiratory tract infection. However, during the RSV season, it is an important cause of lower respiratory tract infection in adults and elderly people and it is estimated to cause 2 to 9% of the hospitaliza- tions and deaths associated with pneumonia in elderly individuals. Much of this morbidity is clinically indistinguishable from influenza. RSV (as well as parainfluenza and influenza) infections in the immunocompromised patient can be life threatening. They usu- ally occur during community outbreaks, but a significant propor- tion are nosocomially acquired. The disease typically commences as an upper respiratory tract infection but can progress to involve the lower respiratory tract with more serious consequences. Factors that increase risk of disease progression appear to include stem cell and organ transplant recipients who acquire the infection in the period prior to engraftment and oncology patients with neutrophil counts less than 0.5 × 109/litre. Those immunocompromised by HIV appear to tolerate community acquired respiratory viruses better than on- cology patients and transplant recipients. Treatment and prevention Ribavirin has activity against RSV in vitro. Administration of small particle aerosols via a mist tent, mask, oxygen hood, or ventilator has been recommended because it results in much higher concen- trations in the respiratory tract than can be achieved by intravenous administration. However, there seems little therapeutic benefit of ribavirin therapy in RSV disease in immunocompetent children or adults. In patients at high risk for severe RSV disease such as stem cell transplant recipients, inhaled ribavirin together with intra- venous immune globulin (selected batches with high neutralizing antibody titre) appeared to be beneficial when compared to histor- ical controls. Intermittent delivery (2 hours' therapy every 8 hours) appeared to be more effective in preventing progression to lower re- spiratory tract disease than continuous administration. Ribavirin is a potential teratogen and there are concerns over healthcare worker exposure. Oral ribavirin is currently being explored as an alternative to inhaled ribavirin in this setting.

 Monthly intravenous administration of a polyclonal immune globulin enriched in neutralizing antibodies to RSV (RespiGam) or a humanized monoclonal

antibody to RSV (palivizumab) during the RSV season protects against disease of the lower respiratory tract and otitis media in children with pre-existing risk factors. Palivizumab appears to be more effective than RespiGam and there is less of a problem with fluid overload in children with chronic heart disease. High-titre RSV intravenous immunoglobulin by itself is ineffective in treatment of established RSV disease. Newer modifications de- rived from Palivizumab with higher virus neutralizing competence (Motavizumab; MEDI-524) and longer half-life in the circulation (MEDI-557) have been developed but are not licensed for clinical use, in part because of increased cutaneous side effects observed with Motavizumab. Candidate vaccines for RSV are undergoing clinical trials at pre- sent but none is yet available for routine use. Experience of early trials with inactivated RSV vaccines that led to enhanced RSV dis- ease, rather than protection continues to haunt the field. Parainfluenza virus Parainfluenza viruses, despite their name, are not related to influ- enza viruses, and are more akin to respiratory syncytial virus with which they are classified (Table 8.5.1.1). They carry two envelope glycoproteins: HN containing both haemagglutinin and neuramin- idase activity, and F carrying fusion activity. Epidemiology The total impact on hospitalization of children by all four types of parainfluenza viruses taken together is similar to that of RSV but, in contrast to RSV, their impact is in later infancy and childhood. In temperate countries, parainfluenza virus type 3 occurs annu- ally and infects two-thirds of all infants in their first year of life. Parainfluenza types 1 and 2 tend to occur in alternate years and infection is acquired more slowly over childhood. Reinfection with parainfluenza viruses occurs, but rarely leads to lower respiratory tract infection. Pathogenesis The virus is confined to the respiratory epithelial cells, macrophages, and dendritic cells within the respiratory tract. Dissemination is rarely documented even in immunocompromised patients. Immunity Reinfection with parainfluenza viruses continues throughout life. Presence of virus-specific IgE in nasopharyngeal secretions has been implicated in the development of parainfluenza croup or bronchiolitis. Clinical features Parainfluenza type 1 predominantly causes croup, while types 2 and 3 also cause bronchiolitis and pneumonia. Croup (or laryngotracheobronchitis) in children is associated with fever, hoarseness, and a barking cough, and may progress to inspiratory stridor due to narrowing of the subglottic area of the trachea. The differential diagnosis is epiglottitis due to Haemophilus influenzae type b. Parainfluenza type 4 infection is less common, but causes bronchiolitis and pneumonia in children, often in those with underlying disease. Reinfection in adults, when symptomatic, is a coryzal illness with hoarseness being prominent. Parainfluenza viruses (type 3 in par- ticular) are significant causes of lower respiratory tract infection in adults when the virus is active in the community. As with RSV, parainfluenza viruses cause problems in immuno- compromised patients. Lower respiratory tract involvement is associated with wheezing, rales, dyspnoea, and diffuse intersti- tial infiltrates, and a fatal outcome in one-third of patients with stem cell transplants. When pneumonia occurs, the histological appearance of the lung is that of a giant cell or an interstitial pneumonia. Treatment and prevention The need for specific antiviral therapy arises, particularly in the im- munocompromised. Ribavirin is effective in vitro and was associ- ated with a reduction of viral replication in vivo in anecdotal cases but there are no controlled trials documenting its clinical efficacy. DAS181 is a sialidase that removes the sialic acid receptors neces- sary for parainfluenza virus attachment to the cell membrane. It is currently in clinical trials for treatment of parainfluenza disease in immunocompromised patients. There are no options for prevention at present, either using vac- cines or passive immunization. A live attenuated bovine-derived vaccine strain is currently undergoing clinical trials. Human metapneumovirus Human metapneumovirus (HMPV) belongs to the genus Metapneumovirus within the virus family Paramyxoviridae, sub- family Pneumovirinae. It closest known relative is the avian pneumovirus, an upper respiratory

tract disease of turkeys and among human viruses is RSV which also belongs to the subfamily Pneumovirinae. It was first recognized in 2001 but is a virus that has circulated unrecognized in humans for many decades. There are at least two serotypes A and B which are antigenically distinct and ap- pear to provide partial cross-protection. Epidemiology The virus is ubiquitous and most children have been infected with one or both serotypes by the age of 5 years. HMPV is a common cause of hospitalization of children under 5 years of age and ac- counted for 12% of all lower respiratory tract infection hospitaliza- tion in one long-term study. However, the incidence in any given year may vary widely. The peak age for HMPV morbidity is between 6 and 12 months, which is later than that for RSV (2–4 months). Symptomatic reinfection is common through life. Infection is com- monest in the winter months in temperate regions and in late spring or summer in subtropical areas. Clinical manifestations Clinical features of HMPV are similar to that of RSV and range from upper respiratory tract infection to bronchiolitis and pneumonia. In common with rhinovirus and RSV, HMPV appears to trigger ex- acerbations of asthma. Diarrhoea, vomiting, rash, febrile seizures, conjunctivitis, and otitis media have been reported. HMPV has on

8.5.1 Respiratory tract viruses 731 one occasion been isolated as the sole pathogen from the brain in a patient with encephalitis. Risk factors for severe HMPV disease in children are: aged less than 2 years, gestational age less than 37 weeks, and underlying comorbidities. HMPV can cause respiratory disease in elderly or immunocom- promised individuals, and those with underlying conditions at any age. Since HMPV is difficult to grow in vitro, laboratory diagnosis is reliant on the detection of viral RNA in clinical specimens by mo- lecular methods. Treatment and prevention There are currently no available vaccines. As with RSV, the F and G proteins are the main targets of the neutralizing antibody response and while the former is antigenically conserved, the latter is more variable. Thus the F protein has been the focus of vaccine devel- opment. Ribavirin has comparable in vitro activity against HMPV as against RSV but there is no clinical trial data that demonstrates therapeutic efficacy. Influenza viruses Influenza viruses contain a segmented RNA genome. Types A, B, and C are antigenically distinct; of these, types A and B are clin- ically important causes of human disease. The viral envelope con- tains two glycoproteins, the haemagglutinin (H) and neuraminidase (N) which are critical in host immunity. While protective antibody to H and N are largely subtype specific, antibody to conserved re- gions of the H stalk region appear to provide cross-subtype protec- tion and are currently being targeted for passive immunotherapy and vaccine development. The M2 transmembrane protein is also found on the virion surface and can provide broadly cross-reactive immunity following experimental immunization but does not ap- pear to elicit a significantly protective host response following nat- ural infection. Human influenza viruses are designated by the virus type, place of isolation, strain designation, year of isolation, and the H and N antigen subtype, for example, A/Sydney/5/1995 (H3N2). There are two lineages of influenza B, the Yamagata and Victoria lineages, which are antigenically distinct with only partial cross-protection. Epidemiology The H and N genes of influenza types A and B undergo mutational change resulting in the emergence of antigenic variants (‘antigenic drift’). Every few years, a variant successful in evading the prior im- munity of the human population emerges, to cause a global epidemic. Influenza viruses have a marked winter seasonality in temperate re- gions, making the disease burden of the virus more obvious. The more diffuse seasonality in tropical and subtropical regions leads to an obscuring of the clinical impact of the virus, leading to the il- lusion in some quarters that influenza is less significant in warmer climates. However, careful epidemiological studies demonstrate that the burden of mortality and morbidity in temperate and tropical re- gions are very similar. In those 65 years or

older, influenza is as- sociated with approximately one excess death per 1000 population annually in both the temperate and tropical regions. In aquatic birds, the natural reservoir of the virus, 16 H and 9 N subtypes of influenza A are found. Recently, influenza viruses have been found in bats that carry H17, H18 and N10, N11 subtypes. From 1918 to 1957, human influenza A viruses carried H1N1 surface antigens. In 1957, this virus acquired the novel H, N, and additional polymerase gene (PB1) from an avian influenza virus through gen- etic reassortment of its segmented genome giving rise to the H2N2 subtype virus (‘antigenic shift’). As the human population lacked im- munity to these novel viral antigens, this led to the ‘Asian flu’ pan- demic. A similar reassortment event gave rise to the H3N2 virus and the ‘Hong Kong influenza’ pandemic of 1968. Although all three influ- enza pandemics of the 20th century resulted in significant morbidity and mortality, the toll exacted by the ‘Spanish flu’ of 1918 was particu- larly horrendous—over 40 million deaths, greater than that of both World Wars combined. Since influenza B (and C) have no significant zoonotic reservoirs, antigenic shift and pandemics do not occur. In early 2009, a novel H1N1 virus of swine origin gave rise to the first pandemic of the 21st century. The pandemic arose in Mexico and rapidly spread worldwide along routes of air-travel. Unlike the two previous pandemics (1957, 1968) that arose through gen- etic reassortment of an avian virus with the prevailing human sea- sonal influenza virus, the pandemic virus of 2009 arose through reassortment between swine viruses previously documented in North America (so called ‘triple reassortant’ swine viruses that con- tained virus gene segments of swine, avian and human origin) and ‘Eurasian-swine’ viruses. Although the H1 haemagglutinin of both seasonal human and swine influenza viruses was originally derived from the 1918 ‘Spanish flu’ H1N1 virus, they had antigenically di- verged during their subsequent evolution in these two hosts so that the contemporary seasonal human H1N1 virus offered little cross-protection against the pandemic H1N1 virus of swine origin. However, people born prior to the 1950s had substantial cross- protection against the novel pandemic virus, presumably derived by infection with H1N1 viruses circulating in the first half of the 20th century. Thus, the pandemic was associated with explosive out- breaks in children and young adults while there was less infection in older adults. When infection did occur, severity of disease in older adults was much more severe than that in children. Overall, the 2009 pandemic was less severe than previous pandemics. However, com- plications, severe illness, and fatalities did occur, especially in those who were pregnant or with underlying comorbidities including asthma and other lung disease, cardiovascular diseases, diabetes, neurological disorders, autoimmune disorders, and morbid obesity. While some of those with severe disease had secondary bacterial infections, others developed a primary viral pneumonia leading to acute respiratory distress syndrome. Avian viruses (e.g. subtype H5N1, H9N2, H7N7, H7N9, H5N6) can zoonotically infect humans occasionally without undergoing prior reassortment with existing human strains. Currently, an H5N1 virus that is highly pathogenic for chickens has become en- trenched in poultry flocks in several Asian and African countries and continues to zoonotically transmit to humans, often causing se- vere disease. Similarly, a descendent of this virus, H5N6 is now be- coming dominant in poultry and causing zoonotic human disease. Such transmission has so far not led to sustained human-to-human transmission, which is the prerequisite for the generation of a new pandemic. However, recent studies with experimentally mutated H5N1 viruses have shown that these viruses can acquire droplet

 transmission capacity in ferrets, the best available surrogate for vir- uses with human transmission potential. H7N9 viruses emerged in 2013 and have caused zoonotic disease, many of those with severe disease are elderly or have underlying comorbidities

(unlike H5N1 disease). Pathogenesis Viral replication occurs in the columnar epithelial cells leading to its desquamation down to the basal cell layer. The pathology typically involves the upper respiratory tract and the tracheobronchial tree. Infection results in decreased ciliary clearance, impaired phago- cyte function, and increased adherence of bacteria to viral infected cells, all of which promote the occurrence of secondary bacterial infection. While there may be differences in viral virulence, pre-existing cross-reactive immunity is a major determinant in reducing dis- ease severity. Virus dissemination outside the respiratory tract is uncommon with human influenza viruses. However, zoonotic in- fections with the avian H5N1 virus may disseminate, and virus has been often detected in the gastrointestinal tract and occasionally in the central nervous system. Immunity Infection by an influenza virus results in long-lived immunity to homologous reinfection. However, the continued antigenic change in the virus allows it to keep ahead of the host immune response. Cross-immunity to 'drifted' strains within the same H or N subtype may provide partial protection, but there is believed to be little cross- protection between different subtypes. Local and systemic antibody responses and cytotoxic T cells contribute to host protection. Clinical features The severity of influenza ranges from asymptomatic infection, through the typical influenza syndrome, to the complications of influenza. Although it cannot always be distinguished from other viral infections on clinical grounds, the typical influenza syndrome is relatively characteristic in the adult. It is associated with fever, chills, headache, sore throat, coryza, nonproductive cough, my- algia, and sometimes prostration. The onset of illness is abrupt and the fever lasts 1–5 days. The pharynx is hyperaemic but has no ex- udate. Cervical lymphadenopathy is often present and crackles or wheezing are heard in around 10% of patients. While the acute illness usually resolves in 4–5 days, cough and fatigue can persist for weeks afterwards. Common (>10% of symptomatic patients) complications of influ- enza include otitis media (in children) and exacerbation of asthma, chronic airways obstruction, and cystic fibrosis. Less common complications are acute bronchitis, primary (viral) and secondary (bacterial) pneumonia, myocarditis, febrile convulsions, encephal- opathy, encephalitis, and myositis (especially in patients with influ- enza B infection). Age, prior immunity, virus strain, the presence of underlying diseases, pregnancy, and smoking all influence mor- bidity and severity. Treatment and prevention Antiviral therapy Antiviral drugs with proven clinical efficacy for treatment of influ- enza A are the ion channel (M2) blockers that interfere with viral uncoating (amantadine, rimantadine) and the neuraminidase in- hibitors (e.g. zanamivir, oseltamivir) which block virus release from infected cells. The neuraminidase inhibitors are also active against influenza B, while amantadine and rimantadine are only active against influenza A. However, seasonal H3N2 and H1N1 viruses increasingly acquired resistance to amantadine and rimantadine and the current 2009 pan- demic H1N1 which is has now replaced the previous seasonal H1N1 virus in humans is resistant to amantadine and rimantadine. Thus, these are no longer drugs of choice in the treatment or prophylaxis of human influenza. Oseltamivir resistance to seasonal H1N1 vir- uses emerged in early 2008 and spread worldwide but this strain has largely been replaced by the pandemic H1N1 that emerged in 2009. Thus the influenza A (pandemic H1N1 virus and seasonal H3N2 viruses) and influenza B viruses now remain sensitive to oseltamivir. Although resistant pandemic H1N1 viruses have been occasionally reported, these have not so far become dominant within the human population. Zanamivir remains uniformly effective against seasonal and pandemic influenza viruses. Zanamivir is administered by inhalation and oseltamivir orally. Inhaled zanamivir can occasionally cause bronchospasm in those with underlying airways disease or asthma. In patients infected with viruses sensitive to these drugs, zanamivir or oseltamivir treatment commenced within the first 48 h of disease onset leads to a 1 to 2 days reduction in the time to alleviation of clinical symptoms and also reduces incidence of influenza

associated complications. Some studies have indicated benefit in reducing the complications of influenza even for patients in whom treatment commenced after the second day of clinical illness. However, the sooner the drugs are used, the better the chance of clinical benefit. With a virus such as the highly pathogenic H5N1 virus which can disseminate beyond the respiratory tract, a systemically administered drug (oseltamivir) is likely to be superior to one administered by inhalation (zanamivir). Oseltamivir provides clinical benefit in H5N1 disease, earlier commencement being associated with improved outcome. Parenteral therapy (intravenous peramivir or zanamivir) may be preferable for treatment of severe influenza. Intravenous peramivir is presently licensed for clinical use in Japan, South Korea, and United States. Baloxavir marboxil is a virus endonuclease inhibitor (with mech- anisms of action that is different to other licensed influenza drugs) and is approved for use in Japan. Aspirin should be avoided in children with influenza because of the increased risk of Reye's syndrome. Vaccines Influenza vaccine is a trivalent or quadrivalent vaccine containing antigens from the two currently circulating subtypes of human influ- enza A (H3N2 and H1N1) and B viruses. Trivalent vaccines would have the lineage of influenza B (Victoria or Yamagata) considered most likely to be dominant in the forthcoming influenza season while the quadrivalent vaccines include both Victoria and Yamagata lin- eage viruses in the vaccine. To keep abreast of change in the surface antigens of the virus, vaccine composition must be modified on an annual basis and annual reimmunization is required. This updating of the vaccine is achieved through a collaborative effort of the global in- fluenza virus surveillance network coordinated by the World Health Organization (WHO). As a result of this surveillance, the WHO

8.5.1 Respiratory tract viruses 733 makes recommendations of candidate vaccine viruses twice annually for vaccine production for the northern and southern hemispheres. Vaccines currently in use are based on antigen derived from vir- uses grown in embryonated eggs or (less commonly) cell cultures and contain detergent-treated virus (split virus vaccines) or puri- fied surface antigens (subunit of surface antigen vaccines). These vaccines have fewer side effects than killed vaccines containing the whole virus which were used in the past and are licensed for use in anyone 6 months of age or older. Previously unvaccinated children require two doses at least 1 month apart, whereas a single dose ap- pears adequate for adults. These vaccines are generally safe, the most common side effect being soreness at the injection site lasting a few days. Vaccine efficacy is best when there is a good antigenic match between the vaccine and outbreak virus. Adjuvented (e.g. MF59) vaccines are used to enhance immunogenicity in older people or for dose-sparing in pandemic contexts. An intranasally administered, cold-adapted, live attenuated vac- cine is now also licensed for use in those aged 2 to 49 years and offers the advantages of broader cross-protection across antigenic drifted viruses as well as easier administration and greater patient acceptability. Immunogenicity and clinical protection are better in healthy young adults compared to patients with chronic renal failure and immunocompromised or elderly patients (all groups most at need of the vaccine). However, the vaccine is still effective in reducing in- fluenza and pneumonia-related hospitalization and mortality in eld- erly people and is cost-saving. An additional option for protecting such high-risk individuals is the immunization of children and care- givers in contact with these individuals. In young adults, vaccination is associated with decreased absenteeism from work. The duration of protection is limited and therefore vaccine administration should be timed to precede the expected peak of influenza activity. Influenza vaccine recommendations vary from country to country. Most countries recommended annual seasonal influenza vaccine for those groups at highest risk of influenza related complications including (1) those aged 6 months to 5 years of age; (2) those aged 65 years or older; (3) pregnant women who will be in the second or third trimester during the influenza season; and (4) those with chronic

medical conditions including persons with chronic disorders of pulmonary or cardiovascular systems (except hypertension), those with renal dysfunction, haemoglobinopathies, metabolic disorders, or immunodeficiency, and those aged 6 months to 18 years who are on long-term aspirin therapy. Furthermore, vaccine is also recom- mended for healthcare workers and for persons living or caring for those at high risk, who may transmit influenza to such high-risk in- dividuals. Some countries (e.g. United States) recommend influenza vaccine to all ages over 6 months of age, irrespective of risk factors as long as there are no contraindications to vaccination. Bocavirus and polyomavirus KI and WU Human bocavirus is a member within a newly discovered genus Bocavirus within the family Parvoviridae. As with other parvoviruses, they are relatively resistant to inactivation by acid or alkaline pH or moderate heat (e.g. 56°C). Molecular detection by PCR in respiratory clinical specimens is the main option for diagnosis. The virus can also be sometimes detected in serum. There are four species of human bocaviruses (HBoV). There is evidence demonstrating an association between HBoV1 and respiratory disease in children, while HBoV2 is associated with gastroenteritis. However, because HBoV1 is shed in the human respiratory tract for prolonged periods, HBoV1 infec- tions are often (>80%) coinfections with other respiratory pathogens. High viral loads and viremia are often associated with symptoms and viremia may be associated with systemic manifestations such as en- cephalopathy. The peak age of detection is in children aged 6 months to 2 years and occasionally in adults. KI and WU are two novel polyomaviruses recently discovered in the respiratory tract of patients with acute respiratory infections. There are found in a proportion of children and adults with acute re- spiratory infection but often found as coinfections with other known respiratory pathogens. Their contribution to disease causation is still unclear. Nosocomial infection Respiratory viruses are efficient nosocomial pathogens. Though paedi- atric units face the brunt of the problem, adult wards are not exempt. Transmission can occur from patient to patient, patient to staff, and staff to patient, with visitors making their own contribution. Although influenza and RSV are the most notorious among the endemic respira- tory viruses, even rhinoviruses cause problems when transmitted to immunocompromised patients. Once infected, immunocompromised patients have a prolonged period of viral shedding and pose a signifi- cant risk of transmission to other high-risk patients. Transmission of many respiratory virus infections occurs by large respiratory droplets gaining access to the mucosa of a susceptible in- dividual. Large respiratory droplets have a relatively short dispersal range (<1 m). On the other hand, direct hand contact is an important means of transmission within healthcare settings and adherence to strict hand-washing is the most critical preventive measure. Gloves will only be effective if they are changed between patients. Cohorting infected patients, either by symptoms (during the outbreak season) or by rapid viral diagnostic results, is useful. Influenza A vaccination of healthcare workers, especially those caring for high-risk children, is to be recommended. Staff education is vital, including awareness of the fact that some of these viruses manifest themselves as a mild ‘cold’ in adults, and that infected staff members can transmit to pa- tients under their care. The most dramatic example of the impact of nosocomial trans- mission with a respiratory virus occurred with SARS and MERS where healthcare facilities served as a major hub of virus transmis- sion. Much of this transmission was preventable by implementation of good infection control and prevention practices including droplet and contact precautions, although protection from small particle aerosols was important when carrying out aerosol-generating pro- cedures such as intubation. FURTHER READING Abed Y, Boivin G (2006). Treatment of respiratory virus infections. Antiviral Res, 70, 1–16. Dolin R, Wright PF (eds) (1999). Viral infections of the respiratory tract. Marcel Dekker, Basel, pp. 1–432.

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