Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 57 Respiratory Diseases

Alberto Matteelli and Nuccia Saleri

KEYPOINTS

- The emergent viral respiratory infectious diseases can spread throughout the world because people can be exposed in one place and be half a world away a day later when they become symptomatic
- The estimated monthly incidence of acute febrile respiratory tract infections is 1261/100 000 travelers
- Lower tract respiratory infections account for 50% of all RTI in travelers
- There are no definitive factors associated with an increased risk of acquiring respiratory infections
- High-risk groups such as infants, small children, the elderly and subjects with chronic tracheobronchial or pulmonary disease are at increased risk of developing severe clinical consequences should infection occur
- Prevention of RTI in the traveler usually relies on vaccines
- Travel to endemic countries is associated with an increased risk for infection with *M. tuberculosis,* while risk for disease is unknown

INTRODUCTION

Respiratory diseases represent a frequent,[1] potentially life-threatening[2] health problem in travelers, and a reason for concern due to the possibility of importation of infections such as influenza, diphtheria, or tuberculosis.[3–5]

This chapter gives a general overview of the pathogens causing respiratory tract infections (RTI), their clinical presentation and standard management procedures. Some details are given for the etiologic agents responsible for outbreaks in travelers. A few diseases with limited tropical distribution which may represent a specific hazard for travelers to these destinations are also shortly discussed. Tuberculosis is presented in a separate paragraph later in the chapter.

CAUSATIVE AGENTS AND CLINICAL PRESENTATION

It is generally assumed that travelers are infected by the same sort of organisms of the respiratory tract regardless of the destination of travel. The resulting clinical picture is determined by the combined effect of the type of causative agent and the site of the inflammatory response. Multiple signs are usually combined in a given patient but it is often possible to distinguish upper from lower tract infections.

Usual causative agents of acute upper respiratory tract infections are listed in Table 57.1. Most of the cases are due to viruses and evolve as uncomplicated disease resolving without specific treatment.

Table 57.1 Most common etiologic agents of upper respiratory tract infections

	Viral	Bacterial
Coryzal syndrome	Rhinovirus Parainfluenza virus Respiratory syncytial virus Enterovirus Coronavirus	
Laryngitis	Influenza virus A and B Parainfluenza virus Rhinovirus Adenovirus	*Corynebacterium diphtheriae* *Haemophilus influenzae* *Branhamella catarrhalis*
Pharyngitis	Rhinovirus Adenovirus Coronavirus Enterovirus Influenza virus Parainfluenza virus Respiratory syncytial virus Epstein-Barr virus Herpes Simplex Virus Human immunodeficiency virus type 1	*Streptococcus pyogenes* *Group C β-hemolytic Streptococci* *Corynebacterium diphtheriae* *Mycoplasma pneumoniae* *Chlamydia pneumoniae*

The infection of the nasal airways determines an acute coryzal illness, traditionally referred to as a common cold, presenting with nasal discharge and obstruction, sneezing and sore throat. It is caused by a group of infections, all of viral nature, for the most part belonging to five families: rhinovirus, parainfluenza virus, respiratory syncytial virus, enterovirus (especially coxsackievirus A21), and coronaviruses. Acute laryngitis is characterized by hoarseness of voice with a deepened pitch with possible episodes of aphonia. Often these signs are associated to those of coryza and pharyngitis. The large majority of episodes are due to viral agents, including parainfluenza virus, rhinovirus, influenza virus, and adenovirus. Bacteria, represented by *C. diphtheriae, Branhamella catarrhalis* and *Haemophilus influenzae*, may rarely play a role in this condition, and are almost invariably associated to pharyngitis. The acute inflammation of the pharynx causes the pharyngitis syndrome, which presents with soreness, scratchiness and irritation. Most cases are of viral etiology, and appear in the context of the coryzal syndrome or influenza, rather than as an isolated entity. Rhinovirus and coronavirus are the most common causative agents, but adenovirus and herpes simplex virus may also be implicated, usually in more severe clinical cases. Other viral causes of pharyngitis in the context of a generalized infection are Epstein–Barr virus (EBV) and the human immunodeficiency virus (HIV). The pharyngitis/tonsillitis syndrome is caused by bacteria in

Table 57.2 Most common etiologic agents of pneumonia

Bacterial	Fungal	Viral	Other
Streptococcus pneumoniae	*Histoplasma capsulatum*	Influenza A	*Coxiella burnetii*
Staphylococcus aureus	*Coccidioides immitis*	Influenza B	*Mycobacterium tuberculosis*
Haemophilus influenzae	*Aspergillus* spp	Adenovirus type 4 and 7	*Ascaris lumbricoides*
Mixed anaerobic bacteria		Hantavirus	*Strongyloides stercoralis*
Escherichia coli		Corona virus	*Paragonimus westermani*
Klebsiella pneumoniae			
Pseudomonas aeruginosa			
Legionella spp.			
Mycoplasma pneumoniae			
Chlamydia pneumoniae			
Chlamydia psittaci			

up to 15% of the cases, the most important agent being represented by *Streptococcus* pyogenes (Group A β-hemolytic streptococcus) and, more rarely, *Corynebacterium diphtheriae*.

Lower respiratory infections are characterized by bronchial and pulmonary parenchyma involvement. The most common etiologic agents of pneumonia are listed in Table 57.2. Viruses commonly occur, but bacteria are responsible for a significant proportion of community acquired cases. *S. pneumoniae* and *H. influenzae*, as well as *M. pneumoniae* and *C. pneumoniae* are most frequent but pneumonia may also be caused by mycobacterial, fungal, and parasitic agents. Young children may sometimes be affected by severe forms of tracheobronchitis, characterized by dyspnea accompanied on inspiration by characteristic stridulous notes caused by inflammation in the subglottic area. The large majority of cases are due to viruses with a few being due to diphtheria, *H. influenzae* or *M. pneumoniae* infection.

A list of common complications of RTI is presented in Table 57.3. Otitis media is the most common, especially among young children. *Streptococcus pneumoniae* is responsible for most such cases.

Table 57.3 Common complications of respiratory tract infections and common etiologic agents of otitis media

Complications	Agents of otitis media
Otitis media	*Streptococcus pneumoniae*
Sinusitis	*Streptococcus Group A*
Epiglottitis	*Staphylococcus aureus*
Mastoiditis	*Haemophilus influenzae*
Periorbital cellulitis	*Branhamella catarrhalis*
Peritonsillar abscess	
Retropharyngeal abscess	
Adenitis	

EPIDEMIOLOGY

Steffen estimated the monthly incidence of acute febrile respiratory tract infections to be 1261/100 000 travellers.[1] In that analysis RTI ranked third after travelers' diarrhea and malaria among all infectious problems of travelers. However, that rate, which is equivalent to 0.2 episodes/person per year, is much lower than the incidence of common respiratory diseases among adults in the USA, which is around four episodes per person per year.[6] The difference is likely to be attributable to under-reporting among travelers, because a large proportion of RTI are mild, not incapacitating, and do not require hospital care.

The incidence of RTI is similar in developing and developed nations. In a classic study comparing incidence rates in travelers to different areas RTI occurred in 3.7/1000 travel days to Latin America, 3.5/1000 to Oceania, and 3.1/1000 to the Caribbean.[7]

In the literature, there are large variations in the proportion of respiratory infections among all causes of illness in returning travelers. Comparison among studies, however, is difficult and differences are likely to reflect diverse diagnostic procedures and definition of syndromes rather than true epidemiologic differences. Still, RTIs consistently rank in the highest belt of most frequently diagnosed conditions. Incidence rates have been recently reviewed by Denny and Kallings, ranging from 4–42%.[8] As they correctly point out, proportions made on a population group should be differentiated from those made on an ill group. A few additional reports have become available since the above review has been published. Among 1469 British package holiday tourists 7.6% had respiratory infection, and this condition was over-ranked by travelers' diarrhea only.[9] Respiratory illness occurred in 26% of 748 travelers from the USA, second only to diarrhea.[10] O'Brien et al. studied a group of 232 sick travelers at a tertiary hospital in Australia mainly returned from Asian destinations: RTIs were second after malaria, accounting for 24% of the cases.[11] Leder and colleagues have found that 7.8% of ill travellers overall had respiratory illness in the GeoSentinel Surveillance System.[12]

In that series, lower tract infections accounted for 50% of all RTIs, and were almost equally distributed between bacterial pneumonia and influenza.[11] Bacterial pneumonia was significantly more common in patients aged >40 years with an OR of 5.5. One-quarter of upper tract infections were due to group *A streptococcus*. In a multicenter hospital study in Italy including 541 travelers with fever, 8.1% of the patients had a respiratory syndrome, one third of whom had pneumonia. TB was responsible for 29% of pneumonia cases. Among cases with RTI and no signs of pneumonia, malaria was the underlying disease in 11 of 27, despite the fact that malaria is reportedly not associated with respiratory symptoms.[13]

RISK FACTORS

There are no definitive factors associated with an increased risk of acquisition of respiratory infections. However, some persons are at increased risk of developing severe clinical consequences should infection occur. High-risk groups include people at the extremes of age, infants, small children and the elderly, and subjects with chronic tracheobronchial or pulmonary disease. There is convincing evidence that chilling is not an important risk factor for these diseases. The reduced pressure of inspired oxygen found on airline flights or high altitude destinations may adversely affect infants' breathing patterns.[14] It has been suggested that if a concomitant respiratory tract infection is present hypoxia can reach levels to be a significant risk for sudden infant death.

Respiratory infections are the most common diagnosis for passengers and crew seeking medical care on board ships.[15] In addition, cruise travelers are at increased risk for legionellosis, influenza or pneumococcal disease.[2] Reasons for increased susceptibility of cruise ship travelers to respiratory infections include passenger factors, such as age, underlying illnesses and physical conditions, as well as environmental factors, like the heavy use of secretional spas (increasing difficulties in maintaining safe water systems) and the confinement in relatively close quarters.[16]

TRANSMISSION

The spread of agents such as *streptococci* or *meningococci* is by direct, person-to-person contacts transmitted by large droplets. Common occurrence is as sporadic and isolated cases, because droplets are too large to contaminate the air environment, and fall quickly to the ground unless they come in contact with mucous membranes in very close proximity to the source case.

Other pathogens are transmitted by tiny droplet nuclei (<10 μm in diameter), that are dispersed widely and randomly, remain viable in the air for hours, may be inhaled and pass easily through the narrow bronchioles. These agents lead to infection in a large number of people, presenting as clusters of disease among those exposed. Influenza virus and *M. tuberculosis* disseminate in this way.

Legionella is an air-borne disease with a unique chain of transmission. It is a free living bacteria which multiplicates in water systems, forming biofilms in cooling towers, water pipe fittings, and showers. From the domestic water systems, legionella spreads to the human host in the aerosols generated by showerheads, whirlpools, or cooling systems. This transmission chain explains the existence of out-breaks in hotels and cruise ships.

MANAGEMENT OF THE RESPIRATORY SYNDROME

An example of a decision algorithm for respiratory tract infections in travelers is presented in Figures 57.1 and 57.2. A syndromic management algorithm should effectively differentiate upper from lower respiratory tract infections to anticipate causative agents and guide treatment decisions. It should also identify complications requiring specific treatment. There is no generally accepted definition for the respiratory syndrome: cough with runny nose, or either of these with any one of headache, fever or shortness of breath are widely used for study purposes.

Among upper respiratory tract infections (Fig. 57.1) the isolated coryzal syndrome is rarely a cause of medical consultation. It is easily identified through the patient history and typical manifestations, no additional diagnostic procedures are required and symptomatic treatment provides quick relief. The diagnosis of laryngitis is clinical, and antibiotic treatment is not routinely envisaged. The diagnosis of pharyngitis is also clinical. It is important to differentiate group *A streptococcal* infections in this group of patients because this condition may determine late complications which are readily preventable by antibiotic treatment. Reportedly, bacterial pharyngitis is associated with more severe pharyngeal pain, odynophagia and higher fever, with grayish-yellow exudate on the tonsils and enlarged cervical lymphatic glands. However, clinical criteria are unreliable to identify bacterial pharyngitis/tonsillitis, because a typical presentation occurs in <50% of the cases. Rapid antigen detection tests are available with reported specificity of over 90% and sensitivity of 60–95%, and should be performed on initial evaluation on specimens collected by throat swab. The need to perform a bacterial culture if a rapid test is negative is still debated. Supportive care is the only therapy for the majority of cases which are due to viruses. Antibiotic treatment is warranted

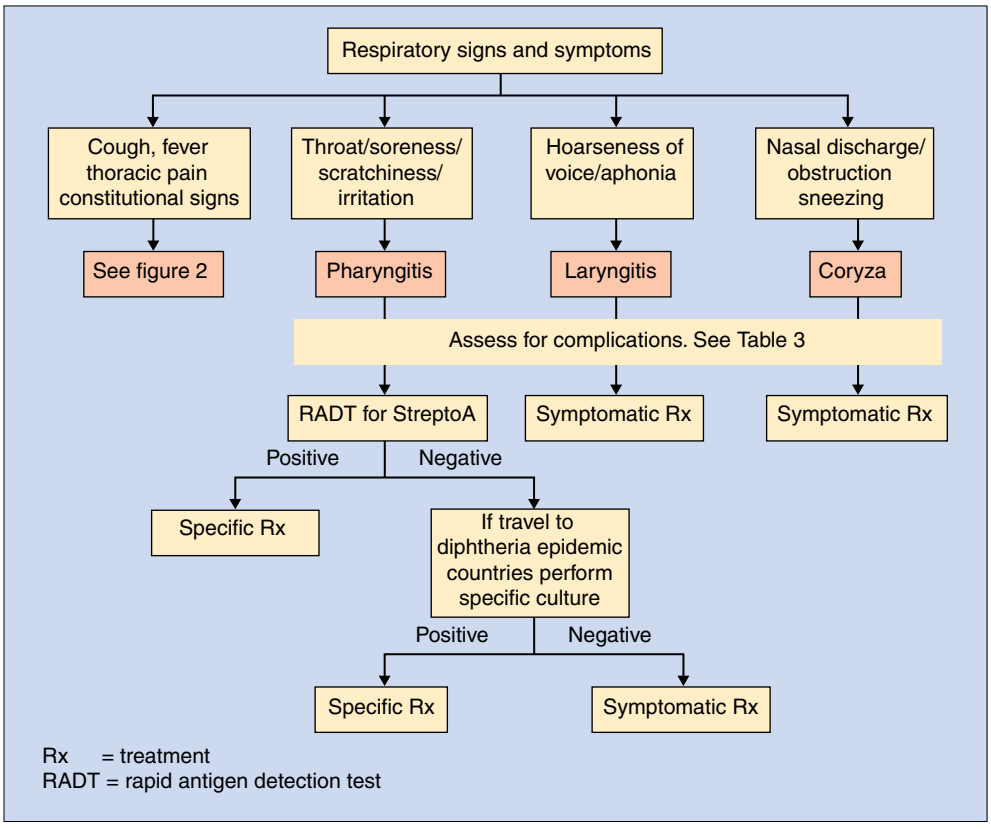

Figure 57.1: Decision algorithm for acute upper respiratory tract infections.

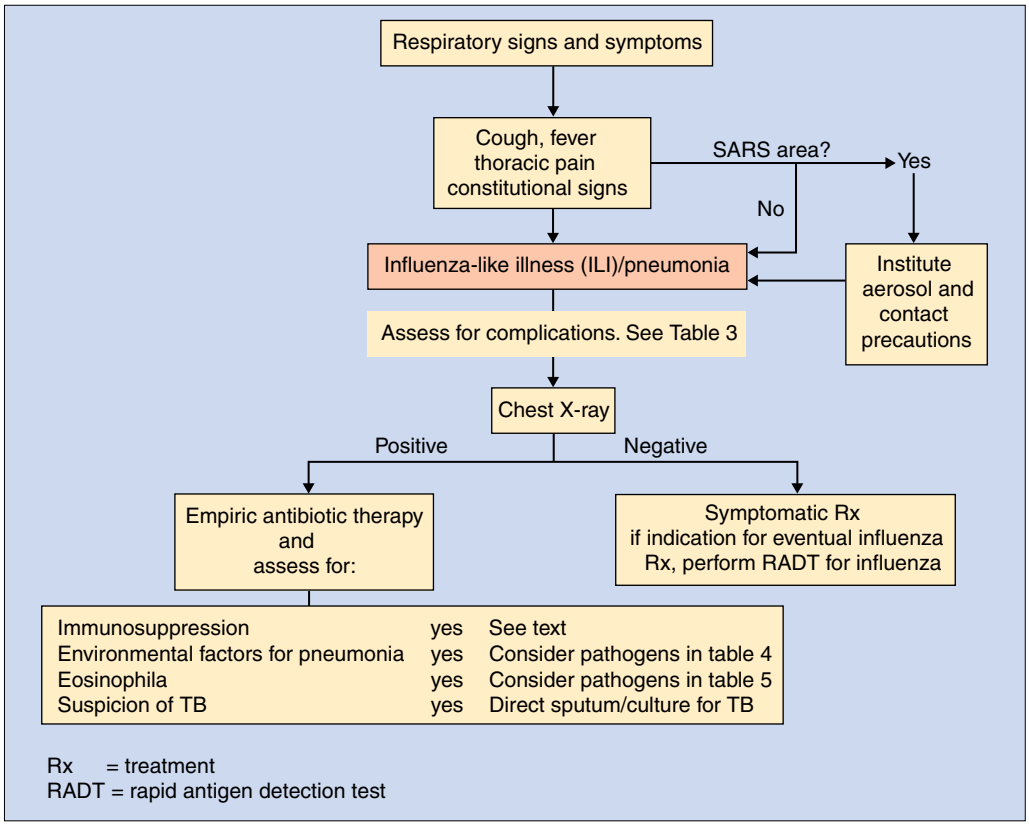

Figure 57.2: Decision algorithm for acute lower respiratory tract infections.

if the rapid test demonstrates streptococcal infection. Presumptive antibiotic treatment may be prescribed to cases when clinical suspicion of streptococcal infection is high and the clinical manifestations are severe, to be discontinued if the culture result is negative. A treatment course with penicillin for 10 days is appropriate to treat pharyngitis due to *S. pyogenes*. Diphtheria is a rare cause of pharyngitis, with potentially fatal outcome. It is characterized by thick and gray pharyngeal and tracheal membranes, bleeding upon attempted removal. Microscopic examination of direct stained pharyngeal smear is unreliable, and clinical suspicion of diphtheria must be confirmed by culture isolation of a toxigenic strain of *Corynebacterium diphtheriae*. The mainstay of therapy is diphtheria antitoxin, associated with antibiotic treatment with penicillin or macrolides.

Complications of upper RTI include focal inflammation and toxin-mediated toxicity. The most frequent forms of focal inflammation are otitis and sinusitis (Table 57.3), usually sustained by bacterial infections. *Streptococcus pneumoniae* is responsible for most cases, and initial treatment should be effective against this agent. Pharyngotonsillitis may be complicated by pharyngeal abscess which also requires prompt and appropriate antibacterial therapy. The selected treatment regimen should be effective not only against group *A streptococcus*, but also against *S. pneumoniae*, *H. influenzae*, *B. catarrhalis* and *S. aureus,* which are more troublesome agents. Protected penicillins and third generation cephalosporins may be the treatment of choice. Toxin mediated toxicity is basically observed in the case of diphtheria.

Clinical signs suggestive of pneumonia include productive cough, thoracic pain, and shortness of breath. A chest X-ray should be routinely performed, because the demonstration of an abnormal chest radiograph consistent with pneumonia differentiates a patient population that may benefit from antibiotic therapy from patient populations that will not (Fig. 57.2). Although the majority of cases with radiologic evidence of pneumonia may still have a viral infection, the proportion of cases due to bacteria is high enough to warrant systematic antibacterial treatment. The chest film is not helpful in making a specific etiologic diagnosis; however, lobar consolidation, cavitation and large pleural effusions support a bacterial cause. Pneumococcal disease is often characterized by abrupt onset of fever, cough, rapid respiration, and lobar consolidation on chest film. Atypical pneumonias caused by *M. pneumoniae* and *C. pneumoniae* are characterized by gradual onset of symptoms, cough progressive from dry to productive, chest film worse than symptoms, and normal peripheral white blood cell counts. Overall, however, clinical presentation is not specific enough to make etiologic diagnosis, and effective methods to recognize the causative agent of pneumonia are not available. The sputum Gram stain is a simple, quick and inexpensive procedure but its helpfulness for aiding in the etiologic diagnosis is unclear. The main advantages are the identification of *P. carinii* in patients with AIDS or acid-fast bacilli in patients with tuberculosis. The utility of the sputum culture is also unclear, since the procedure is insensitive, only half of patients with pneumonia may produce sputum and contamination occurs in one third. An advantage of routine sputum Gram stain and culture is that these procedures would capture rare causes of pneumonia like melioidosis. Because the cause of pneumonia cannot be determined on the basis of any specific clinical, radiographic, or laboratory parameter, antibiotic therapy is usually begun empirically. Treatment should be effective on *S. pneumoniae*, the most frequently responsible agent, and on agents of atypical pneumonia: *M. pneumoniae*, *C. pneumoniae*, and legionella infections. Amoxicillin and amoxicillin-clavulanic acid should be associated with a macrolide. Alternatively, the new respiratory tract quinolones can be used alone. Presumptive treatment should be replaced by more specific treatment when a high degree of suspicion of the etiology of diagnosis is reached.

Immunocompromised patients are susceptible to diseases which are very rarely observed in the immunocompetent host, such as

Table 57.4 Important environmental factors in respiratory tract infections

Pneumonia	
Anthrax	Biological war; exposure to cattle
Melioidosis	Travel to endemic areas
Brucellosis	Exposure to cattle
Plague	Travel to endemic areas and contact with rats
Tularemia	Hunting or other exposure to wild animals
Psittacosis	Exposure to birds
Leptospirosis	Adventurous travel
Coccidioidomycosis	Travel to endemic areas
Histoplasmosis	Exposure to bat droppings
Q fever	Exposure to infected animals
Legionnaires' disease	Ship trip or enclosure in epidemic foci
Hantavirus	Exposure to rodents
Pharyngitis	
Diphtheria	Travel to epidemic countries

P. carinii, cytomegalovirus or *Cryptococcus neoformans* pneumonia. Determining the presence of malignancy, neutropenia, chronic use of steroids or myelosuppressive agents, or the presence of HIV infection is therefore an important component of the patient history. Environmental factors may be risk markers for some specific causes of pneumonia and pharyngitis, as summarized in Table 57.4. Information on the type of recent travel is important as a history of ship cruise should alert for the possibility of legionella or influenza infections. Tropical destinations are a prerequisite to suspect exotic infections like melioidosis, paragonimiasis or fungal infections. Behavioral parameters, like possible contact with rats or bats are necessary to suspect plague/Hantavirus or histoplasmosis, respectively. Pneumonia with eosinophilia in a traveler is often suggestive of specific infections, a list of which is presented in Table 57.5. Treatment of tuberculosis should be started only following a positive sputum smear and other specimens for culture have been obtained.

Influenza is often included among the causes of lower tract respiratory infection. The definition of influenza-like illness (ILI) requires the presence of fever or feverishness with cough or sore throat. Quick laboratory evidence of influenza infection can be obtained by detection of viral antigens in nasopharyngeal aspirates. This may be important for groups of patients at increased risk of influenza morbidity and mortality. Antiviral treatment may be considered for patients with ILI aged >65 years or who have certain underlying chronic conditions like pulmonary or cardiac disease. Amantadine and rimantadine are effective against type A virus, neuraminidase inhibitors (Zanamivir and Oseltamivir) work against all human strains of influenza.

Table 57.5 Causes of pneumonia and eosinophilia

Ascaris lumbricoides
Strongyloides stercoralis
Mycobacterium tuberculosis
Chlamydia psittaci
Coccidioides immitis
Histoplasma capsulatum
Paragonimus spp
Echinococcus granulosus
Visceral larva migrans
Schistosoma spp
Dirofilaria immitis
Ancylostoma spp

Table 57.6 Prevention of respiratory tract infections in travelers

Prevention strategy	Preventable condition
Vaccine	Primary vaccination *Haemophilus influenzae* Diphtheria Influenza *Streptococcus pneumoniae* Booster Diphtheria
Early presumptive treatment	Influenza
Public health interventions	Influenza Guidelines for international response Legionellosis Alert networks (EWGLI) Guidelines for safe water systems
Behavioral interventions	Paragonimiasis Avoid eating raw crabs or crayfish Histoplasmosis Avoid bat caves Leptospirosis Avoid adventurous travel Plague Avoid contacts with rodents Anthrax/Q fever Avoid contact with cattle and sheep

PREVENTION IN TRAVELERS

Prevention of RTI in the traveler usually relies on vaccines, and, in a few specific conditions such as influenza in the elderly, on self-administered treatment to ameliorate the course of the resulting disease (Table 57.6). Public health interventions are important to minimize the risk of acquiring a new RTI, or limit the scale of epidemic outbreaks, while behavioral interventions and chemoprophylaxis play a little role.

Diphtheria is one of the major vaccine-preventable diseases, which can be virtually eliminated by effective immunization programs, using diphtheria toxoid. The primary vaccination schedule consists of 4 doses of the toxoid before 2 years of age. Boosters every 10 years are required to sustain a protective immunologic response, especially in areas of low transmission of the bacteria. Sporadic cases of diphtheria have been reported in adult travelers who had received full childhood vaccination including diphtheria toxoid.[17] A booster dose of combined diphtheria-tetanus toxoid (Td) is an acceptable option to protect travelers to countries with epidemics of the disease. Influenza virus vaccines are available against current epidemic types. In Table 57.7 are shown influenza vaccine indications and considerations.[18] Vaccination is a cost-saving intervention among the elderly and subjects with chronic cardiac and pulmonary diseases under influenza epidemic conditions, as it effectively reduces influenza-related morbidity and mortality.[19] Special groups may be considered for influenza vaccination for reasons of convenience, such as athletes participating at the Olympic games. As a consequence of the 1998 epidemic of influenza in Alaska and the Yukon Territory, The National Advisory Committee on Immunization of Canada recommended influenza vaccination for people at high risk of influenza complications before embarking on travel to destinations where influenza was likely to be circulating.[20] At the same time, some cruise lines initiated policies to vaccinate crew members to decrease the risk for influenza transmission to travelers.[21]

Table 57.7 Influenza vaccine: indications and considerations for travelers

Recommend vaccination if:
Travelers of age 6–23 months or >65 years old
Travelers of any age with any chronic or immunocompromising conditions
Travelers of any age planning to:
Go to the tropics at any time of the year
Go on cruises at any time of the year
Travel with organized tour groups at any time of the year
Travel to or within temperate climates during the flu season at that destination
Recommend vaccination if:
Traveler wishing to decrease the risk of influenza illness or the risk of having respiratory symptoms mistaken for SARS/Avian flu

Subjects who have received the influenza vaccine in the previous 6 months do not deserve to be re-vaccinated because specific antibody titers remain high for at least 6 months.[22] Vaccination against *H. influenzae* (type B only) is now part of the childhood immunization program in many industrialized countries; its possible role in adult unimmunized travelers is unclear. The capsular polysaccharide vaccine against *S. pneumoniae* is of questionable efficacy in the elderly[23] and it is not recommended in children below 2 years of age. An effective vaccine against group *A streptococcus* is currently under development but will not be available for many years.

Control measures for legionellosis are based on the application of guidelines for maintaining safe water systems in international tourist locations and cruise ships.[24] These include proper disinfection, filtration and storage of source water, avoidance of dead ends in pipes, proper cleaning and maintenance of spas, and periodic replacement of devices likely to amplify or disseminate the organism.

The early recognition of outbreaks is exceedingly important in the management of individual cases of diseases like legionellosis. The European Working Group for Legionella Infections (EWGLI) is a network created to report legionella cases diagnosed in patients who have been traveling within the likely incubation period of 2 weeks, together with geographic location of suspected source of transmission. Members of the group report cases of Legionnaires' disease to the coordinating center, which then notifies all EWGLI members of any disease cluster. Other international global and regional surveillance networks, including GeoSentinel and TropNetEurop, play a pivotal role in early detection and public warning of travel-related epidemics.[25,26]

The response to emerging influenza pandemics is an important task for public health interventions. International guidelines were established after the identification in Hong Kong of the first known human outbreak of infection by the influenza A (H5N1) virus, previously known to infect only birds. Massive efforts were put in place by international organizations for the identification and containment of the outbreak, including the slaughtering of 1.6 million chickens, the putative source of the infection.[27] Several measures can help minimize the global public health risks that could arise from large outbreaks of highly pathogenic H5N1 avian influenza in birds: (1) to halt further spread of epidemics in poultry populations; (2) to vaccinate persons at high risk of exposure to infected poultry, using existing vaccines effective against currently circulating human influenza strains; (3) to protect workers involved in the culling of poultry flocks by proper clothing and equipment; (4) To give antiviral drugs as a prophylactic measure to the same workers. The World Health Organization (WHO) does not recommend screening of travelers coming from H5N1-affected areas. WHO continues to recommend that travelers to affected areas should avoid contact with live animal markets and poultry farms, and any free-ranging or caged poultry.

Persons at high risk for complications of influenza infection who have no access to vaccination because of shortage in vaccine supplies might receive a prescription for self-administered oseltamivir, which can reduce the duration of illness and viral shedding if administered within the first 24–48 h of onset of influenza-like illness.

INFECTIONS OF THE RESPIRATORY TRACT ASSOCIATED WITH EPIDEMICS

SARS

In November 2002, reports from Guangdong Province in Southern China suggested that more than 300 cases of a mysterious, highly contagious pneumonia had occurred. This severe atypical pneumonia appeared to be particularly prevalent among healthcare workers and their families. As the condition began to spread from China, on March 13, 2003, the World Health Organization issued a global alert about the outbreak and subsequently named this condition Severe Acute Respiratory Syndrome (SARS). From November 2002 to July 2003, 8098 cases and 774 deaths were reported from 28 countries with a fatality rate of 9.6%.[28] From April 2004 to date not a single cases of SARS has been reported worldwide.

A novel coronavirus distinct from those previously reported in animals and humans causes SARS; the parent virus has not yet been discovered.[29,30] The virus is transmitted person-to-person by inhalation of droplets, but aerosol transmission may occur in 'super spreaders,' patients who are severely ill and excreting large viral loads. Since the virus can remain viable on surfaces for several days, mucous membrane contamination (i.e. conjunctiva) or ingestion have not been ruled out as possible modes of transmission. Some 60% of SARS cases occurred among healthcare workers who had not been adequately protected.[31] The incubation period of SARS is 3–11 days with a median of 5 days. The syndrome often begins with a prodrome of headache, myalgia and fatigue, progressing a day later to fever above 38°C and subsequently to a non-productive cough and/or shortness of breath. Patients may present with fever and non-specific symptoms 1–3 days before respiratory symptoms begin. Gastrointestinal symptoms (nausea, vomiting and diarrhea) occur in approximately 20% of patients.[32] In the series of 144 patients seen in Toronto hospitals, the chest X-ray was normal in 25% of individuals on admission.[33] Unilateral and bilateral infiltrates were observed in 46% and 29% of the patients, respectively. Most patients eventually developed multifocal opacities. Laboratory investigations typically show lymphopenia and to a lesser extent thrombocytopenia; during hospitalization many patients developed hypocalcemia, hypomagnesemia, hypokalemia and hypophosphatemia.

The diagnosis of SARS was based on a case definition, which included a possible contact history, fever and respiratory symptoms. Although not available for use by routine laboratories, serology and PCR used for viral RNA detection were used more and more widely during the epidemic.[34] The treatment of SARS has not yet been determined. Corticosteroid therapy and the antiviral drug ribavirin have been used most frequently with little certainty of their efficacy. Recent reports suggest that most patients recovered in spite of not receiving these drugs. The mortality rate from SARS has a median of 10%. Those with the highest mortality rate are the elderly (>60 years) and those with underlying co-morbid conditions such as diabetes and chronic lung disease.

Since healthcare providers are at the greatest risk of acquiring SARS, a high index of suspicion, based on the travel history and knowledge of current epidemics, is needed so that aerosol and contact prevention measures can be initiated even before direct contact with the patient occurs. A face shield, N-95 masks, gown, gloves and booties are recommended. All surfaces must be carefully wiped down with a disinfectant after the patient has left the room.

Prevention of SARS among travelers will be difficult during epidemic periods. The only sure way to prevent infection is to avoid locations where outbreaks have occurred. Air travel appears to be relatively safe since only 14 cases have been reported from 35 flights carrying infected passengers. Twelve occurred among passengers seated within four rows of the index case and two were flight attendants.

Avian influenza

In 2005, highly pathogenic H5N1 influenza A viruses were endemic in avian populations in SE Asia, and human cases continue to accumulate. To 5 February 2008 359 cases of Avian flu were reported in 14 countries with 226 deaths.[35]

Transmission requires direct contact with birds or their droppings. Large amounts of the virus are known to be excreted in the droppings from infected birds. Populations in affected countries are advised to avoid contact with dead migratory birds or wild birds showing signs of disease.[36]

Usually, pneumonia that occurs in patients with influenza is not directly caused by influenza virus, but is caused by bacterial infection. In human cases of avian influenza pneumonia was caused directly by the virus, it did not respond to antibiotics, and it frequently was rapidly fatal.[37]

Although currently incapable of sustained human-to-human transmission, H5N1 represents a serious pandemic threat owing to the risk of a re-assortment or mutation generating a virus with human-to-human transmissibility. If more humans become infected over time, the likelihood also increases that humans, if concurrently infected with human and avian influenza strains, could serve as the 'mixing vessel' for the emergence of a novel subtype with sufficient human genes to be easily transmitted from person to person. Such an event would mark the start of an influenza pandemic. It is impossible to anticipate when the next influenza pandemic might occur or how severe its consequences might be. If H5N1 viruses develop the ability for efficient human-to-human transmission, an influenza pandemic would likely result. Problems associated with such an event include the notion that little pre-existing natural immunity to H5N1 infection exists in the human population, that genetic sequencing shows that H5N1 is naturally resistant to the two antiviral medications most commonly used for treating influenza, and that there is no demonstration on efficacy of neuraminidase inhibitors.[38]

Influenza

Influenza is the most important of the viral respiratory infections, sustained by the influenza viruses type A and B. The virus is responsible for recurrent epidemics due to the emergence and spread of a novel type of virus. Worldwide pandemics resulting in a high number of illnesses and millions of deaths occurred in 1918, 1957, and 1968, each one lasting for approximately 2–3 years. While large epidemics are due to human viral strains, small outbreaks have been associated with avian and swine viruses.

Travelers acquire influenza both as sporadic cases and as clusters from a common source aboard ships, airplanes, or in tour groups. All described outbreaks are caused by the type A virus, and are characterized by the involvement of a large proportion of the population at risk, and the explosive nature of the epidemic. In 1998, approximately 40 000 tourists and tourism workers were affected by an influenza outbreak in Alaska and the Yukon Territory.[39] Influenza is a common infection also among *Hajj* pilgrims, with 24 000 estimated cases per *Hajj* season.[40]

Influenza is a self-limiting disease, which produces high morbidity and is responsible for lethal cases among the youngest and the eldest. The hallmark of the clinical presentation of influenza is a febrile illness with cough, resulting from involvement of trachea and bronchi. Fever characteristically lasts 3–5 days, but dry cough may persist for much longer. Pneumonia is the most frequent complication. Part of the cases are due to direct involvement of the lungs by the influenza virus, the remainder being attributable to bacterial superinfections, mainly from *S. pneumoniae, H. influenzae*, and group *A Streptococcus*. Otitis media and sinusitis are other serious complications. Complications are more frequent and severe among patients with chronic diseases of the lung or the heart. Early diagnosis of influenza can be based on rapid antigen detection tests. Viral isolation is the method of reference but it is seldom used in clinical care. Antibody determination is also rarely used for diagnosis in clinical settings. Treatment is symptomatic in most cases. For severe cases in debilitated subjects the M2 inhibitor antivirals amantadine and rimantadine are effective on type A virus, and reduce the duration of the illness and viral shedding if administered within 48 h of symptom onset. Oseltamivir is the only practical choice for self-treatment in the traveler, because M2 inhibitors have important adverse effects and zanamivir requires use of a difficult inhaler device.[18]

Legionellosis

Legionella infections occur worldwide as sporadic cases. Endemic legionellosis is responsible for approximately 2% of community acquired pneumonia; the highest incidence is in people aged over 40 years, but only a fraction of these cases are recognized. Legionellosis also presents as clusters in large, common-source, outbreaks. A number of such outbreaks have been described among travelers. A European Working Group on Legionella Infection involving 29 countries was started in 1987. During 2000–2002, a total of 113 travel-associated Legionnaires' disease clusters were reported, with the majority linked to hotels.[41] In Sweden 15–30% of all legionella infections are related to travel, either international or domestic.[42] In the UK this proportion presents an increasing trend since the 1970s, with a peak at 46%.[43] Countries whose tourist industries are expanding appear to have higher rates of infection. The Mediterranean region in Europe has been the origin of most reported outbreaks, but no area is immune from the risk, as exemplified by the recent identification of the first cluster of cases associated with a hotel in Bangkok.[44]

Transmission is air-borne, but the source of infection is the environment, rather than other persons.

The incubation period is classically considered as 2–10 days, although 16% of 188 cases described in a recent large outbreak in the Netherlands reported incubation periods exceeding 10 days.[45] The clinical spectrum is wide, ranging from subclinical to lethal manifestations. The overt picture of legionellosis is that of a lobar pneumonia with abrupt onset characterized by high fever, severe headache and confusion.[42] Patchy infiltrates are often present bilaterally. Mortality may be as high as 20% if diagnosis and antibiotic treatment are delayed. Diagnosis is challenging because sensitive and friendly diagnostic tests are not widely available. Urine antigen tests are very helpful for rapid diagnosis, but they are not widely used as legionellosis is considered a rare disease. Serological diagnosis requires a four-fold or higher rise in antibody titers in paired acute and convalescent phase sera, and its usefulness is very limited in clinical terms. Isolation of the bacteria from respiratory secretions is possible but cumbersome; however, this is essential to apply molecular techniques to match patients' isolates with those of the environment, in order to provide evidence for clusters and the common source of the infection. Macrolides are the treatment of choice, clarithromycin and erythromycin should be administered for 3 weeks to avoid relapses. Co-trimoxazole and fluoroquinolones are also effective.

Diphtheria

Diphtheria is considered eliminated in the immunized population of industrialized countries, with toxigenic strains no longer circulating among the native population. However, importation of the organism from developing countries where diphtheria remains endemic poses a constant threat, particularly among subgroups of travelers with low vaccination levels. Eastern Europe has been the theater of a large-scale resurgence of diphtheria during the 1990s, due to the collapse of the health systems and consequent disruption of the vaccination programs. Almost 20 000 cases of diphtheria were reported in 1993, mainly in the former Russia Federation and Ukraine, with cases identified in neighboring countries including Poland, Norway, Finland, and Germany.[46] Re-emergence of diphtheria has been described in susceptible travelers to these areas.[47] Travelers to endemic areas may act as asymptomatic carriers of the bacterium, and determine secondary cases in unimmunized children in non-endemic areas.[48]

Diphtheria presents as a respiratory disease with cough and fever, characterized by pseudomembranous pharyngitis with membrane formation and cervical lymphadenitis, sometimes evolving to cervical edema (bull-neck). Pharyngeal and tracheal membranes are described as thick and gray, bleeding upon attempted removal. A chest X-ray may show subglottic narrowing and bilateral lung hyperinflation. Lethal complications are due to airway mechanical obstruction at laryngeal level and to myocarditis and neuritis resulting from acute systemic toxicity caused by a toxin. Cardiac toxicity consists of both cardiac heart failure and potentially fatal arrhythmia. Clinical suspicion of diphtheria must be confirmed by culture isolation of the bacteria, which demonstrates the presence of a toxigenic strain of *Corynebacterium diphtheriae*. Microscopic examination of direct stained pharyngeal smear is unreliable. The mainstay of therapy is diphtheria antitoxin, which must be administered as early as possible to neutralize circulating, unbounded toxin. Antibiotic treatment with penicillin or macrolides is indicated to eradicate the organism and terminate toxin production. The notification of a diphtheria case must prompt the implementation of control measures to prevent the spread of toxigenic *C. diphtheriae*, including taking nose and throat swabs from close contacts, antibiotic prophylaxis, and full immunization or booster doses depending on contacts' immunization history.

TROPICAL RESPIRATORY INFECTIONS

This term identifies infectious diseases that are particularly or uniquely prevalent in tropical countries. The climate in such regions offers an ideal environment for pathogenic organisms, their vectors, or their intermediate hosts.

Melioidosis

The most common clinical manifestations of melioidosis is a localized infection with regional lymphadenitis, but community acquired septicemia and pneumonia are also common. The disease is caused by *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*), an aerobic Gram negative bipolar staining bacillus which is free living in earth and water in many tropical and subtropical countries. Melioidosis is rare outside the main endemic regions, namely SE Asia and Northern Australia. Reactivation melioidosis has been reported among tourists, immigrants and Vietnam veterans decades after leaving endemic regions. The infection is acquired by inhalation, ingestion or from contaminated injuries. Many big mammals (cows, horses, pigs) are the reservoir. Human-to-human transmission is extremely rare. Melioidosis remains a risk for travelers to endemic areas, especially in presence of recognized risk factors like adventure tours resulting in extensive exposure to wet season soils and surface water.[49]

Lung involvement consists of acute necrotizing pneumonia or chronic granulomatous or fibrosing lung disease mimicking tuberculosis. The diagnosis of pulmonary melioidosis is difficult. It might be suspected in travelers from endemic areas, though cases have reported from areas considered to be non-endemic.[50] The diagnosis can be confirmed by Gram stain and culture of respiratory specimens. The presumptive diagnosis of melioidosis may be based on a positive IHA or ELISA serology.[51,52] IHA titers above 1:80 are suggestive of active infection but can also be seen in asymptomatic subjects in endemic regions.[52] Current therapy recommendations are ceftazidime or imipenem plus trimethoprim-sulfamethoxazole, doxycycline or amoxicillin-clavulanic acid, for a period of 2–6 weeks. Maintenance therapy for 3–6 months using either trimethoprim-sulfamethoxazole, doxycycline or amoxicillin clavulanic acid is also necessary. A vaccine against melioidosis is not available, and there is no role for chemoprophylaxis. Low-risk behaviors, like avoiding bathing or walking in rice paddies and still water should be recommended for short-term travelers.

Leptospirosis

Pulmonary involvement in leptospirosis is not rare, usually manifested by a dry cough, occasionally with blood stained sputum. Although being a zoonosis of worldwide dimension the infection has significantly higher diffusion in the tropical belt.

Leptospirosis is due to several serovars of a spirochetal bacterium, *Leptospira interrogans*. Transmission occurs by accidental contact with urine, contaminated water, and soil. Clinical manifestation of leptospirosis may vary from asymptomatic infection to fulminant disease. Severe cases are characterized by liver and renal failure with mortality as high as 30% in untreated cases. Pulmonary complications often contribute to the fatal outcome: they include extensive edema and alveolar hemorrhages in the context of an ARDS episode. The radiologic findings are those of ARDS. The diagnosis requires the isolation of the bacteria from blood or urine samples. As an alternative, a microhemagglutination serological test provides evidence of the disease in coupled sera of acute and convalescent phases. Penicillin and tetracyclines are effective for the treatment of the disease.

Prevention of leptospirosis is difficult, especially in tropical areas where the disease is not limited to high-risk groups. Prevention of rodent-human contacts is important. A human vaccine and the use of tetracycline chemoprophylaxis (200 mg/week) are available but are indicated for well defined high-risk populations only.

Anthrax

Pulmonary anthrax is caused by the inhalation of spores produced by the bacterium *Bacillus anthracis*. Cutaneous disease is the commonly observed form in natural infection. The pulmonary form is of concern for the use of anthrax aerosols as a biological weapon against a civilian population, due to the possibility of rapid dissemination and rapidly fatal outcome.[53] Naturally-acquired anthrax may occur in developing countries where the risk is still significant in rural parts of Asia, Africa, Eastern Europe, South and Central America as a result of contaminated soil and a few cases have been described in travelers who import souvenirs.

Inhalation anthrax results in an extremely severe mediastinitis due to the penetration of the pathogen from the pulmonary alveoli and its spread to hilar lymph nodes. The incubation period is 2–5 days, but the spores can germinate up to 60 days after exposure. Pathogenesis is mediated by a toxin responsible for hemorrhagia, edema, and necrosis. The presenting symptoms are non-specific, with mild fever, malaise, and a non-productive cough. After a period of a few days in which the patient's condition apparently improves, a second phase begins with

high fever, respiratory distress, cyanosis, and subcutaneous edema of the neck and thorax. Crepitant rales are evident on auscultation. The chest film reveals mediastinal widening and frequently a pleural effusion. Inhalation anthrax is almost invariably fatal with a very short time between the onset of the second phase, mediastinal signs, and death. The diagnosis of inhalation anthrax is extremely difficult outside epidemic conditions. PCR and ELISA tests for a protective antigen are available at specialized centers. The most useful bacteriologic test in case of suspicion, however, is blood culture of *B. anthracis*.

Direct examination and Gram stain of the sputum specimen are unlikely to be diagnostic. A serologic ELISA test is available, although a significant increase in titer is usually obtained only in convalescent subjects who survive. Treatment of inhalation anthrax should be as early as possible to provide chances of success. *B. anthracis* is sensitive to penicillin, and penicillin 1.2 million units (or i.v. 18–24 million units daily in severe cases) or doxycycline for 7–10 days are the drug of choice for the naturally-acquired disease. In the context of biological war, because of the high likelihood that *B. anthracis* strains are engineered to be resistant to these two classes of antibiotics, the treatment of choice is ciprofloxacin 400 mg i.v. every 12 h. Ancillary treatment to sustain vascular volume, cardiac, pulmonary, and renal functions is essential in severe cases. A human inactivated cell free vaccine is available in case of biological attack. Post-exposure prophylaxis following exposure to an anthrax aerosol would require the use of ciprofloxacin for a period of 60 days.

Plague

Plague usually presents as lymphadenitis and septicemia. Pulmonary forms are rarely observed, secondary to inhalation of the causative agent, *Yersinia pestis*, from coughing patients affected by the disease. Plague is considered a re-emerging disease because of the increase of the worldwide number of reported cases, the occurrence of epidemics (such as the one in India in 1994), and the gradual expansion in areas of low endemicity (including the USA). Over 85% of the cases of 1996 were reported from Africa, where >85% of the cases occurred in just two countries, Madagascar and United Republic of Tanzania.[54] The major recent worldwide plague epidemic occurred in India, where a total of 5150 suspected pneumonic or bubonic cases occurred from August to October 1994, causing travel and trade disruption and resulting in severe economic repercussions.[55] Travelers are rarely affected by plague while visiting endemic areas; for example, no visitors were affected during the 1994 epidemic in India. Campers or visitors staying in rodent infested lodges are exposed to the highest risk of infection.

In humans, pneumonia may follow septicemia or may be a primary event in the case of air-borne transmission. Plague should be suspected in febrile patients who have been exposed to rodents or other mammals in the known endemic areas of the world. The presence of buboes in this setting is highly suspicious. The bacterium may be isolated on standard bacteriologic media from culture samples of blood and bubo aspirate. The Gram stain may reveal Gram negative coccobacilli with polymorphonuclear leukocytes. Rapid diagnostic tests like the direct immunofluorescence test for the presumptive identification of *Y. pestis* F1 antigen are of interest for the quick management of patients with the suspicion of the disease.[56] Serologic tests to detect antibodies to the F1 antigen by passive hemoagglutination assay or enzyme-linked immunosorbent assay methods are available. A four-fold increase in titer (or a single titer of 1:16 or more) may provide presumptive evidence of plague in culture negative cases. Antibiotic treatment should be started on the basis of clinical suspicion. Streptomycin 30 mg/kg per day intramuscularly in two divided doses for 10 days is the drug of choice. Whenever streptomycin is contraindicated due to allergy, tetracyclines or chloramphenicol should be administered.

A formalin-killed whole cell vaccine is licensed and available for subjects at specific risk for plague, but its efficacy is questionable. Those who may have contact with rodents in endemic areas are candidates for vaccination. Personal hygiene (avoidance of lice by using insect repellents) and safe behaviors (avoidance of contacts with rodents) represent the most important preventive measures for travelers. Plague is an internationally quarantinable disease. Pulmonary infections present a particular risk for human epidemics due to the contagiousness of the organism. Doxycycline (100 mg twice daily for 7 days) prophylaxis of family members of index cases is indicated within the standard 7-day maximum plague incubation period.

Paragonimiasis

Lung involvement is constant in paragonimiasis because the adult stage of the causative agent lives in the pulmonary district, and may survive up to 20 years in the human host. Paragonimiasis is an helmintic disease caused by trematodes of the genus *Paragonimus*: *P. westermani* is the most diffuse species. The infection is endemic in SE Asia (including Thailand, the Philippines, Vietnam, China and Taiwan), South America and Africa. The distribution is determined by the presence of the intermediate host and the human habit eating them raw. The disease is well described, though rare, in travelers to endemic regions.[57] The incubation period may vary from one to several months after exposure.

Symptoms are characterized by a chronic bronchopneumonic process with productive cough, thoracic pain and low grade fever, sometimes hemoptysis. The chest X-ray is not characteristic, and may present with single or bilateral infiltrates and cavity formation. The main differential diagnosis is with tuberculosis: in paragonimiasis, there are no constitutional signs and general conditions may remain good for several years despite persistent respiratory signs. The diagnosis requires the identification of the eggs in the sputum or in feces by the use of concentration methods. The treatment of choice is praziquantel 25 mg/kg t.i.d. for 2 consecutive days. Prevention is based on avoidance of eating raw crayfish and crabs.

Coccidioidomycosis and histoplasmosis

Coccidioidomycosis and histoplasmosis are two fungal infections acquired by the respiratory route and therefore primarily involving the respiratory system. Coccidioidomycosis is caused by inhalation of *Coccidioides immitis*, a dimorphic fungus found in the dust and soil. The pathogen is present only in semiarid regions of the Americas. Symptomatic disease develops in approximately 40% of individuals infected by *C. immitis*, presenting as a flu-like syndrome. The radiologic finding is often that of hilar pneumonia with lymphadenitis and pleural involvement. In a recently described outbreak of coccidioidomycosis in a 126-member church group traveling to Mexico the average incubation period was 12 days (range 7–20 days), and chest pain was present in 76% and cough in 66% of the affected travelers.[58] The diagnosis is serological, antibodies appear 1–3 weeks after the onset of symptoms.

Histoplasmosis is caused by infection with a soil-inhabiting dimorphic fungus, *Histoplasma capsulatum*. The agent is ubiquitous, but diffusion is higher in the tropical belt and the USA. Outbreaks of acute histoplasmosis among travelers have been repeatedly reported.[59–61] The disease may evolve as a mild, spontaneously resolving condition, but severe and systemic disease may develop in immunocompromised patients. In an outbreak of histoplasmosis among college students from the USA visiting Acapulco 229 persons developed an acute febrile respiratory illness with cough, shortness of breath, chest pain, or headache.[62] The chest X-ray may show patchy infiltrates or interstitial pneumonia. Diagnosis may be extremely difficult unless the

disease is considered in the differential diagnosis, and most cases are unrecognized and considered as bacterial bronchitis or flu. Confirmation of the disease requires testing of acute- and convalescent-phase serum specimens. A urine antigen test for histoplasmosis is not sensitive, but it is highly specific for diagnosis of acute pulmonary disease.

Both fungal infections are sensitive to the azoles (fluconazole and itraconazole) and amphotericin B.

Tuberculosis

Tuberculosis (TB) is a widely distributed infection and a leading cause of human morbidity and mortality. Travel interacts with TB increasing the risk of reactivated TB among immigrants and the risk of infection among travelers. The problem of TB among immigrants is beyond the scope of this chapter. We discuss here the risk of TB among travelers from low to high endemicity countries and that associated with air flights.

TB among travelers from low to high endemicity areas

There is mounting evidence on the association between travel and increased risk for infection with *M. tuberculosis*. Lobato first demonstrated that US children who had traveled abroad had a significantly higher probability to have a positive tuberculin skin test compared to children without a history of travel.[63] More recently Cobelens et al. have measured the risk of acquiring *M. tuberculosis* infection among long-term (≥3 months) Dutch travelers to Africa, Asia, and Latin America at 3.3% per year. This rate is very similar to that of native populations in the visited countries, and much higher than the 0.01% yearly risk in the Netherlands.[5] Other factors identified for increased TB risk among travelers were: being a healthcare worker, a longer cumulative duration of travel, and a longer total time spent in TB endemic countries.[64] Thus, this demonstrates a previously unrecognized high risk for TB infection among travelers, limited to travels with a duration of ≥3 months.

The evidence of association between travel and TB disease is, on the contrary, elusive. In the most well-known report describing health associated diseases, TB was not mentioned[1] and TB was not present in a list of causes of mortality among American missionaries in Africa.[65] We have recently actively searched for TB diagnosis among travelers in the data generated by GeoSentinel, a surveillance network of travel/tropical medicine clinics, designed to monitor global trends and disease occurrence among travelers. From January 1997 to November 2000, the system registered seven TB cases among travelers/expatriates which were likely to be linked to travel.[66] It is likely that TB cases associated with travel do occur, but they go unrecognized.

Prevention of tuberculosis in the traveler

Three possible preventive strategies against TB may be envisaged: vaccination, chemoprophylaxis, and detection and treatment of travel-acquired latent tuberculosis infection.

A vaccine against *M. tuberculosis* is available since 1921, consisting of an attenuated strain of *M. bovis*. The protective efficacy from this vaccine ranged from 0–80%, in a series of prospective studies. The general understanding of its action is that the vaccine protects against disseminated disease but does not prevent infection and, possibly, focal disease. The consequence, confirmed by clinical trials, is that BCG effectively protects against a potentially fatal form of tuberculosis in infant and child populations only.[67] Based on this knowledge, the vaccine cannot be recommended to adult travelers because of its unproven efficacy, but it might be administered to children <5 years of age who travel to TB endemic areas for periods of ≥6 months.

Chemoprophylaxis with isoniazid during travel is usually not indicated, independently from the estimate of the risk of infection, because of inconclusive evidence of the capacity of chemoprophylaxis to reduce the risk of acquisition of infection with *M. tuberculosis*.

The rationale for tuberculin skin testing and preventive therapy of latent tuberculosis infections acquired during travel is that the risk of disease following infection is highest in the first 1–2 years, and that preventive therapy is effective in eradicating dormant tubercle bacilli. Travelers acquiring the infection during travel may be identified by skin conversion in pre- and post-travel tests (Fig. 57.3). However, tuberculin skin testing and preventive therapy have several drawbacks of operational feasibility, lack of sensitivity/specificity, and poor adherence that will be discussed shortly. At present, the detection of tuberculosis infection is based on the skin reaction to the intradermal injection of *M. tuberculosis* antigens and detection of an area of induration (conventionally ≥10 mm) at 72 h. Skin-testing of travelers is useful only if the pre-travel test is negative and a post-travel test is conducted 3 months after returning home, to allow time for the immune system to mount a significant skin reaction in case of infection. This therefore requires at least two encounters with the traveler before and two after travel. The possible interference of the booster effect on the significance of a positive tuberculin test might even require two tests (four encounters) before travel,[5] though this is considered unnecessary by most. Sensitivity and specificity of the tuberculin skin test are far from optimal. Rieder estimated that the positive predictive value of a positive tuberculin test with a basic

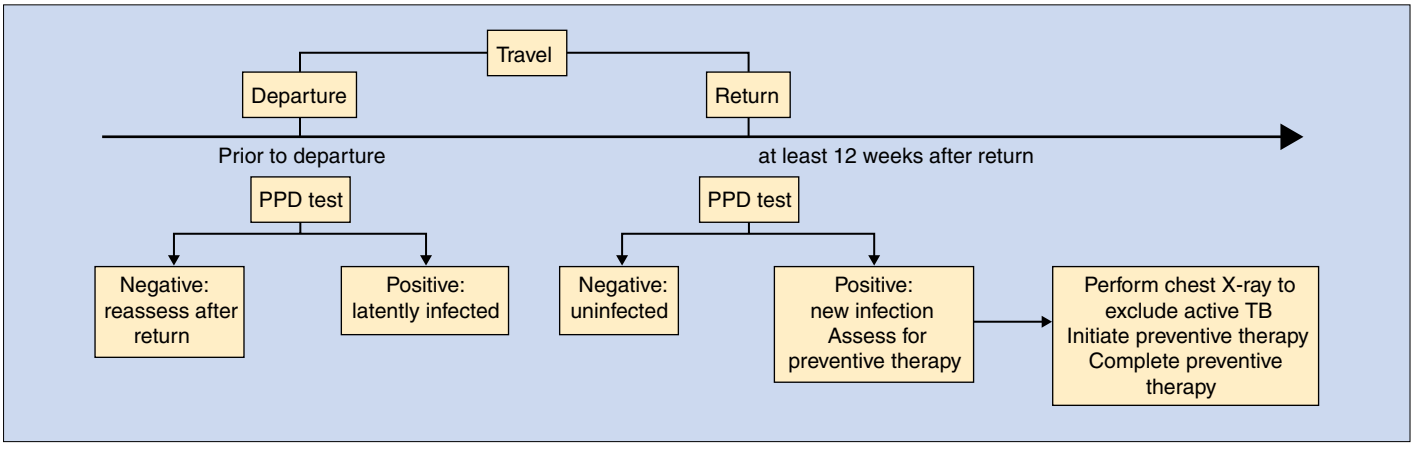

Figure 57.3: Prevention of TB disease in long-term travelers: identification and treatment of new infections.

prevalence of 2% is 16%, and is increased only marginally even by a 1% risk of infection during a travel.[68]

Until recently, there were no alternatives to the TST for diagnosing latent tuberculosis infection. Alternative tests have now emerged which measure the in vitro production of gamma-interferon by leukocytes stimulated by specific *Mycobacterium tuberculosis* antigens (such as early secretory antigenic target 6 and culture filtrate protein 10). Such tests may have advantages over the TST, in terms of higher specificity, better correlation with exposure to *M. tuberculosis*, and no cross-reactivity due to BCG vaccination and non-tuberculous mycobacterial infection. The role of these tests in clinical practice still needs to be defined.[69]

Preventive therapy carries additional operational problems. Clinical trials have consistently demonstrated that a standard course of 6–12 months of daily isoniazid is over 90% effective in preventing reactivated TB.[70] However, under field conditions adherence is less than optimal and efficacy is significantly reduced. Finally, the isoniazid chemoprophylaxis regimen is not effective against isoniazid-resistant strains, which now may represent from 5–10% of all strains in resource-poor countries. Because of all these drawbacks, Rieder has estimated that 14 travelers should be exposed to isoniazid treatment in order to eradicate a single case of latent infection.[71] In summary, a universal strategy of tuberculin testing and preventive therapy for travelers cannot be advocated, at this moment, for both economic and epidemiologic reasons.

TB and air travel

In the past few years, several episodes of potential transmission of TB infection during air travel have been reported, raising anxiety in both the general population and health authorities. As a consequence of this, WHO has produced a summary report on this issue, the main conclusion of which is that tuberculosis acquired during air travel is of little epidemiologic importance.[71] This statement is based on the review of seven investigations of 2600 persons exposed to one infectious crew member and six passengers over a total of 191 flights.[71] No active TB cases occurred, and possible transmission of infection occurred in only two instances. The risk was limited to flights of over 8 h duration, and for the seats in close proximity to the index case. In fact, airplane-cabin air is exchanged every 3–4 min in contrast to the air in offices and homes, which is exchanged every 5, and 12 min, respectively. A laminar flow ventilation system is in place on airplanes, and despite modern airplanes re-circulating up to 50% of the cabin air, this seems not to disseminate small droplet nuclei.

Prevention guidelines are that persons with infectious TB should postpone air travel. Epidemiologic investigation for contacts of infectious passengers are indicated only within 3 months from exposure for passengers on travels of >8 h duration.[71]

The risk of TB transmission on ship[72] or train[73] has been described as well, but, similarly, it is of little epidemiologic importance.

CONCLUSION

Respiratory infections represent the third most frequent health problem for international travelers. Incidence is underestimated, mainly because the majority of infections are mild and not incapacitating. Most are due to cosmopolitan agents and 'tropical' infections are rare.

Travel facilitates the spread of cluster epidemics such as influenza and legionellosis, and is associated with an increased risk of infection with *M. tuberculosis*. The route of acquisition for most respiratory infection is by direct contact, which makes prevention through behavioral interventions very difficult. Preventive therapy mainly relies on vaccines.

The clinical management of respiratory infections would greatly be enhanced by the use of standardized management algorithms, based on a better understanding of disease epidemiology. International health policies and regional and global networking can also play a pivotal role in the control of these infections.

REFERENCES

1. Steffen R. Health risk for short term travellers. In: Steffen R, Lobel HO, Haworth J, Bradley DJ, eds. Travel medicine. Proceedings of the First Conference on International Travel Medicine. Berlin: Springer-Verlag; 1989:27–36.
2. Jernigan DB, Hofmann J, Cetron MS, et al. Outbreak of Legionnaires' disease among cruise ship passengers exposed to a contaminated whirlpool spa. Lancet 1996; 275:545–547.
3. Mutsch M, Tavernini M, Marx A, et al. Influenza virus infection in travelers to tropical and subtropical countries. Clin Infect Dis 2005; 40:1282–1287.
4. Centers for Disease Control and Prevention (CDC). Fatal respiratory diphtheria in a U.S. traveler to Haiti-Pennsylvania, 2003. MMWR 2004; 52:1285.
5. Cobelens FGJ, Van Deutekom H, Draayer-Jansen IWE, et al. Risk of infection with mycobacterium tuberculosis in travellers to areas of high tuberculosis endemicity. Lancet 2000; 356:461–465.
6. Dingle JH, Badger GF, Jordan WS Jr, et al. Illness in the home: study of 25 000 illnesses in a group of Cleveland families, Cleveland: The Press of the Western Reserve University; 1969.
7. Kendrick MA. Study of illness among Americans returning from international travel; July 11–August 24, 1971 (preliminary data). J Infect Dis 1972; 126:684–685.
8. Denny FW Jr, Kallings I. Respiratory tract infections. In: DuPont HL, Steffen R, eds. Textbook of travel medicine and health. 2nd edn. Hamilton: Decker; 2001:269–279.
9. Evans MR, Shickle D, Morgan MS. Travel illness in British package holiday tourists: prospective cohort study. J Infect 2001; 43:140–147.
10. Hill DR. Health problems in a large cohort of Americans travelling to developing countries. J Travel Med 2000; 7:259–266.
11. O'Brien D, Tobin S, Brown GV, et al. Fever in returned travellers: review of hospital admissions for a 3-year period. Clin Infect Dis 2001; 33: 603–609.
12. Leder K, Sundararajan V, Weld L, et al. Respiratory tract infections in travellers: a review of the GeoSentinel Surveillance Network. Clin Infect Dis 2003; 36:399–406.
13. Matteelli A, Beltrame A, Saleri N et al. Respiratory syndrome and respiratory tract infections in foreign-born and national travellers hospitalised with fever in Italy. J Travel Med 2005; 12:190–196.
14. Parkins KJ, Poets CF, O'Brien LM, et al. Effect of exposure to 15% oxygen on breathing patterns and oxygen saturation in infants: interventional study. BMJ 1998; 316:887–894.
15. Dreake DE, Gray CL, Ludwig MR, et al. Descriptive epidemiology of injury and illness among cruise ship passengers. Ann Emerg Med 1999; 33:67–72.
16. Edelstein P, Cetron MS. Sea, wind, and pneumonia. Clin Infect Dis 1999; 29:39–41.
17. Hart PE, Lee PYC, Macallan DC, et al. Cutaneous and pharyngeal diphtheria imported from the Indian subcontinent. Postgrad Med J 1996; 72:619–620.
18. Freedman DO, Leder K. Influenza: changing approaches to prevention and treatment in travellers. J Travel Med 2005; 12:36–44.
19. Gross PA, Hermogenes AW, Sacks HS, et al. The efficacy of influenza vaccine in elderly persons: a meta analysis and review of the literature. Ann Intern Med 1995; 123:518–527.
20. National Advisory Committee on Immunisation (NACI). Statement on influenza vaccination for the 1998–1999 season: an Advisory Committee Statement (ACS). Can Commun Dis Rep 1998; 24:1–12.
21. Centres for Diseases Control and Prevention. Outbreak of influenza A infection – Alaska and the Yukon territory. MMWR 1999; 48:545–546.
22. Buxton JA, Skowronski DM, Ng H, et al. Influenza revaccination of elderly travellers: antibody response to single influenza vaccination and revaccination at 12 weeks. J Infect Dis 2001; 184:188–191.

23. Ortquist A, Hedlund J, Burman LA, et al. Randomised trial of a 23-valent pneumococcal capsular polysaccharide vaccine in the prevention of pneumonia in middle-aged and elderly people. Lancet 1998; 351:399–403.
24. Health and Safety Executive. The control of Legionellosis including Legionnaires' disease. London: Health and Safety Executive; 1991:1–19.
25. Freedman DO, Kozarsky PE, Weld LH, et al. GeoSentinel: the global emerging infections sentinel network of the international society of travel medicine. J Travel Med 1999; 6:94–98.
26. Jelinek T, Corachan M, Grobush M, et al. Falciparum malaria in European tourists to the Dominican Republic. Emerg Infect Dis 2000; 6:537–538.
27. World Health Organisation. Influenza pandemic preparedness plan. Responding to an influenza pandemic or its treatment: the role of WHO and guidelines for national and regional planning. Geneva: The World Health Organisation; 1999.
28. WHO. Cumulative number of reported probable cases of severe acute respiratory syndrome. Online. Available: www.who.int/csr/sars/country/en/index.html (accessed Nov 28, 2005).
29. Drosten C, Gurther S, Preiser W, et al. Identification of a novel coronavirus in patients with Severe Acute Respiratory Syndrome. N Engl J Med 2003; 348:1967–1976.
30. Ksiazek TG, Edman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003; 348:1953–1966.
31. Lee N, Hui D, Wu A, et al A major outbreak of severe acute respiratory syndrome. N Engl J Med 2003; 348:1986–1994.
32. Poutamen SM, Low DE, Henrey B, et al. Identification of severe acute respiratory syndrome in Canada. N Engl J Med 2003; 348:1995–2005.
33. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the Greater Toronto Area. JAMA 2003; 289:1–9.
34. Centers for Disease Control and Prevention. Severe acute respiratory syndrome and coronavirus testing. United States 2003. Online. Available: www.cdc.gov/mmwr/preview/mmwrhtml/mm5214al.html
35. WHO. Online. Available: http://www.who.int/csr/disease/avian_influenza/updates/en/index.html (accessed Jan 13, 2008).
36. WHO. WHO recommendations relating to travellers coming from and going to countries experiencing outbreaks of highly pathogenic H5N1 avian influenza. Online. Available: http://www.who.int/csr/disease/avian_influenza/travel2005_11_3/en/print.html (accessed November 2005).
37. WHO. Avian influenza: assessing the pandemic threat. WHO/CDS/2005.29. January 2005.
38. Ligon BL. Avian influenza virus H5N1: a review of its history and information regarding its potential to cause the next pandemic. Semin Pediatr Infect Dis 2005; 16:326–335.
39. Zane S, Uyeki T, Bodnar U, et al. Influenza in travellers, tourism workers, and residents in Alaska and the Yukon Territory, summer 1998 (poster). Presented at the 6th Conference of the International Society for Travel Medicine, Montreal, Canada, June 6–10, 1999.
40. Balkhy HH, Memish ZA, Bafaqeer S, et al. Influenza a common viral infection among Hajj pilgrims: time for routine surveillance and vaccination. J Travel Med 2004; 11(2):82–86.
41. Joseph CA. European Working Group for Legionella Infections. Legionnaires' disease in Europe 2000–2002. Epidemiol Infect 2004; 132:417–424.
42. World Health Organisation. Epidemiology, prevention and control of legionellosis: memorandum of a WHO meeting. Bull WHO 1990; 68:155–164.
43. Joseph CA, Harrison TG, Ilijic-Car D, et al. Legionnaires' disease in residents of England and Wales: 1997. Communicable Dis Public Health 1998; 1:252–258.
44. Anonymous. Cluster of cases of Legionnaire's disease associated with a Bangkok hotel. Communicable Dis Report CDR Weekly 1999; 9:147.
45. Den Boer JW, Yzerman EPF, Schellekens J, et al. A large outbreak of Legionnaires' disease at a flower show, the Netherlands, 1999. Am Infect Dis 2002; 37–43.
46. World Health Organisation. Plan of action for the prevention and control of diphtheria in the European Region (1994–1995). WHO Document ICP/EPI 038, Copenhagen, 1994.
47. Anonymous. Diphtheria acquired during a cruise in the Baltic Sea. Commun Dis Rev 1997; 7:210.
48. Farizo KM, Strebel PM, Cen RT, et al. Fatal respiratory disease due to Corynebacterium diphtheriae: case report and review of guidelines for management, investigation, and control. Clin Infect Dis 1993; 16:59–68.
49. Currie BJ. Melioidosis: an important cause of pneumonia in residents of and travellers returned from endemic regions. Eur Respir J 2003; 22:542–550.
50. Peetermans WE, Wijngaerden EV, Eldere JV, et al. Melioidosis brain and lung abscess after travel to Sri Lanka. Clin Infect Dis 1999; 28:921–922.
51. Dharakul T, Anuntagool SS, Chaowagul N, et al. Diagnostic value of an antibody enzyme-linked immunosorbent assay using affinity-purified antigen in an area endemic for melioidosis. Am J Trop Med Hyg 1997; 56:418–423.
52. Appassakij H, Silpojakul KR, Wansit R, et al. Diagnostic value of indirect hemoagglutination test for melioidosis in an endemic area. Am J Trop Med Hyg 1990; 42:248–253.
53. Inglesby TV, Henderson DA, Bartlett JG, et al. Anthrax as a biological weapon. Medical and public health management. JAMA 1999; 281:1735–1745.
54. Perry RD, Fetherston RD. Yersinia pestis – aetiologic agent of plague. Clin Microbiol Rev 1997; 10:35–66.
55. World Health Organisation. Human plague in 1996. Wkly Epidemiol Rec 1998; 47:366–369.
56. Chanteau S, Rabarijaona L, O'Brien T, et al. F1 antigenaemia in bubonic plague patients, a marker of gravity and efficacy of therapy. Trans R Soc Trop Med Hyg 1998; 92:572–573.
57. Guiard-Scmid JB, Lacombe K, Osman D, et al. La paragonimose: une affection rare à ne pas méconnaitre. Presse Med 1998; 27:1835–1837.
58. Cairns L, Blythe D, Kao A, et al. Outbreak of coccidioidomycosis in Washington State residents returning from Mexico. Clin Infect Dis 2000; 30:61–64.
59. Morgan J, Cano MV, Feikin DR, et al. A large outbreak of histoplasmosis among American travelers associated with a hotel in Acapulco, Mexico, spring 2001. Am J Trop Med Hyg 2003; 69:663–669.
60. Lyon GM, Bravo AV, Espino A, et al. Histoplasmosis associated with exploring a bat-inhabited cave in Costa Rica, 1998–1999. Am J Trop Med Hyg 2004; 70:438–442.
61. Salomon J, Flament Saillour M, De Truchis P, et al. An outbreak of acute pulmonary histoplasmosis in members of a trekking trip in Martinique, French West Indies. J Travel Med 2003; 10:87–93.
62. Centres for Diseases Control and Prevention. Outbreak of acute febrile respiratory illness among college students – Acapulco, Mexico, March, 2001. MMWR 2001; 50:359–360.
63. Lobato MN, Hopewell PC. Mycobacterium tuberculosis infection from countries with a high prevalence of tuberculosis. Am J Respir Crit Care Med 1998; 158:1871–1875.
64. Cobelens FGJ, van Deutekom H, Draayer-Jansen IWE, et al. Association of tuberculin sensitivity in Dutch adults with history of travel to areas with a high incidence of tuberculosis. Clin Infect Dis 2001:33:300–304.
65. Frame JD, Lange DR, Frankenfield DL. Mortality trends of American missionaries in Africa, 1945–1985. Am J Trop Med Hyg 1992; 46:686–690.
66. Matteelli A, Gurtman A, Torresi J, et al, Tuberculosis in travellers and long term immigrants. Presented at the 7th conference of the International Society of Travel Medicine, Innsbruck, Austria, May 27–31, 2001: Abstract FC05.05:88.
67. Smith PG, Fine PEM. BCG vaccination. In: Clinical tuberculosis. London: Chapman and Hall Medical; 1998:417–431.
68. Rieder HL. Risk of travel-associated tuberculosis. Clin Infect Dis 2001; 33:1393–1396.
69. Pai M, Riley LW, Colford JM Jr. Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review. Lancet Infect Dis 2004; 4:761–776.
70. International Union against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bull WHO 1982; 60:555–564.
71. World Health Organisation. Tuberculosis and air travel: guidelines for prevention and control. WHO/TB/98.256.
72. Houk VN, Baker JH, Sorensen K, et al. The epidemiology of tuberculosis infection in a close environment. Arch Environ Health 1968; 16:26–50.
73. Moore M, Valvay SE, Ihle W, et al. A train passenger with pulmonary tuberculosis: evidence of limited transmission during travel. Clin Infect Dis 1999; 28:52–56.