Chapter 10

Respiratory Diseases

Upper respiratory tract infections are the most common type of infectious diseases and a leading cause of outpatient illness *(1,2)*.

Serious pneumococcal infections are a major global health problem. The World Health Organization estimates that more than 1.6 million people—including more than 800,000 children under the age of 5—die every year from pneumococcal infections. Nearly all of these deaths occur in the world's poorest countries. Pneumococcal meningitis is the most severe form of pneumococcal disease and one of the most fatal childhood illnesses. In developing countries, it kills or disables 40% to 70% of children who get it (http://www3.niaid.nih.gov/research/topics/bacterial/AboutPneumococcalDisease.htm).

The primary causes of death from pneumococcus are pneumonia, in which fluid fills the lungs, hindering oxygen from reaching the bloodstream; meningitis, an infection of the fluid surrounding the spinal cord and brain; and sepsis, an overwhelming infection of the bloodstream by toxin-producing bacteria.

It is estimated that each adult in the United States will experience two to four respiratory infections annually *(1)*. Persons older than 65 have the highest rate of pneumonia admissions.

Although serotypes of the rhinoviruses account for 20% to 30% of episodes of the common cold, the specific causes of most upper respiratory infections are still undefined.

Pneumonia remains an important cause of morbidity and mortality for nonhospitalized adults despite the widespread use of antimicrobial therapy. There are no accurate numbers of episodes of pneumonia occurring annually in ambulatory patients. However, pneumonia ranks as the sixth leading cause of death in the United States. In younger adults, the atypical pneumonia syndrome is the most common clinical presentation *(1)*.

Mycoplasma pneumoniae is the most frequently identified causative agent. Other less common agents include *Legionella pneumophila*, influenza viruses, adenoviruses, and *Chlamydia*.

The pathogens responsible for community-acquired pneumonias are changing. Thus, about four decades ago, *Streptococcus pneumoniae* accounted for the majority of community-acquired infections. Today, a broad array of community-acquired pathogens have been implicated as etiologic agents for respiratory infections, including *Legionella* species, Gram-negative bacilli, *Haemophilus influenzae*, *Staphylococcus aureus*, and nonbacterial pathogens *(1)*.

10.1 Adenoviruses

The adenoviruses represent a group of pathogens found in all regions of the world *(3)*. In addition to human adenovirus types, there are simian types, and there are other types, such as bovine, avian, canine, and murine (rodent). Many of them have induced malignancy in certain species.

A family of more than 42 serotypes of human adenoviruses has been associated with a wide variety of infections, including respiratory infections, conjunctivitis, hemorrhagic cystitis, and gastroenteritis.

Primary adenovirus infections with serotypes 1, 2, and 5 (parts of subgenus C) are common in infancy. The infection is usually restricted to the upper respiratory tract, and the adenovirus may persist after infancy in tonsillar, adenoidal, and other lymphoid tissues. Although not very common, infections of the central nervous system such as meningoencephalitis have been reported as complicating infections of the respiratory tract.

Nosocomial hospital outbreaks of adenovirus infections have been reported in both pediatric and adult units. In addition, acute respiratory disease associated with adenovirus in the military is also well documented *(2)*.

10.1.1 Adenovirus Modulation of the Immune Response

Several interesting *in vitro* studies have revealed the ability of some adenovirus early proteins to modulate the host's immune responses by interfering with the expression of major histocompatibility complex (MHC) class I

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antigens *(4)*. Taken into account, these protein-protein interactions indicate that inhibition of the normal processing and transport of the MHC antigens would result in their reduced expression on the cell surface *in vivo*. Because class I MHC antigens are necessary for cytotoxic T-lymphocyte recognition of virus-infected cells, a reduction in the level of cell surface MHC antigens may not only modulate acute adenovirus pathogenicity *(5)* but also play a role in the establishment of viral persistence and latency *(4)*.

10.1.2 Adenovirus Infections in Immunocompromised Hosts

Although immunocompromised patients are no more at risk for adenovirus infections than are immunocompetent persons, in immunocompromised patients these infections are manifested by higher morbidity and mortality *(3)*. Patients (renal transplant recipients, hematologic malignancies, and AIDS) have shown increased incidence of infections involving serotypes 11, 34, 35 (subgenus B1), and 43 (subgenus D). Other studies have revealed serotype 5 (subgenus C) as the frequent cause of serious infections in patients undergoing chemotherapy, in severe combined immunodeficiency (SCID), and in children receiving liver transplants *(3)*. In addition, adenoviruses of subgenus C have been implicated in cases of disseminated infections in immunocompromised host disease.

Although cell-mediated immune deficiency appears to be a major predisposing factor for severe adenovirus disease, overwhelming infection cannot be limited to a particular immune defect, and the diagnosis should be considered in a broad range of immunocompromised hosts. Adenovirus infections can also be a consequence of reactivation of persistent infection acquired during childhood.

Clinical manifestations include pharyngitis, pneumonia, hematuria, diarrhea, liver dysfunction, disseminated intravascular coagulation, hepatitis, and multiorgan involvement *(3)*. Fulminant hepatitis has been diagnosed in association with AIDS and inherited immunodeficiency syndromes and after liver or bone marrow transplantation. Frequent co-infections with HSV, CMV, or both have been recognized.

10.2 Mycoplasma pneumoniae

Mycoplasma pneumoniae is among the smallest free-living microorganisms, being intermediate in size between bacteria and virus *(6)*. Its small genome and small size is the cause of diagnostic difficulties. The organism is not visible on Gram stains and does not grow on standard bacteriologic media.

Based on cultural isolation directly from the affected site, in combination with one or more additional diagnostic tests, there can no longer be doubt that *M. pneumoniae* causes pneumonia that can be fatal in all age groups and that in some persons this same organism has the ability to produce invasive infection resulting in protean clinical manifestations. A common cause of pharyngitis and bronchopneumonia, *M. pneumoniae* may also cause fulminant pneumonia, cardiac disease, arthritis, dermatologic conditions, and CNS disease *(7)*.

10.3 Bordetella pertussis

Bordetella pertussis, the causative agent of pertussis (whooping cough), is a very small Gram-negative aerobic coccobacillus that appears singly or in pairs. The bacterium colonizes the cilia of the mammalian respiratory epithelium. In general, it is thought that the bacterium does not invade the tissues. However, recent evidence has shown the presence of *B. pertussis* in alveolar macrophages.

Whooping cough is a relatively mild disease in adults, although it can in some cases become incapacitating *(8)*. On the other hand, it has a significant mortality rate in infants *(8)*. Until immunization was introduced in the 1930s, whooping cough was one of the most frequent and severe diseases in infants. However, since the early 1980s, the reported cases of whooping cough have increased steadily *(9–11)*.

10.4 Respiratory Syncytial Virus

The respiratory syncytial virus (RSV) remains the most common cause of viral lower airway disease in infants and children *(12)*. It is a medium-sized membrane-coated RNA virus that can exert a significant immunosuppressive effect, thereby preventing the development of effective immunity by the host *(13)*.

Although symptomatic RSV-induced disease is most often associated with the very young, the virus may be found in the respiratory secretion of infected persons at any age.

Compared with immunocompetent hosts, immunocompromised patients, either children or adults, are at greater risk of developing much more severe lower respiratory tract infection due to RSV *(12–15)*. Underlying conditions include solid organ (kidney, pancreas) and bone marrow transplantations and hematologic malignancies (T-cell lymphoma) *(15)*.

In HIV-related immunodeficiency in children, the RSV infection frequently resulted in pneumonia, whereas bronchiolitis with wheezing occurred rarely *(16)*.

The use of aerolized ribavirin in the treatment of RSV-induced infections, particularly in severe disease, has been well documented *(12,16)*.

10.5 Human Metapneumovirus

The human metapneumovirus (hMPV) is a recently discovered virus from the Metapneumovirus genus *(17)*. Genetically, hMPV is similar to avian pneumovirus. Serologic studies have provided evidence that hMPV is not a newly evolved virus. Instead, it has been the common but undetected cause of many human respiratory diseases for at least 50 years.

The clinical symptoms of the children from whom the virus was isolated were similar to those caused by human RSV infection, ranging from upper respiratory tract disease to severe bronchiolitis and pneumonia *(17)*. However, although initial studies have involved children, hMPV infection has been detected in adults of all ages and may account for a significant portion of persons hospitalized with respiratory infections *(18)*.

10.6 Human Parainfluenza Viruses

The human parainfluenza viruses (HPIVs) are negative-sense, single-stranded RNA viruses that possess fusion and hemagglutinin-neuraminidase glycoprotein "spikes" on their surface. There are four serotypes of HPIV (1 through 4) and two subtypes (4a and 4b) *(19, 20)*.

The HPIVs are second to RSV as common causes of lower respiratory tract infections in young children *(21)*. Like RSV, HPIVs can cause repeated infections throughout life, usually manifested by an upper respiratory tract illness (e.g., cold and/or sore throat). However, HPIVs can also cause serious lower respiratory tract disease with repeat infection (e.g., pneumonia, bronchitis, bronchiolitis), particularly in elderly and/or immunocompromised patients.

Each of the four HPIVs has different clinical and epidemiologic features. The most distinctive clinical manifestation of HPIV-1 and HPIV-2 is croup (i.e., laryngotracheobronchitis). HPIV-1 is most common in children, whereas HPIV-2 is less frequently detected. In addition, both HPIV-1 and HPIV-2 can cause other upper and lower respiratory tract illnesses. Of the other two HPIVs, HPIV-3 is more often associated with bronchiolitis and pneumonia, whereas HPIV-4 in general is less frequently detected, possibly because it is less likely to cause severe illness.

Currently, there is no vaccine to protect against HPIV infections. However, research efforts are being directed at developing vaccines against HPIV-1 and HPIV-3 infections.

10.7 Respiratory Diphtheria

Diphtheria is an acute bacterial disease caused by toxigenic strains of *Corynebacterium diphtheriae* and occasionally *C. ulcerans (22)*. The disease affects the mucous membranes of the respiratory tract (respiratory diphtheria), skin (cutaneous diphtheria), and occasionally other sites (eyes, nose, vagina).

In the prevaccine era, children were at higher risk for respiratory diphtheria. Recently, diphtheria has primarily affected older children and adults in the sporadic cases reported in the United States (0 to 5 cases annually) and in the largest outbreaks in Russia and the newly independent states of the former Soviet Union *(23)*. The latter have reported outbreaks such as the one that began in 1990 involving more than 150,000 cases.

Myocarditis, polyneuritis, and airway obstruction are common complications of respiratory diphtheria. Unlike cutaneous diphtheria, death occurs in 5% to 10% of the respiratory cases *(23)*.

10.8 Chlamydia pneumoniae

Chlamydia pneumoniae is an important cause of an acute respiratory infection but can also be associated with chronic disease *(24)*. Because *Chlamydia pneumoniae* is distinct from other *Chlamydia* species, a new name has been proposed for this bacterium, *Chlamydophila pneumoniae.*

According to CDC estimates, although the overall incidence is unknown, each year an estimated 2 million to 5 million cases of pneumonia and 500,000 pneumonia-related hospitalizations occur in the United States. Although all ages are at risk, the infection is most common in school-age children. Re-infection throughout life appears to be common (http://www.cdc.gov/ncidod/dbmd/diseaseinfo/chlamydiapneumoniae_t.htm).

The clinical manifestations of *Chlamydia* pneumonia or bronchitis will start with little or no fever and the gradual onset of cough. Less common presentations include pharyngitis, laryngitis, and sinusitis. The spectrum of illness can range from asymptomatic infection to severe disease. In addition, according to some investigators, *C. pneumoniae* infection may be associated with atherosclerotic vascular disease, as well as with Alzheimer's disease, asthma, and reactive arthritis.

10.9 Pseudomonas aeruginosa and Cystic Fibrosis

Pseudomonas aeruginosa is a hydrophilic bacterium that is commonly found in moist environments, such as sink drains and vegetables.

P. aeruginosa is the predominant respiratory pathogen in patients with cystic fibrosis (CF), but means by which the organism is acquired is controversial *(24)*. Most patients with CF are ultimately infected with *P. aeruginosa*, and once acquired the infection is not readily eradicated *(25)*. The unique tropism of *P. aeruginosa* for the CF respiratory tract has not been adequately explained: competing and complementary hypotheses have been postulated, but none of these theories has been widely accepted as the single unifying explanation for the peculiar propensity of *P. aeruginosa* to infect the CF airway *(25)*.

It has been suggested that the peculiar "CF phenotype" of *P. aeruginosa* evolves in the CF respiratory tract during chronic infection after patients become culture-positive for a more typical phenotype—nonmucoid, lipopolysaccharide, smooth, and motile. Therefore, it seems logical to postulate that patients with CF can acquire bacteria with the typical phenotype from the environment and that transition to the "CF phenotype" will occur under the conditions found in the CF endothelial space *(26)*.

It is estimated that more than 90% of cystic fibrosis patients colonized with *P. aeruginosa* will succumb to the disease. The median age of survival is in the mid-thirties, and 40% of cystic fibrosis patients are age 18 and over *(27)*.

10.10 Bacterial Meningitis

Meningitis is a serious infection of the fluid in the spinal cord and the fluid that surrounds the brain caused by either a virus or a bacterium. Knowing whether meningitis is caused by a virus or a bacterium is important because of differences in the seriousness of the illness and the treatment needed.

Viral meningitis is usually a mild illness. It clears up within 1 to 2 weeks without specific treatment. Viral meningitis is also known as *aseptic meningitis*.

Bacterial meningitis, also known as *meningococcal meningitis*, is a much more serious, even severe, disease that can result in brain damage and even death. It is most commonly caused by one of three types of bacteria: *Haemophilus influenzae* type b (Hib), *Neisseria meningitides,* and *Streptococcus pneumoniae*. Worldwide, there are estimates of 1.2 million cases annually with a death toll of about 135,000. Especially dangerous is meningococcal meningitis in sub-Saharan Africa, where the disease causes severe epidemics, as well as in Europe, the Americas, and New Zealand *(28)*.

The bacteria are spread by direct close contact with the discharges from the nose or throat of an infected individual (http://www.cdc.gov/ncidod/dbmd/diseaseinfo/meningococcal_g.htm).

Before the 1990s, Hib was the leading cause of bacterial meningitis, but new vaccines being given to children as part of their routine immunizations have reduced the occurrence of serious Hib disease. Today, together with *Streptococcus pneumoniae*, *Neisseria meningitidis* are the leading source of bacterial meningitis worldwide that results in serious morbidity and mortality, mainly in children and young adults *(23)*. New data have shown an increased risk for freshman college students living on campus.

Meningitis caused by *Neisseria meningitides* is also called *meningococcal meningitis,* whereas meningitis caused by *Streptococcus pneumoniae* is known as *pneumococcal meningitis.*

The bacteria often live harmlessly in a person's mouth and throat. In rare instances, however, bacteria can break through the body's immune defenses and travel to the fluid surrounding the brain and the spinal cord. There they began to multiply quickly. Soon thereafter, the thin membrane that covers the brain and spinal cord (meninges) becomes swollen and inflamed, leading to the classic symptoms of meningitis.

In persons over age 2, common symptoms include high fever, headache, and stiff neck. In advanced illness, bruises will develop under the skin and spread quickly. In newborns and infants, the typical symptoms of fever, headache, and neck stiffness may be difficult to detect. Other signs in infants may be inactivity, irritability, vomiting, and poor feeding. As the disease progresses, *patients of any age* can have seizures. Advanced bacterial meningitis can lead to brain damage, coma, and death.

10.10.1 Treatment of Bacterial Meningitis

Pneumococcal infections are becoming more difficult to treat as bacteria become resistant to some of the most commonly used antibiotics. Antibiotic resistance has economic as well as clinical consequences. Overuse of antibiotics leads to increased resistance and threatens the effectiveness of existing therapy, which in turn increases the cost of treatment by requiring the use of more expensive antibiotics.

Data from a recently published study suggest that the problem of pneumococcal disease will increase in the wake of increasing HIV infection. Data from a South African study show that children with HIV/AIDS are 20 to 40 times more likely to get pneumococcal disease than are children without HIV/AIDS (http://www3.niaid.nih.gov/research/topics/bacterial/AboutPneumococcalDisease.htm).

If detected early, bacterial meningitis may be treated effectively with vaccines. New, lifesaving pneumococcal vaccines are safe and highly effective in preventing pneumococcal disease.

Since 2000, when infants in the United States began receiving routine vaccination against pneumococcal disease, the country has nearly eliminated childhood pneumococcal

disease caused by vaccine serotypes. In addition, vaccination of infants has reduced the spread of pneumococcal bacteria, so that adults have less contact with pneumococci and are thus indirectly protected from pneumococcal disease.

There are vaccines against Hib, some strains of *N. meningitides*, and many types of *S. pneumoniae.* The vaccines against Hib are very safe and effective. The vaccine against *N. meningitides* (meningococcal vaccine) is not routinely used in adults and is relatively ineffective in children under age of 2. It is used mainly to control outbreaks of some types of meningococcal meningitis. The vaccine against *S. pneumoniae* (pneumococcal meningitis) is not effective in persons under 2 years of age but is recommended for all persons over age 65 and younger persons with certain medical problems.

Routine vaccination with meningococcal vaccine is recommended for college students, as well as other high-risk populations (29).

10.11 Recent Scientific Advances

Novel Cytotoxin of Mycoplasma pneumoniae May Explain the Cause of Clinical Signs and Symptoms. Unlike many bacterial pathogens, *Mycoplasma pneumoniae* is not known to produce classic toxins, and precisely how *M. pneumoniae* injures the respiratory epithelium has remained unknown. However, recently the identification of a virulence factor (MPN372) has been reported *(30)* that is possibly responsible for the airway cellular damage and other sequelae associated with *M. pneumoniae* infections in humans. MPN372 encodes a 68-kDa protein that possesses ADP-ribotransferase (ART) activity. Furthermore, a dramatic seroconversion to MPN372 was observed in patients diagnosed with *M. pneumoniae*–associated pneumonia, indicating that this toxin is synthesized *in vivo* and possesses highly immunogenic epitopes *(30)*.

10.12 NIAID Involvement in Respiratory Diseases Research

The NIAID supports research on more effective prevention and treatment approaches to control pneumonia and its causes (http://www3.niaid.nih.gov/healthscience/ healthtopics/pneumonia/research.htm), including:

- Developing and testing vaccines and treatments for the disease-causing microbes that cause pneumonia
- Stimulating research on the structure and function of these microorganisms
- Developing better and more rapid diagnostic tools
- Understanding the long-term health impact respiratory pathogens have in various populations
- Examining the effect of vaccines in high-risk populations
- Determining how pneumococcus causes disease and becomes resistant to antibiotics

NIAID research has made important contributions to developing the pneumococcal conjugate vaccine for children. This vaccine helps to prevent pneumococcal diseases in newborns and toddlers and is the latest advance in developing vaccines against common bacterial infections.

10.12.1 The Gambia Pneumococcal Vaccine Trial

NIAID also supports studies to develop and evaluate improved pneumococcal vaccines for children worldwide. In one such study, NIAID researchers worked with the government of The Gambia and scientists from several international research institutions to test a pneumococcal conjugate vaccine. Health care experts have consistently identified pneumococcus as the most common cause of bacterial pneumonia in The Gambia. In a pattern typical of many developing areas, infant and child mortality rates in The Gambia are high, acute respiratory infections are a leading cause of death, and pneumococcus is the most common cause of these infections. Results of a 4-year, randomized, controlled clinical trial showed that the vaccine reduced childhood mortality by 16% in children who received the pneumococcal conjugate vaccine. The vaccine contained 9 of the pneumococcal serotypes (subtypes) that are most common in The Gambia. The vaccine was 77% effective in preventing infections caused by the vaccine serotypes (www.niaid.nih.gov/dmid/gambia).

The Gambia Pneumococcal Vaccine Trial was the first major randomized, controlled vaccine clinical trial in nearly 20 years to show a statistically significant reduction in overall child mortality. Findings indicate that vaccinating infants against *Streptococcus pneumoniae* could substantially reduce death and illness among children in developing countries, including in rural areas with limited access to public health systems. If used widely, a pneumococcal conjugate vaccine could prevent hundreds of thousands of child deaths each year.

The Gambia Pneumococcal Vaccine Trial Partners. The study was supported by a broad coalition of international partners including the National Institute of Allergy and Infectious Diseases/National Institutes of Health; the British Medical Research Council/United Kingdom; the London School of Hygiene and Tropical Medicine; WHO; the U.S. Agency for International Development; the U.S. Centers for Disease

Control and Prevention; Wyeth-Lederle Vaccines; and the Program for Appropriate Technology in Health (PATH) Children's Vaccine Program.

10.13 Clinical Trials

- Since 2003, NIAID continues to support preclinical and clinical studies to control selected human respiratory pathogens through two 7-year contracts (Bacterial Respiratory Pathogens Research Unit; BRPRU) to the University of Iowa and the Baylor College of Medicine. Studies at the University of Iowa involve pneumococci, meningococci, group A streptococci, pseudomonas, *Chlamydia pneumoniae*, and nontypeable *Haemophilus influenzae* (http://www.uihealthcare.com/news/news/2003/09/15respiratory.html). Studies at the Baylor College of Medicine involve viral pathogenesis and evaluation of new viral vaccines and therapeutics against influenza, RSV, and SARS (http://www.bcm.edu/molvir/eidbt/eidbt-mvm-flu.htm).
- A randomized, double-blind, placebo-controlled trial to evaluate the effects of zinc supplementation in children age 6 to 36 months hospitalized with acute pneumonia is under way at the Mohimbili Hospital in Dar-es-Salaam, Tanzania. The presence of pneumonia will be radiographically confirmed (http://www.clinicaltrials.gov/ct/show/NCT00133432;jsessionid=02E7D36B5FAD07DE08E3546B86B4D78A?order=9).
- A randomized, controlled, Phase III efficacy trial (co-sponsored by NIAID, WHO, USAID, Children's Vaccine Program at PATH, and the MRC in London) was successfully completed in The Gambia in 2005 (http://www.niaid.nih.gov/dmid/gambia/default.htm).
- Rhinosinusitis is a common health problem with significant patient morbidity and lost productivity, in which antibiotics are frequently prescribed, often unnecessarily. A randomized clinical trial is under way to evaluate the effectiveness of a 10-day course of amoxicillin versus placebo in patients with a clinical diagnosis of acute bacterial rhinosinusitis. The study will evaluate symptoms, disease recurrence, satisfaction with health care, and direct costs (http://clinicaltrials.gov/ct/show/NCT00377403;jsessionid=34221EDAA8AE01841C7B59D0D21EC014?order=10).

References

1. Garibaldi, R. A. (1985) Epidemiology of community-acquired respiratory tract infections in adults. Incidence, etiology, and impact, *Am. J. Med.*, **78**(6B), 32–37.
2. Gray, G. C., Callahan, J. D., Hawksworth, A. W., Fisher, C. A., and Gaydos, J. C.(1999) Respiratory diseases among U.S. military personnel: countering emerging threats, *Emerg. Infect. Dis.*, **5**(3), 379–387.
3. Georgiev, V. St. (1998) Adenoviruses. In: *Infectious Diseases in Immunocompromised Hosts*, CRC Press, Boca Raton, FL, pp. 171–179.
4. Flomenberg, P. R., Chen, M., and Horwitz, M. S. (1987) Characterization of a major histocompatibility complex class I antigen-binding glycoprotein from adenovirus type 35, a type associated with immunocompromised hosts, *J. Virol.*, **61**(12), 3665–3671.
5. Doherty, P. C. and Zinkernagel, R. M. (1975) H-2 compatibility requirement for T-cell-mediated lysis of target cell infected with lymphocytic choriomeningitis virus, *J. Exp. Med.*, **141**, 1427–1436.
6. Cassell, G. H., Clyde, W. A., and Davis, J. K. (1985) Mycoplasmal respiratory infections. In: *The Mycoplasmas*, vol 4 (Razin, S. and Barile, M. F., eds), Academic Press, Orlando, FL, pp. 65–106.
7. Cassell, G. (1995) Severe mycoplasma disease—rare or underdiagnosed? *West. J. Med.*, **162**(2), 172–175.
8. Jenkinson, D. (1995) Natural cause of 500 consecutive cases of whooping cough: a general practice population study, *Lancet*, **310**, 299–302.
9. Cherry, J. D., Brunell, P. A., Golden, G. S., and Karzon, D. T. (1988) Report of the task force on pertussis and pertussis immunization-1988, *Pediatrics*, **81**(6), 933–984.
10. Pertussis Report (2005), *Morb. Mortal. Wkly Rep.*, **53**(52), 1213–1220.
11. Tanaka, M. (2003) Trends in pertussis among infants in the United States, 1980–1999, *J. Am. Med. Assoc.*, **290**, 2968–2975.
12. Georgiev, V. St. (1998) Respiratory syncytial virus. In: *Infectious Diseases in Immunocompromised Hosts*, CRC Press, Boca Raton, FL, pp. 191–198.
13. Stark, J. M. (1993) Lung infections in children, *Curr. Opin. Pediatr.*, **5**, 273–280.
14. Ogra, P. L. and Patel, J. (1988) Respiratory syncytial virus infection and the immunocompromised host, *Pediatr. Infect. Dis. J.*, **7**, 246–249.
15. Englund, J. A., Sullivan, C. J., Jordan, M. C., Dehner, L. P., Vercillotti, G. M., and Balfour, H. H., Jr. (1988) Respiratory syncytial virus infection in immunocompromised adults, *Ann. Intern. Med.*, **109**, 203–208.
16. Chandwani, S., Borkowsky, W., Krasinski, K., Lawrence, R., and Welliver, R. (1990) Respiratory syncytial virus infection in human immunodeficiency virus-infected children, *J. Pediatr.*, **117**, 251–254.
17. van den Hoogen, B. G., de Jong, J. C., Groen, J., Kuiken, T., de Groot, R., Fouchier, R. A. M., and Osterhaus, A. D. M. E. (2001) A newly discovered human pneumovirus isolated from young children with respiratory tract disease, *Nat. Med.*, **7**, 719–724.
18. Falsey, A., Erdman, D., Anderson, L. J., and Walsh, E. E. (2003) Human metapneumovirus infections in young and elderly adults, *J. Infect. Dis.*, **187**, 785–790.
19. Collins, P. L., Chanock, R. M., and McIntosh, K. (1995) Parainfluenza viruses. In: *Fields Virology*, 3rd ed. (Fields, B. N., Knipe, D. M., and Howley, P. M. eds.), Lippincott-Raven, Philadelphia, pp. 1205–1241.
20. Glezen, W. P. and Denny, F. W. (1997) Parainfluenza viruses. In: *Viral Infections in Humans: Epidemiology and Control*, 4th ed. (Evans, A. and Kaslow, R. eds.), Plenum, New York, pp. 551–567.
21. Counihan, M. E., Shaym D. K., Holman, R. C., Lowther, S. A., and Anderson, L. J. (2001) Human parainfluenza virus-associated hospitalizations among children less than five years of age in the United States, *Pediatr. Infect. Dis. J.,* **20**(7), 646–653.
22. Respiratory Diphtheria Caused by *Corynebacterium ulcerans*—Terre Haute, Indiana, 1996 (1997) *Morb. Mortal. Wkly Rep.* **46**(15), 330–332.

23. Morbidity and Mortality Report for Pertussis Disease (2002) *Morb. Mortal. Wkly Rep.*, **51**(04), 73–76.
24. Govan, J. R. W. (2000) Infection control in cystic fibrosis: methicilin-resistant *Staphylococcus aureus*,*Pseudomonas aeruginosa* and the *Burkholderia cepacia* Complex, *J. R. Soc. Med.*, **93**, 40–45.
25. Speert, D. P., Campbell, M. E., Henry, D. A., Milner, R., Taha, F., Gravelle, A., Davidson, A. G. F., Wong, L. T. K., and Mahenthiralingam, E. (2002) Epidemiology of *Pseudomonas aeruginosa* in cystic fibrosis in British Columbia, Canada, *Am. J. Respir. Clin. Care Med.*, **166**, 988–993.
26. Speert, D. P., Farmer, S. W., Campbell, M. E., Musser, J. M., Selander, R. K., and Kuo, S.(1990) Conversion of *Pseudomonas aeruginosa* to the phenotype characteristic of strains from patients with cystic fibrosis, *J. Clin. Microbiol.*, **28**, 188–194.
27. Saiman, L. and Siegel, J. (2004) Infection control in cystic fibrosis, *Clin. Microbial. Rev.*, **17**(1), 57–71.
28. Rosenstein, N. E., Perkins, B. A., Stephens, D. S., Popovic, T., and Hughes, J. M. (2001) *Meningococcal* diseases, *N. Engl. J. Med.*, **344**(18), 1378–1388.
29. Centers for Disease Control and Prevention (2005) Prevention and control of *meningococcal* disease: recommendations of the Advisory Committee on Immunization Practices (ACIP), *Morb. Mortal. Wkly Rep.*, **54**(RR-7), 1–21.
30. Kannan, T. R. and Baseman, J. B. (2006) ADP-ribosylating and vacuoling cytotoxin of *Mycoplasma pnaumoniae* represents unique virulence determinant among bacterial pathogens, *Proc. Natl. Acad. Sci. U.S.A.,* **103**(17), 6724–6729.