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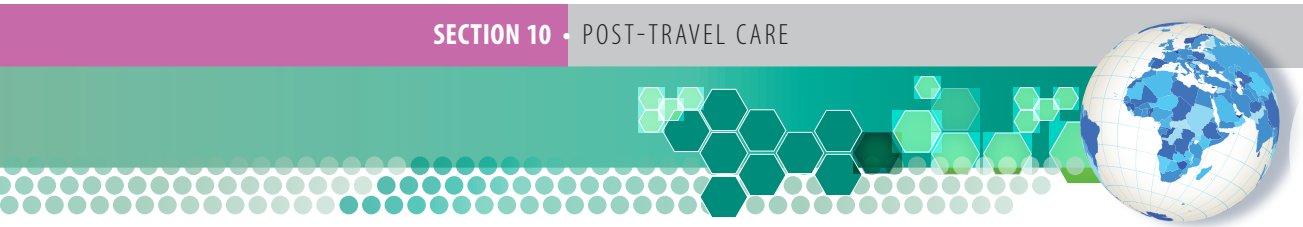

56

Respiratory Infections

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Key points

- Respiratory tract infections (RTIs) are among the most common illnesses reported by travelers. The estimated monthly incidence of acute febrile respiratory tract infections is 1261/100 000 travelers
- Most RTIs are viral in nature, involve the upper respiratory tract, and do not require specific diagnosis or treatment
- Lower respiratory tract infections, including pneumonia, often require antimicrobial therapy
- 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
- Influenza is often considered the most important travel-related infection. Travelers play an integral role in the yearly and global spread of influenza
- All travelers 6 months of age and older should receive yearly influenza vaccination, and travelers should be instructed in hand-hygiene and sneeze and cough hygiene
- All travelers should be up to date on any indicated vaccines that prevent RTIs, including measles, pneumococcal diseases, Hib, meningococcal disease, diphtheria, and pertussis
- Travelers may be at increased risk of geographically restricted RTIs, and clinicians should be familiar with the major manifestations of these illnesses

Introduction

Respiratory diseases are a frequent[1–3] and potentially life-threatening[4] health problem in travelers. Travelers may be at increased risk of certain respiratory tract infections (RTIs) due to travel itself (mingling and close quarters in airports, airplanes, cruise ships and hotels, and risk of influenza, legionella, and tuberculosis) and due to unique exposure at travel destinations (melioidosis, plague, Q fever, and coccidioidomycosis). Travel-related respiratory infections can lead to importation and secondary transmission, as occurred during the global SARS (severe acute respiratory syndrome) outbreak in 2003, and have occurred repetitively with influenza and tuberculosis.[5,6] This chapter reviews causative agents, clinical manifestations, and management approaches for travel-related RTIs.

Causative Agents and Clinical Presentation

Respiratory infections may manifest as upper tract disease (rhinitis, sinusitis, otitis, pharyngitis, epiglottitis, tracheitis), lower tract disease (bronchitis, pneumonia), or both. Systemic manifestations may include fever, headache, and myalgia. The vast majority of RTIs are caused by agents with global distribution.

The usual causative agents of acute upper respiratory tract infections are listed in Table 56.1. Most upper RTIs are caused by viruses, evolve as uncomplicated disease, and resolve without specific treatment. Acute coryzal illness, traditionally referred to as a 'common cold', manifests as nasal discharge and obstruction, sneezing and sore throat, and is most commonly caused by viruses, including rhinovirus, parainfluenza virus, influenza virus, respiratory syncytial virus, adenovirus, enterovirus (especially coxsackievirus A21), coronaviruses, and metapneumonia virus. 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. Common causes of laryngitis include parainfluenza virus, rhinovirus, influenza virus, and adenovirus. Less frequently, laryngitis can be caused by bacteria including *Corynebacterium diphtheriae, Branhamella catarrhalis*, and *Haemophilus influenzae*. Pharyngitis is also most commonly viral in origin, although streptococcal disease accounts for a significant minority. Other causes of pharyngitis include Epstein–Barr virus (EBV) and the human immunodeficiency virus (HIV).

Lower respiratory infections (LRTIs) are characterized by bronchial and/or pulmonary parenchymal involvement. The most common etiologic agents of pneumonia are listed in Table 56.2. Viruses commonly occur, but bacteria are responsible for a significant proportion of community-acquired cases of LRTI, and include *Streptococcus pneumoniae* and *Haemophilus influenzae*, as well as *Mycoplasma* spp. and *Chlamydia* spp., *Legionella* spp., and mycobacteria (tuberculosis). Fungal and parasitic involvement of the lung is also well recognized in travelers. Young children may sometimes be affected by severe forms of tracheobronchitis and croup, characterized by the stridorous croup-cough. The majority of these cases are due to viruses.

Travel destination, exposure, and activities should be considered in returned travelers with an RTI, as shown in Table 56.3. A list of common manifestations and complications of RTIs is presented in Table 56.4.

DOI: 10.1016/B978-1-4557-1076-8.00056-9

Epidemiology

Steffen et al. estimated the monthly incidence of acute febrile RTIs to be 1261/100 000 travelers.[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/year, is much lower than the incidence of common respiratory diseases among adults in the USA, which approximates four episodes per person per year.[7] The difference is likely to be attributable to under-reporting among travelers, because a large proportion of RTIs are mild, not incapacitating, are not reported, 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.[8]

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 definitions of syndromes rather than true epidemiologic differences. Still, RTIs consistently rank among the most frequently diagnosed and/or reported conditions among travelers. Attack rates in reported studies have ranged from 5% to 40%.[9–15]

In a large database of ill travelers from all continents within the GeoSentinel Surveillance System, Freedman described a frequency of respiratory disorders of 77 per 1000 ill returned travelers, ranging from 45/1000 in the Caribbean to 97/1000 in Southeast Asia.[2] In that analysis, respiratory disorders that prompted the seeking of medical care were less commonly reported than systemic febrile illnesses, acute diarrhea, dermatologic disorders, chronic diarrhea, and non-diarrheal gastrointestinal disorders.[2] Using the same database, Leder and colleagues found that 7.8% of ill travelers seeking medical care through GeoSentinel sites reported a respiratory illness.[16] In that series, of 1719 patients with respiratory infection, approximately 65% had an upper RTI, 75% of which were labeled as 'non-specific' and 20% were categorized as pharyngitis. Approximately 35% of all RTIs were characterized as lower tract infection, with 35% of these classified as pneumonia and over 50% being classified as bronchitis.[16] Prolonged travel, travel involving visiting friends and relatives, and travel during the northern hemisphere winter increased the likelihood of influenza and lower respiratory tract infections in this cohort.[16]

O'Brien et al. studied a group of 232 sick travelers at a tertiary hospital in Australia who had largely traveled through Asian countries: RTIs were second after malaria, accounting for 24% of cases.[17] In that series, lower tract infections accounted for 50% of all RTIs, and were almost equally distributed between bacterial pneumonia and influenza.[17] Bacterial pneumonia was significantly more common in patients aged >40 years, with an odds ratio (OR) of 5.5. One-quarter of upper tract infections were due to group A *Streptococcus*. In a multicenter hospital study in Italy, of 541 travelers with fever, 8.1% of the

Table 56.1 Most Common Etiologic Agents of Upper Respiratory Tract Infections

	Viral	Bacterial
Coryzal syndrome	Rhinovirus Parainfluenza virus Influenza virus Respiratory syncytial virus Enterovirus Coronavirus Metapneumonia virus Measles	
Laryngitis	Influenza virus 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*

Table 56.2 Most Common Etiologic Agents of Pneumonia and/or Pulmonary Involvement

Bacterial	Fungal	Viral	Other
Streptococcus pneumoniae	*Histoplasma capsulatum*	Influenza A	*Mycobacterium tuberculosis*
Staphylococcus aureus	*Coccidioides immitis*	Influenza B	*Coxiella burnetii*
Haemophilus influenzae	*Aspergillus* spp.	Adenovirus type 4 and 7	*Yersinia pestis*
Mixed anaerobic bacteria	Cryptococcus neoformans	Hantavirus	*Francisella tularensis*
Klebsiella pneumoniae	Paracoccidioides brasiliensis	Coronavirus	*Burkholderia pseudomallei*
Pseudomonas aeruginosa			*Bacillus anthracis*
Legionella spp.			*Leptospira* spp.
Mycoplasma pneumoniae			*Schistosoma spp. (acute)*
Chlamydia pneumoniae			*Ascaris lumbricoides*
Chlamydia psittaci			*Strongyloides stercoralis*
			Hookworm
			Paragonimus westermani
			Wuchereria bancrofti (Tropical pulmonary eosinophilia)

Table 56.3 Diagnostic Possibilities Based on The Region of Travel

	Africa	Asia	Central and South America	Europe	North America
Bacteria	Tuberculosis, plague	Tuberculosis, melioidosis, plague	Tuberculosis, plague	Legionellosis	Plague
Viruses	Hemorrhagic fever viruses, influenza	Hemorrhagic fever viruses, influenza	Hantavirus pulmonary syndrome, influenza	Influenza	Hantavirus pulmonary syndrome, influenza
Parasites	Paragonomiasis, schistosomiasis, strongyloidiasis, tropical eosinophilia	Paragonomiasis schistosomiasis strongyloidiasis tropical eosinophilia	Schistosomiasis, strongyloidiasis, tropical eosinophilia		
Fungi	Histoplasmosis		Histoplasmosis, coccidioidomycosis	Histoplasmosis, coccidioidomycosis	

Modified by Gluckman SJ, Chest 2008;134;163–171.

Table 56.4 Common Manifestations and 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	

patients had a respiratory syndrome, one-third of whom had pneumonia. TB was responsible for 29% of pneumonia cases in this cohort. Among cases with RTI and no signs of pneumonia, malaria was the underlying disease in 11 of 27.[18]

In a recent analysis of GeoSentinel data on ill children after international travel, approximately 86% of ill children who were brought by their parents for medical care had four major syndromes: 28% had a diarrheal process; 25% had a dermatologic disorder; 23% had a systemic febrile illness; and 11% had a respiratory disorder. Upper respiratory tract infections (38%), hyperactive airway disease (20%), and acute otitis media (17%) accounted for the majority of the cases of respiratory syndrome in these children.[19]

Risk Factors

In the GeoSentinel Surveillance System, women were more likely than men to present with upper respiratory tract infection associated with travel (OR 1.3).[10] Prolonged travel, travel involving visiting friends and relatives, and travel during the northern hemisphere winter increased the odds of being diagnosed with influenza and lower respiratory tract infection rather than upper tract disease in this cohort, and male gender was associated with twofold increased risk odds of pneumonia compared with female gender.[10]

Air travel itself is not a major risk factor for transmission of RTI owing to the high cabin air exchange rate, air filtering, and relatively laminar-down pattern air flow active during flight,[20] although sitting in close proximity to a person who is highly infectious can result in infection.[21–23] Sitting for a prolonged period in a confined air cabin not in flight and not with air flow can also markedly increase the risk of infection.[24] The reduced pressure of inspired oxygen found on airline flights or at high-altitude destinations may adversely affect infants' breathing patterns.[25]

Respiratory and intestinal infections are the most common diagnosis for passengers and crew seeking medical care on board ships,[26] and cruise travelers are at increased risk for legionellosis, influenza, and pneumococcal disease.[4] Reasons for increased susceptibility of cruise ship travelers to respiratory infections may include contaminated ventilator-cooling systems and spas, common points-of-fomite contact (e.g., salad bars), as well as passenger factors such as age, underlying illnesses, and physical condition.[27]

Infants, small children, the elderly, and subjects with chronic tracheobronchial or cardiopulmonary diseases are at increased risk of developing severe clinical consequences from RTIs.

Transmission

The spread of agents such as streptococci or meningococci is by direct, person-to-person contact, and via large droplets. These droplets usually fall to the ground within 1 m (3 ft) of an infectious person.

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

Legionellosis is a respiratory disease with a unique chain of transmission. It is a bacterium that multiplies in water systems, often within free-living ameba, forming biofilms in cooling towers, water-pipe fittings, and showers. *Legionella* can be disseminated in the aerosols generated by showerheads, whirlpools, and cooling systems. Such transmission contributes to outbreaks in hotels and cruise ships.

Management of the Respiratory Syndrome

An example of a decision algorithm for approaching patients with a RTI is presented in Figures 56.1 and 56.2. A syndromic management algorithm should effectively differentiate upper from lower respiratory tract infections, incorporating probable causative agents to guide treatment decisions. It should also assist in identify complications that

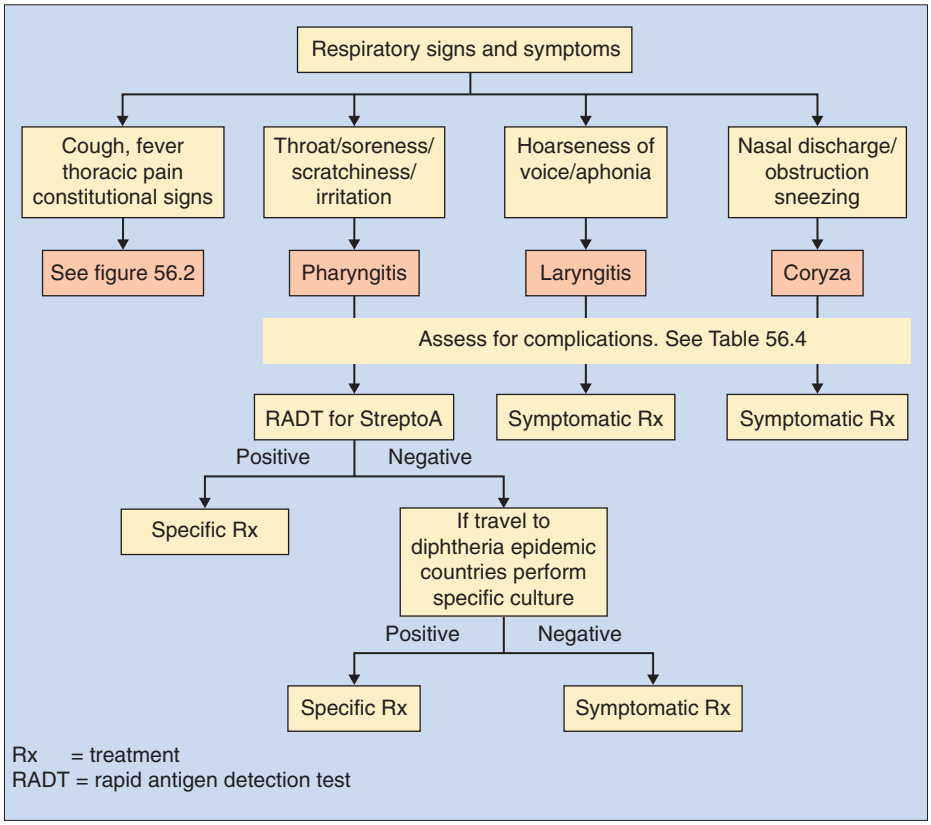

Figure 56.1 Decision algorithm for acute upper respiratory tract infections.

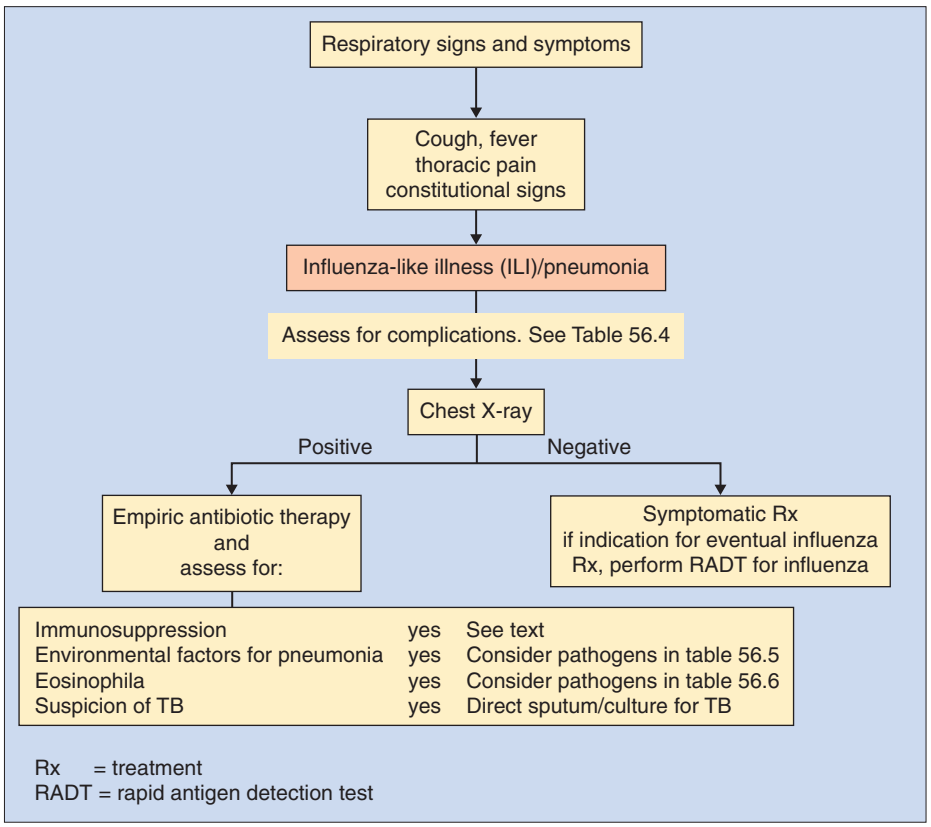

Figure 56.2 Decision algorithm for acute lower respiratory tract infections.

require specific treatment approaches. For practical purposes, a cough with rhinorrhea, or either of these with headache, fever, or shortness of breath can be used to generally define a RTI.

Among upper respiratory tract infections (Fig. 56.1), the isolated coryzal syndrome is rarely a cause of medical consultation. No additional diagnostic procedures are required and treatment is usually supportive. The diagnosis of laryngitis is also clinical, and treatment is usually supportive. Although the diagnosis of pharyngitis is also clinical, it is important to identify individuals with pharyngitis caused by group A streptococcal infection from other causes to lessen the likelihood of subsequent sequelae, including glomerulonephritis and rheumatic fever. Bacterial pharyngitis is reportedly associated with more severe pharyngeal pain, odynophagia, and higher fever, with grayish-yellow exudate on the tonsils and enlarged cervical lymph nodes. However, clinical criteria are unreliable to identify bacterial pharyngitis/tonsillitis because a typical presentation occurs in <50% of cases. Rapid antigen detection tests are available with a specificity >90% and sensitivity of 60–95%, and should generally be performed in patients ill enough to seek medical care for pharyngitis, especially in young children, in whom the risk of streptococcal disease is highest. The need to perform a bacterial culture if a rapid test is negative is debated. A treatment course with penicillin or amoxicillin for 10 days is appropriate to treat pharyngitis due to *S. pyogenes*. Diphtheria is a rare cause of pharyngitis, with a potentially fatal outcome. It is characterized by a thick and gray pharyngeal and tracheal membrane that bleeds upon attempted removal. Diagnosis is based on clinical recognition and culture isolation of a toxigenic strain of *Corynebacterium diphtheriae*. The mainstay of therapy is diphtheria antitoxin, associated with antibiotic treatment with penicillin or macrolides. Vaccination effectively eliminates the risk of travel-related pharyngeal diphtheria.

Otitis media and sinusitis can complicate air travel secondary to barotrauma. Viral and bacterial causes are common, and empiric treatment usually involves some combination of supportive care and hydration, with or without antibiotics. If an antibiotic is prescribed, it should primarily target an *S. pneumoniae* infection. Upper RTIs can occasionally be complicated by peritonsillar and retropharyngeal abscess formation. Treatment usually involves mechanical drainage and antibiotics.

Clinical signs suggestive of pneumonia include productive cough, thoracic pain, and shortness of breath. Examination usually discloses pulmonary crepitation, rhonchi, and adventitial sounds. Chest imaging should be used to further characterize and define pulmonary involvement. Complications of pneumonia include pulmonary cavitation, pneumothorax, and empyema formation. In many facilities, it is now standard to collect nasopharyngeal swabs or washings from patients with severe RTIs and pneumonia, and to apply rapid antigen tests to assess for common respiratory viruses, including influenza, parainfluenza, respiratory syncytial virus, adenovirus, and metapneumonia virus. 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 usually warrant systematic antibacterial treatment, especially if a viral screen is unrevealing. 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* may be 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, the clinical presentation is not specific enough to make an 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 in establishing a specific etiologic diagnosis is uncertain. The utility of the sputum culture is also unclear, since the procedure is insensitive: only half of patients with pneumonia 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 such as tuberculosis and melioidosis in travelers. 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.

A thorough travel and exposure history (Table 56.5) can also help identify diagnostic possibilities, for example legionella, and the differential in immunocompromised patients can be quite broad.

Pneumonia or pulmonary findings with eosinophilia in a traveler may also suggest specific diagnoses (Table 56.6).[28,29]

Table 56.5 Important Environmental Factors in Respiratory Tract Infections

Pneumonia	
Melioidosis	Travel to endemic areas, usually in SouthEast Asia
Brucellosis	Exposure to cattle, unpasteurized dairy products
Plague	Travel to endemic areas and contact with rats
Anthrax	Exposure to husbandry or animal hide or hair products
Tularemia	Hunting or other exposure to wild animals
Psittacosis	Exposure to birds
Leptospirosis	Exposure to rat or animal infested water
Coccidioidomycosis	Travel to dry-arid endemic areas
Histoplasmosis	Exposure to bird or bat droppings, spelunking
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, unimmunized status

Table 56.6 Causes of Pulmonary Involvement and Eosinophilia

Acute Ascaris lumbricoides infection (Loeffler's syndrome)
Strongyloides stercoralis infection (Loeffler's syndrome)
Acute Hookworm infection (Loeffler's syndrome)
Mycobacterium tuberculosis
Coccidioides immitis
Paragonimus spp.
Visceral larva migrans
Acute Schistosoma spp. infection (Katayama fever)
Dirofilaria immitis
Tropical pulmonary eosinophilia (lymphatic filariasis)

Table 56.7 Prevention of Respiratory Tract Infections in Travelers

Prevention strategy	Preventable condition
Hand-washing Alcohol-based hand sanitizers Soap and water	Influenza Respiratory viruses Bacterial fomite transmission
Vaccine	Influenza Measles *Streptococcus pneumoniae* *Haemophilus influenzae* Diphtheria
Early presumptive treatment	Influenza
Public health interventions	Influenza → Guidelines for international response Legionellosis → Alert networks (EWGLI) → Guidelines for safe water systems
Behavioral interventions	Influenza and respiratory viruses → Handwashing 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 RTIs in the traveler as in all individuals usually relies on behavioral changes (hand-washing and avoidance of close contact with sick individuals), vaccination, and rarely chemoprophylaxis (example, anti-influenza medication during an outbreak) (Table 56.7).

Influenza, measles, diphtheria, pertussis, as well as pneumococcal and Hib-associated infections are vaccine-preventable diseases. All travelers should be up to date with anti-measles, anti-influenza, anti-diphtheria and anti-pertussis vaccines (example Tdap: tetanus, anti-diphtheria, acellular pertussis vaccine). All children should be up to date with anti-*H. influenzae* B immunization (Hib) and pediatric pneumococcal polyvalent vaccine. Travel itself is not an indication for adult pneumococcal vaccination, but all adults 65 years of age or older, or with certain indications, should be up to date for adult pneumococcal vaccination.[30] All travelers should be up to date for immunization against influenza.[31,32]

Control measures for legionellosis are based on the application of guidelines for maintaining safe water systems in international tourist locations and cruise ships.[33] 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 such as 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, TropNet, and EuroTravNet play a pivotal role in early detection and public warning of travel-related epidemics.[34,35]

International health authorities may impose and have imposed public health interventions during worrisome outbreaks (example, H5N1 and H1N1 influenza and SARS), including animal culling, travel restrictions, screening at airports and points of arrival and departure, and quarantine in efforts to limit the spread of respiratory infections.

Infections of the Respiratory Tract Associated With Epidemics

SARS

Although SARS is no longer an ongoing public health threat, it can serve as a paradigm infection that underscores the risk and consequences of international travel, and the role that travelers can play in the global, rapid and lethal spread of a highly pathogenic RTI. 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 13 March 2003 the World Health Organization issued a global alert about the outbreak and subsequently named this condition severe acute respiratory syndrome (SARS). The virus spread among travelers, with a focused outbreak radiating out from a single Bangkok hotel to a number of countries, with subsequent ongoing spread. From November 2002 to July 2003, 8098 cases and 774 deaths were reported from 28 countries, with a fatality rate of 9.6%.[36] A global public response was initiated. Fortunately, since April 2004 not a single case of SARS has been reported worldwide.

A novel coronavirus distinct from those previously reported in animals and humans caused SARS.[37,38] The virus was thought to have emerged in the animal and food markets of Asia, and after introduction into a human, was transmitted person-to-person by inhalation of droplets, although aerosol transmission may have occurred in 'super spreaders' patients who are severely ill and excreting large viral loads. Some 60% of SARS cases occurred among healthcare workers who had not been adequately protected.[39] The incubation period of SARS was 3–11 days, with a median of 5 days. The syndrome often began with a prodrome of headache, myalgia, and fatigue, progressing a day later to fever >38°C and subsequently to a non-productive cough and/or shortness of breath. Patients presented with fever and non-specific symptoms 1–3 days before respiratory symptoms began. Gastrointestinal symptoms (nausea, vomiting, and diarrhea) occurred in approximately 20% of patients.[40] In the series of 144 patients seen in Toronto hospitals, the chest X-ray was normal in 25% on admission.[41] Unilateral and bilateral infiltrates were observed in 46% and 29% of the patients, respectively. Most patients eventually developed multifocal opacities. Laboratory investigations typically showed 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.[42] The treatment of SARS was largely supportive. Corticosteroid therapy and the antiviral drug ribavirin were used, with little certainty of efficacy. Most patients recovered in spite of not receiving these drugs, but the mortality rate from SARS had a median of 10%. Those with the highest mortality rate were the elderly (>60 years) and those with underlying comorbid conditions such as diabetes and chronic lung disease.

Avian Influenza

Since 2005, highly pathogenic H5N1 influenza A virus endemic in avian populations in SE Asia has been tracked by the WHO and related agencies. H5N1 has resulted in millions of poultry infections, several hundred recognized human cases, and a high case-fatality rate. Human cases continue to accumulate. Currently, avian influenza H5N1 virus continues to circulate in poultry in some countries, especially in Asia and northeast Africa. In June 2011, Egypt and Indonesia confirmed their 150th and 178th human cases of avian flu, respectively. Of the 150 cases confirmed in Egypt, 52 have been fatal, compared to 146 of 178 in Indonesia.[43] Large amounts of the virus are known to be excreted in the droppings shed by infected birds. Transmission requires direct contact with birds or their droppings. Populations in affected countries are advised to avoid contact with dead birds or birds showing signs of disease. Human-to-human transmission has fortunately been very sporadic thus far, and limited to very close contacts. However, should the virus mutate to become steadily transmissible in the human community, a new deadly pandemic influenza could emerge. Human cases of avian influenza are characterized by severe pneumonia, which is frequently rapidly fatal. Evidence suggests that some antiviral drugs, notably oseltamivir, can reduce the duration of viral replication and improve survival.[44]

Influenza

Influenza is the most important viral respiratory infection of travelers and non-travelers.

Travelers acquire influenza both as sporadic cases and as clusters from common sources aboard ships, airplanes, and in tour groups. All described outbreaks are caused by the type A virus, and are characterized by involvement of a large proportion of the population at risk, and the explosive nature of outbreaks. In 1998, approximately 40 000 tourists and tourism workers were affected by an influenza outbreak in Alaska and the Yukon Territory.[45] Influenza is a common infection also among *Hajj* pilgrims, with 24 000 estimated cases per *Hajj* season.[46]

Influenza is a self-limited disease that produces high morbidity and is responsible for lethal cases, most commonly among the youngest and eldest. The hallmark of the clinical presentation of influenza is a febrile illness with cough. Fever characteristically lasts 3–5 days, but dry cough may persist for much longer. Pneumonia is the most frequent complication, either from direct viral involvement or bacterial suprainfection, the latter most comonly caused by *S. pneumoniae, H. influenzae*, group A *Streptococcus*, and *Staphylococcus aureus*. Otitis media and sinusitis are other serious complications. Complications are more frequent and severe among patients with chronic diseases of the lung or heart.

Diagnosis is usually based on clinical criteria during an outbreak. Rapid diagnostic antigen-based tests are being increasingly used. Viral isolation (which is the method of reference) and antibody determination are seldom used in clinical care. Treatment is symptomatic in most cases. For severe cases and for patients at highest risks of complications and severe disease, anti-influenza therapy with neuraminidase inhibitors can be used. In many countries, yearly influenza vaccination is now indicated for all individuals 6 months of age or older. A live attenuated nasal vaccine is available for use in healthy young individuals 2–49 years of age. Parenteral inactive vaccines are available for use in all those over 6 months of age. All travelers should receive the current year's influenza vaccine.[32] Northern and southern hemisphere influenza vaccine may be different. Influenza in the northern hemisphere occurs mainly from October to February; influenza in the southern hemisphere predominantly occurs in April–August. As one approaches the Equator influenza circulates year-round. Travelers are at high risk of influenza year-round, since they are often mingling with other travelers from current influenza zones, or traveling directly to those zones.

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 over 40 years of age, but only a fraction of cases are recognized. According to the CDC, 20% of patients hospitalized with Legionnaires' disease in the United States acquired their infection while traveling. [47]

A European Working Group on *Legionella* Infection involving 35 countries was started in 1987. During 2008, a total of 866 travel-associated Legionnaires' cases were reported. Travel outside Europe was reported in 12% of the cases. The scheme identified 108 new clusters in 2008, the largest cluster (six cases) being associated with travel to Spain.[48] 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 excluded from risk, as exemplified by the identification of a cluster of cases associated with a hotel in Bangkok.[49]

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.[50] 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.[51] Patchy infiltrates are often present bilaterally. Mortality may be as high as 20% if diagnosis and antibiotic treatment are delayed. Diagnosis is usually based on detection of antigen in urine (for *L. pneumophila* type 1, which accounts for 85% of cases). Culture can also be employed. Treatment is often empiric: macrolides are the treatment of choice. Co-trimoxazole and fluoroquinolones are also effective.

Tropical and Geographically Restricted Respiratory Infections

Travelers may be at risk of a number of geographically restricted respiratory infections, as well as those associated with travel to resource-limited areas.

Melioidosis

Melioidosis is caused by a Gram-negative rod, *Burkholderia pseudomallei*. Cases usually occur within 20° north to 20° south of the Equator,

with the vast majority of cases being reported in Southeast Asia and northern Australia. The bacterium is free-living in soil and water, and humans can become infected through inhalation or through direct contact (wounds). Melioidosis remains a risk for travelers to endemic areas, especially those with exposure to wet-season soils and surface water.[52,53] *B. pseudomallei* was one of the more frequent isolates from travelers and patients affected by the 2005 Asian tsunami.[54] Reactivated melioidosis has been reported among tourists, immigrants, and Vietnam veterans decades after leaving endemic regions. Risk factors for clinical disease include diabetes, chronic alcoholism, chronic lung disease, and chronic renal disease.

Cellulitis, abscess formation, pneumonia and septicemia are the most frequent manifestations. 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 also been reported from areas not typically considered endemic.[55] The diagnosis can be confirmed by Gram stain and culture of respiratory specimen and/or blood. The presumptive diagnosis of melioidosis may be based on a positive IHA or ELISA serology in the appropriate clinical setting.[56,57] IHA titers above 1 : 80 are suggestive of active infection, but can also be seen in asymptomatic subjects in endemic regions.[57] 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.

Leptospirosis

Pulmonary involvement in leptospirosis is not rare, and usually manifests as a dry cough, or occasionally as a cough with blood-stained sputum.

Leptospirosis is due to several serovars of a spirochetal bacterium, often *Leptospira interrogans*, and is a zoonosis. Transmission occurs by accidental contact with water or soil contaminated with the urine of an infected animal, often a rodent. Outbreaks have occurred among adventure travelers on group tours,[58] and leptospirosis with pulmonary hemorrhage has been noted with increasing frequency.[59,60] 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, but this is rarely performed. The diagnosis usually rests on clinical recognition and serology.

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 rarely indicated.

Anthrax

Cutaneous disease is the most commonly observed form of human anthrax. Pulmonary anthrax is less common but more deadly, and is caused by inhalation of *Bacillus anthracis* spores. 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 contact with contaminated soil or animal products; a few cases of anthrax have been described in travelers who import souvenirs.

Inhalation anthrax is notable for its absence of pulmonary infiltrate on chest imaging, but the presence of extensive mediastinal lymphadenopathy, pleural effusions, and severe shortness of breath, toxemia, and sense of impending doom. The incubation period is 2–5 days, but spores can germinate up to 60 days after exposure. Pathogenesis is mediated by a toxin responsible for hemorrhage, 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. 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 of epidemic conditions. Direct examination and Gram stain of the sputum specimen are unlikely to be positive. A serologic ELISA test is available, although a significant increase in titer is usually obtained only in convalescent subjects who survive. The most useful bacteriologic test in case of suspicion, however, is a blood culture demonstrating *B. anthracis*. Treatment of inhalation anthrax should be as early as possible and usually involves a carbapenem, penicillin, doxycycline, and fluoroquinolone such as ciprofloxacin. Ancillary treatment to sustain vascular volume, cardiac, pulmonary, and renal functions is essential.

Plague

Plague is caused by *Yersinia pestis*, a Gram-negative coccobacillus. It is considered a re-emerging disease because of the increase in the number of reported cases worldwide, the occurrence of epidemics (such as the one in India in 1994), and the gradual expansion in areas of low endemicity (including the US). The most heavily affected African countries are the Democratic Republic of Congo, Madagascar, Mozambique, Uganda, and the United Republic of Tanzania. The Central Asian region has active plague foci in the Central Asian desert, affecting Kazakhstan, Turkmenistan, and Uzbekistan. Plague foci are distributed in 19 provinces and autonomous regions of China, and the incidence has been increasing rapidly since the 1990s. Permanent plague foci exist in the Americas among native rodent and flea populations in Bolivia, Brazil, Ecuador, Peru, and the USA.[61] The 1994 Indian epidemic, where a total of 5150 suspected pneumonic or bubonic cases occurred in a 3-month period, caused travel and trade disruption and resulted in severe economic repercussions.[62] 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 (though pneumonic plague is currently very rare). Plague should be suspected in febrile patients who have been exposed to rodents or other mammals in known endemic areas. The presence of buboes in this setting is highly suspicious. The bacterium may be isolated on standard bacteriologic media from culture samples of blood or bubo aspirates. The Gram stain may reveal Gram-negative coccobacilli with polymorphonuclear leukocytes. Rapid diagnostic tests such as the direct immunofluorescence test for the presumptive identification of *Y. pestis* F1 antigen are of interest for the rapid management of patients

with the suspicion of disease.[63] Serologic tests to detect antibodies to the F1 antigen by passive hemoagglutination assay or enzyme-linked immunosorbent assay methods are available. A fourfold 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, usually involving an aminoglycoside (streptomycin, gentamicin) and/or doxycycline or chloramphenicol.

Pulmonary infections present a particular risk for human epidemics owing 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

Paragonimiasis is caused by a lung fluke, often *P. westermani*. Humans become infected through the ingestion of undercooked or raw crabs, crayfish, or their juices. The infection is endemic in SE Asia (including Thailand, the Philippines, Vietnam, China, and Taiwan), South and North America,[64] and Africa, with most cases being reported in Asia. The disease is well described, although rare, in travelers to endemic regions.[65] The incubation period may vary from one to several months after exposure.

The disease presents as a chronic bronchopneumonic process with productive cough, thoracic pain, and low-grade fever. The worms produce extensive inflammation and cavity formation, and the infection should be considered in individuals with nodular cavitating lung lesions, with rusty-brown bloody sputum. Acute paragonimiasis can present as pneumothorax as the worms invade the lung tissue. Diagnosis usually rests on clinical recognition and detection of the worms eggs in expectorated sputum. Treatment involves praziquantel. Prevention is based on avoiding eating raw crayfish and crabs.

Coccidioidomycosis and Histoplasmosis

Coccidioidomycosis and histoplasmosis are two fungal infections acquired by the respiratory route and often involve the respiratory system. Coccidioidomycosis is caused by inhalation of *Coccidioides immitis*, a dimorphic fungus found in dust and soil. The pathogen is present only in semi-arid 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 well-described outbreak of coccidioidomycosis in a 126-member church group traveling to Mexico, the average incubation period was 12 days (range 7–20 days); chest pain was present in 76% and cough in 66% of the affected travelers.[66] 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 US. Outbreaks of acute histoplasmosis among travelers have been repeatedly reported.[67–69] 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 US visiting Acapulco, 229 persons developed an acute febrile respiratory illness with cough, shortness of breath, chest pain, or headache.[70] 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 influenza. Confirmation of the disease usually involves a urine antigen assay, or comparison of acute- and convalescent-phase serum specimens.

Both fungal infections are sensitive to the azoles (fluconazole and itraconazole) and amphotericin-based preparations.

Tuberculosis

Tuberculosis (TB) is a widely distributed infection and a leading cause of human morbidity and mortality. Travel can increase the risk of tuberculosis, especially among individuals traveling to resource-limited settings, those visiting friends and relatives, those performing healthcare or service work overseas, and those traveling for extended periods. Most individuals who become infected with *Mycobacterium tuberculosis* do not become ill (i.e., do not develop the disease), and are diagnosed as having latent TB infection (LTBI), often on the basis of a skin test or interferon-γ-based assays.

TB Among Travelers from Low- to High-Endemicity Areas

There is mounting evidence of the association between travel and an increased risk for LTBI. Lobato first demonstrated that US children who had traveled abroad had a significantly higher probability of having a positive tuberculin skin test than children without a history of travel.[71] More recently, Cobelens et al. estimated the risk of acquiring *M. tuberculosis* infection among long-term (≥3 months) Dutch travelers to Africa, Asia, and Latin America as 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.[72] Abubakar et al. recently provided the first evidence in the UK that travel to countries with high levels of TB infection may be an independent risk factor for acquiring LTBI. This effect was not mitigated by BCG vaccination.[73] A recent systematic review using tuberculin skin testing (TST) conversion as a surrogate for LTBI calculated the cumulative incidence of LTBI in long-term (median 11 months) travelers to be 2%, which is what could be expected among local populations in many developing countries.[74] 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.[72]

Air travel itself is not considered a major risk factor for transmission of tuberculosis: only a few cases of LTBI have been associated with exposure to an infectious traveler on a plane, and no cases of active infection have been linked.[75] The risk of TB transmission on ships[76] and trains[77] has also been described, but is similarly of little epidemiologic importance.

Active TB (as opposed to LTBI) was 16 times more likely to be reported in individuals seeking medical care at a GeoSentinel site among those born in low-income countries and who were now living in high-income countries and traveling to their region of birth to visit friends and relatives, than it was among those born and living in high-income countries and traveling to low-income countries to visit friends and relatives, and more than 60 times more common than it was among tourist travelers.[78] Despite this, the evidence of association between actual travel (as opposed to demographics of travels) and active TB (as opposed to LTBI) is sparse. 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.[79] Jung and Banks[80] found the incidence rate of LTBI to be 1.283/1000 person/months of travel, and active TB 0.057/1000 person/months of travel among Peace Corps volunteers. These rates are significantly higher than in the general US population, but lower than those reported by Cobelens et al.[72]

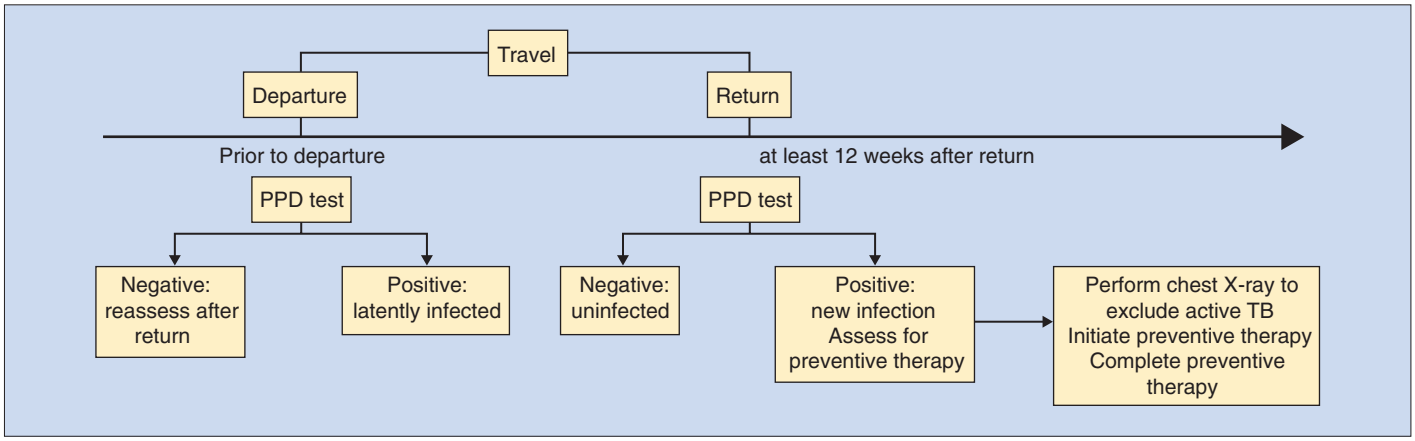

Figure 56.3 Prevention of TB disease in long-term travelers: identification and treatment of new infections.

Prevention guidelines state that persons with infectious TB should postpone air travel. Epidemiologic investigations for contacts of infectious passengers are indicated only within 3 months from exposure for passengers on travels of >8 h duration.[75] Travelers to high TB-endemic areas can employ behavioral modifications (individuals traveling to provide healthcare should use respiratory precautions in caring for patients with probable tuberculosis), and/or post-travel screening to assess for LTBI and evaluation for tuberculosis in individuals with a compatible disease (Fig. 56.3). A vaccine (BCG) is available but it is not protective in the adult population and is not routinely recommended.

Conclusion

Respiratory infections represent the third most frequent health problem for international travelers. The incidence is underestimated mainly because the majority of infections are mild and not incapacitating. Most are due to cosmopolitan agents, and 'tropical' and/or geographically restricted infections are rare. The RTI of perhaps the most significance to travelers is influenza. Travelers represent the primary vehicle of the yearly spread of influenza around the globe, and are critical to the global spread of new pandemics. Effective anti-influenza vaccines exist, and all travelers should receive yearly influenza immunization and be instructed in hand-washing and cough/sneeze hygiene. All travelers should also be up to date for other vaccines, including those that prevent RTIs, including measles, pneumococcal diseases, Hib, diphtheria, and pertussis. Clinicians caring for an ill returned traveler with an RTI should characterize the illness as upper or lower tract RTI, and consider the travel itinerary, exposure history, clinical manifestations, incubation period, and host-specific conditions.

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