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# Respiratory Infections

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## KEY POINTS

- Respiratory tract infections (RTIs) are among the most common illnesses reported by travelers. Most RTIs are viral, involve the upper respiratory tract, and do not require specific diagnosis or treatment.
- Influenza is often considered the most important travel-related infection. Travelers play an integral role in the yearly and global spread of influenza.
- Lower RTIs, 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. All international travelers should be immunized for seasonal influenza unless otherwise contraindicated, 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, *Haemophilus influenzae* b (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<sup>1-3</sup> and potentially life-threatening 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, legionellosis, and tuberculosis [TB]) and due to unique exposure at travel destinations (melioidosis, plague, Q fever, coccidioidomycosis, and histoplasmosis). Travel-related respiratory infections can lead to importation and secondary transmission, as occurred during the severe acute respiratory syndrome (SARS) outbreak in 2003, and more recently with Middle East respiratory syndrome coronavirus (MERS-CoV) and H1N1 influenza.<sup>4</sup> 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 RTIs are listed in [Box 59.1](#). 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 with 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 tract infections (LRTIs) are characterized by bronchial and/or pulmonary parenchymal involvement. The most common etiologic agents of pneumonia are listed in [Box 59.2](#). Viruses commonly occur, but bacteria are responsible for a significant proportion of community-acquired cases of LRTI, and include *Streptococcus pneumoniae* and *H. influenzae*, as well as *Mycoplasma* spp. and *Chlamydia* spp., *Legionella* spp., and mycobacteria (TB).<sup>5</sup> 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 59.1](#). A list of common manifestations and complications of RTIs is presented in [Box 59.3](#).

## EPIDEMIOLOGY

Steffen et al. estimated the monthly incidence of acute febrile RTIs to be 1261/100,000 travelers.<sup>1</sup> In that analysis, RTI ranked third after travelers’ diarrhea and malaria among all infectious problems of travelers.

**Abstract**

Respiratory tract infections (RTIs) are a common health problem of international travelers. Travelers may be at increased risk of RTIs due to travel itself (mingling and close quarters in airports, airplanes, cruise ships, and hotels), and due to unique exposure at travel destinations. The clinical spectrum of RTIs in travelers is broad and includes upper RTIs, pharyngitis, otitis, laryngitis, bronchitis, and pneumonia. Most travelers who acquire an RTI only develop mild disease, and only a minority seek medical attention. All travelers should be up to date on any indicated vaccines based on age and medical condition that prevent RTIs, including influenza, measles, pneumococcal diseases, *Haemophilus influenzae* b, *Neisseria meningitidis*, diphtheria, and pertussis.

**Keywords**

Acute upper respiratory infection  
Influenza  
Influenza vaccine  
Legionellosis  
Lower respiratory infection  
Travel and exposure history  
Tropical and geographically restricted respiratory infections  
Tuberculosis

### BOX 59.1 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	<i>Corynebacterium diphtheriae</i>
	Parainfluenza virus	<i>Haemophilus influenzae</i>
	Rhinovirus	<i>Branhamella catarrhalis</i>
	Adenovirus	<i>Streptococcus pyogenes</i>
Pharyngitis	Rhinovirus	Group C $\beta$ -hemolytic streptococci
	Adenovirus	<i>Corynebacterium diphtheriae</i>
	Coronavirus	<i>Mycoplasma pneumoniae</i>
	Enterovirus	<i>Chlamydia pneumoniae</i>
	Influenza virus	
	Parainfluenza virus	
	Respiratory syncytial virus	
	Epstein-Barr virus	
	Herpes simplex virus	
	Human immunodeficiency virus type 1	

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 United States.<sup>6</sup> The difference is likely to be attributable to underreporting among travelers, because a large proportion of RTIs are mild, not incapacitating, and not reported.

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%.<sup>7-13</sup>

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.<sup>2</sup> 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 nondiarrheal gastrointestinal disorders.<sup>2</sup> Using the same database, Leder and colleagues reported that upper and lower respiratory diagnoses were found in 11% of all travelers. Most respiratory illnesses were due to infections with a worldwide distribution, including nonspecific upper respiratory infections, influenza or influenza-like illness, bronchitis, and pneumonia (lobar and atypical). Influenza A, B, or H1N1 was diagnosed in 8% of travelers with a respiratory illness. There were 35 cases of legionellosis.<sup>14</sup>

### BOX 59.2 Most Common Etiologic Agents of Pneumonia and/or Pulmonary Involvement

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

TABLE 59.1 Diagnostic Possibilities Based on 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	Paragonimiasis, schistosomiasis, strongyloidiasis, tropical eosinophilia	Paragonimiasis, schistosomiasis, strongyloidiasis, tropical eosinophilia	Schistosomiasis, strongyloidiasis, tropical eosinophilia		
Fungi	Histoplasmosis		Histoplasmosis, coccidioidomycosis	Histoplasmosis, coccidioidomycosis	

Modified by Gluckman SJ. Acute respiratory infections in a recently arrived traveler to your part of the world. Chest 2008;134:163-71.

### BOX 59.3 Common Manifestations and Complications of Respiratory Tract Infections and Common Etiologic Agents of Otitis Media

Complications	Agents of Otitis Media
Otitis media	<i>Streptococcus pneumoniae</i>
Sinusitis	<i>Streptococcus</i> group A
Epiglottitis	<i>Staphylococcus aureus</i>
Mastoiditis	<i>Haemophilus influenzae</i>
Periorbital cellulitis	<i>Branhamella catarrhalis</i>
Peritonsillar abscess	
Retropharyngeal abscess	
Adenitis	

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.<sup>15</sup> In that series, lower tract infections accounted for 50% of all RTIs, and were almost equally distributed between bacterial pneumonia and influenza.<sup>15</sup> 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 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.<sup>16</sup>

In an analysis of GeoSentinel data on ill children after international travel, approximately 86% of ill children 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 RTI (38%), hyperactive airway disease (20%), and acute otitis media (17%) accounted for the majority of the cases of respiratory syndrome in these children.<sup>17</sup> In a Swiss study, Hunziker et al. found that leading diagnoses in children aged up to 16 years who presented with travel-associated illness were diarrhea (39%), respiratory (29%), and febrile/systemic illness (13%). Among travelers returning from Asia and America (South, Central, and North), respiratory illness was the most frequent diagnosis.<sup>18</sup>

### RISK FACTORS

In the GeoSentinel data, women were more likely than men to present with upper RTI associated with travel (OR 1.3).<sup>8</sup> 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.<sup>8</sup>

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,<sup>19</sup> although sitting in close proximity to a person who is highly infectious can result in infection.<sup>20–22</sup> Respiratory and intestinal infections are the most common diagnosis for passengers and crew seeking medical care on board ships.<sup>23</sup> Reasons for increased susceptibility of cruise ship travelers to respiratory infections may include contaminated ventilator cooling systems and spas, the use of hot tubs, common points-of-fomite contact (e.g., salad bars), as well as passenger factors such as age, underlying illnesses, and physical condition.<sup>24,25</sup>

Infants, small children, the elderly, and subjects with chronic tracheobronchial or cardiopulmonary diseases are at increased risk of developing severe clinical consequences from RTIs. In a study by Gautret et al., respiratory disease ranked as the second most frequent reason for presentation to a GeoSentinel site in the older adults (age >60 years). Older travelers had a greater proportionate morbidity from lower RTI, including pneumonia and bronchitis.<sup>26</sup>

### 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 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 outbreaks of disease among those exposed. Measles and *Mycobacterium 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 amoeba, 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.<sup>25</sup>

### MANAGEMENT OF RESPIRATORY TRACT INFECTIONS

An example of a decision algorithm for approaching patients with an RTI is presented in Figs. 59.1 and 59.2. A syndromic management algorithm should effectively differentiate upper from lower RTIs, incorporating probable causative agents to guide treatment decisions. It should also assist in identifying complications that 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 an RTI.

Among upper RTIs (see Fig. 59.1), 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 >95% when compared with blood-agar plate cultures and sensitivity of 80%–90%, and should generally be performed in patients ill enough to seek medical care for pharyngitis, especially in young children. A negative rapid test should be followed by a confirmatory throat culture in children and adolescents but not necessarily in adults. Nucleic acid amplification tests including isothermal loop amplification are also available in some locations with a high degree of specificity and sensitivity as well as a rapid turnaround time. A treatment course with penicillin or amoxicillin for 10 days is appropriate to treat pharyngitis due to *Streptococcus pyogenes*. Diphtheria is a rare cause of pharyngitis, with a potentially fatal outcome. It is characterized by a

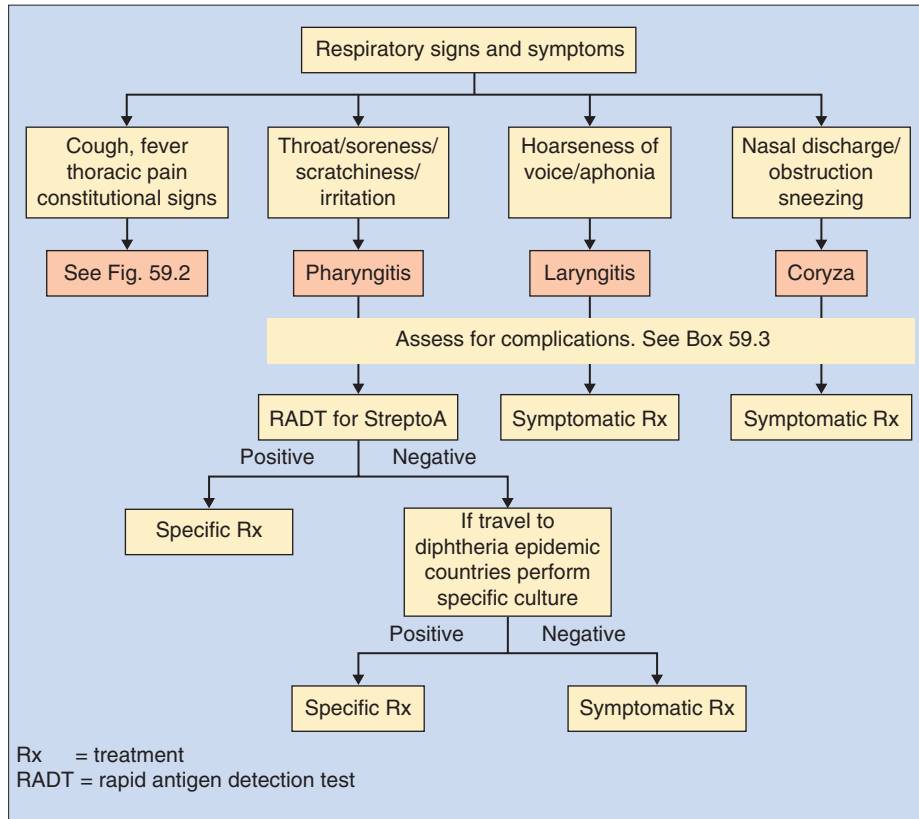


FIG. 59.1 Decision algorithm for acute upper respiratory tract infections.

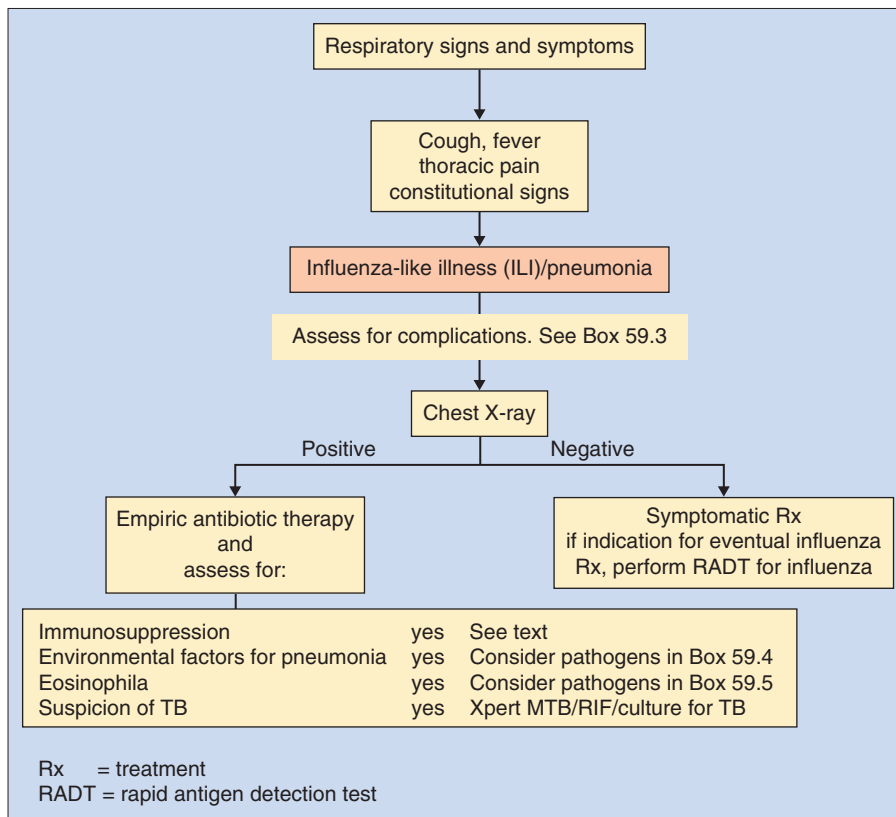


FIG. 59.2 Decision algorithm for acute lower respiratory tract infections.

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 *C. 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 adventitious 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 *Mycoplasma pneumoniae* and *Chlamydia 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 TB 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 initiated 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 (Box 59.4) can also help identify diagnostic possibilities (e.g., 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 (Box 59.5).<sup>27</sup>

## PREVENTION IN TRAVELERS

Prevention of RTIs in the traveler as in all individuals usually relies on behavioral changes (hand-washing or hand disinfection with alcohol-based liquid sanitizers and avoidance of close contact with sick

### BOX 59.4 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-infested 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

### BOX 59.5 Causes of Pulmonary Involvement and Eosinophilia

Acute <i>Ascaris lumbricoides</i> infection (Loeffler syndrome)
<i>Strongyloides stercoralis</i> infection (Loeffler syndrome)
Acute hookworm infection (Loeffler syndrome)
<i>Mycobacterium tuberculosis</i>
<i>Coccidioides immitis</i>
<i>Paragonimus</i> spp.
Visceral larva migrans
Acute <i>Schistosoma</i> spp. infection (Katayama fever)
<i>Dirofilaria immitis</i>
Tropical pulmonary eosinophilia (lymphatic filariasis)

individuals), vaccination, and rarely chemoprophylaxis (e.g., antiinfluenza medication during an outbreak) (Table 59.2).

Influenza, measles, diphtheria, pertussis, as well as pneumococcal and Hib-associated infections are vaccine-preventable diseases. All travelers should be up to date with antimeasles, antiinfluenza, anti-diphtheria, and antipertussis vaccines (e.g., Tdap: tetanus, antidiphtheria, acellular pertussis vaccine). All children should be up to date with anti-*H. influenzae* b immunization (Hib) and pediatric pneumococcal polyvalent vaccine. All adults 65 years of age or older, or with certain indications, should be up to date for adult pneumococcal vaccination.<sup>28</sup> All travelers should be up to date for immunization against influenza.<sup>4,29</sup>

Control measures for legionellosis are based on the application of guidelines for maintaining safe water systems in international tourist locations and cruise ships.<sup>30</sup> The early recognition of outbreaks is exceedingly important in the management of individual cases of diseases such as legionellosis. The European Legionnaires' Disease Surveillance Network (ELDSNET) reports 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 members of any disease cluster. Other international global and regional surveillance networks, including GeoSentinel, TropNet, and EuroTravNet, play a

**TABLE 59.2 Prevention of Respiratory Tract Infections in Travelers**

Prevention Strategy	Preventable Condition
Hand-washing	Influenza
Alcohol-based hand sanitizers	Respiratory viruses
Soap and water	Bacterial fomite transmission
Vaccine	Influenza
	Measles
	<i>Streptococcus pneumoniae</i>
	<i>Haemophilus influenzae</i>
	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
	→Hand-washing
	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
	Melioidosis
	→Avoid contact with contaminated soil or water (always wear shoes)

pivotal role in early detection and public warning of travel-related epidemics.<sup>31,32</sup>

International health authorities may impose and have imposed public health interventions during worrisome outbreaks (e.g., 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

### Severe Acute Respiratory Syndrome

SARS 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. As this severe atypical pneumonia began to spread from China, in mid-March 2003, the World Health Organization (WHO) issued a global alert about the outbreak and subsequently named this condition severe acute respiratory syndrome. The virus spread among travelers, with a focused outbreak radiating 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%.<sup>33</sup> A global public response was initiated. Fortunately, since April 2004 not a single case of SARS has been reported worldwide.

### Avian Influenza

Human infections with avian and zoonotic influenza viruses have been reported. Human infections are primarily acquired through direct contact with infected animals or contaminated environments. In 1997 human infections with the H5N1 virus were reported during an outbreak in poultry in Hong Kong SAR, China. Since 2003 this avian virus has spread from Asia to Europe and Africa, and has resulted in millions of poultry infections, several hundred recognized human cases, and a high case-fatality rate.<sup>34</sup> In 2013 human infections with the H7N9 virus were reported in China.<sup>35</sup> Since then, the virus has spread in the poultry population across the country and resulted in several hundred human cases and many human deaths. Other avian influenza viruses have resulted in sporadic human infections including the H7N7 and H9N2 viruses. Some countries have also reported sporadic human infections with swine influenza viruses, particularly the H1N1 and the H3N2 subtypes. In many patients infected by A(H5) or A(H7N9) avian influenza viruses, common initial symptoms are high fever ( $\geq 38^{\circ}\text{C}$ ) and cough. Signs and symptoms of lower respiratory tract involvement including dyspnea or difficulty breathing are common. Complications of infection include hypoxemia, multiple organ dysfunction, and secondary bacterial and fungal infections. The case fatality rate for A(H5) and A(H7N9) subtype virus infections among humans is much higher than that of seasonal influenza infections. Evidence suggests that some antiviral drugs, notably oseltamivir and peramivir, can reduce the duration of viral replication and improve survival. Since their availability may be limited in some areas, travelers with a high likelihood of exposure (poultry workers, veterinarians, or medical doctors in endemic areas) should consider bringing these drugs with them. Currently no vaccines for avian influenza in humans are commercially available. Particular attention should be given to travelers planning to visit areas endemic for avian influenza in poultry and where human cases have occurred. Such areas are currently found in Asia, Africa, and the Middle East. Advice should focus on avoiding contact with patients suffering from respiratory disease, and contact with birds and their excreta at live bird markets or farms, as well as avoiding contact with and consumption of insufficiently cooked poultry products.<sup>4</sup> Human-to-human transmission has fortunately been highly sporadic thus far, and limited to very close contacts. However, should such viruses mutate to become steadily transmissible in the human community, a new deadly pandemic influenza could emerge.

### Influenza

Influenza is the most important viral respiratory infection of travelers and nontravelers. Several changes in our globalizing world contribute to the growing importance of travelers in spreading influenza: (i) steady increase in total travel volume worldwide, (ii) advent of mass tourism, and (iii) increasing numbers of immunocompromised and elderly travelers.<sup>4</sup> Mutsch et al. found that 1% of the travelers enrolled in a study of influenza virus infection in persons traveling to tropical and subtropical countries seroconverted to influenza during their trip, and that 40% of those who seroconverted had sought medical attention during travel. Influenza virus infections were acquired largely in Asia (48%), Africa (28%), and Latin America (25%).<sup>36</sup> Travelers acquire influenza both as sporadic cases and as clusters from common sources aboard ships, airplanes or in airports, 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. Data collected from GeoSentinel and EuroTravNet indicate that in 2008, prior to the H1N1 pandemic, the number of influenza confirmed cases was at just 0.1%. During 2009, however, the number of confirmed influenza cases in GeoSentinel



rose to 11%, 12%, 18%, and as high as 32% with the majority of these attributable to H1N1.<sup>7,37</sup> Influenza is a common infection also among *hajj* pilgrims, with approximately 20,000 estimated cases per *hajj* season.<sup>38</sup>

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 superinfection, the latter most commonly 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. Although rapid influenza diagnostic tests are often employed because of their ease of use and rapidity, they can have suboptimal sensitivity to detect influenza virus infection, particularly for novel influenza viruses. Sensitivities of rapid diagnostic tests are generally only 50%–70%, compared to viral culture or reverse transcription polymerase chain reaction (PCR). Specificities of rapid diagnostic tests are generally higher, approximately 95%–100%.

If there is clinical suspicion for influenza in a patient at high risk for complications, early empiric treatment should be given regardless of a negative rapid diagnostic test result, and another type of test (e.g., reverse transcription, PCR, direct fluorescent antibody, or viral culture) may be performed for confirmation. Treatment is symptomatic in most cases. For severe cases and for patients at highest risks of complications and severe disease, antiinfluenza therapy with neuraminidase inhibitors can be used.

Northern and Southern Hemisphere influenza vaccines may be different. Influenza in the Northern Hemisphere occurs mainly from October–February; influenza in the Southern Hemisphere predominantly occurs 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. There are several ways to decrease the risk of acquiring influenza. Hygienic measures, including active ventilation of crowded places, hand sanitation, and (possibly) wearing a facemask, can reduce the risk of spreading influenza.<sup>4</sup> Select elderly or other high-risk groups of travelers could be advised to bring a neuraminidase inhibitor for influenza early treatment, if access to medical care at the destination will be limited.<sup>4</sup> Unless contraindicated, international travelers should be vaccinated against seasonal influenza.

### Middle East Respiratory Syndrome Coronavirus

MERS-CoV is a viral respiratory illness that has been reported in Bahrain, Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, United Arab Emirates (UAE), and Yemen. Most patients diagnosed with MERS have developed severe respiratory illness with shortness of breath and cough, and 3 of 10 patients have died. Secondary transmission in households and health care facilities have led to focused outbreaks. MERS-CoV has been reported in some camels; and some patients with MERS have had contact with camels. MERS should be considered in anyone with a severe respiratory illness within 14 days of travel to a country in or near the Arabian Peninsula, and contacts of sick patients who themselves traveled. Travel-related cases have been reported in Algeria, Austria, China, Egypt, France, Germany, Greece, Italy, Malaysia, Netherlands, Philippines, Republic of Korea, Thailand, Tunisia, Turkey, United Kingdom, and United States. Diagnosis is PCR based. Treatment is supportive. Patients should be placed on respiratory and contact precautions.

### 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 >40 years of age, but only a fraction of cases are recognized. According to the Centers for Disease Control and Prevention (CDC), 20% of patients hospitalized with legionnaires disease in the United States acquired their infection while traveling.<sup>39</sup> Between 2000 and 2010, 7869 hotel-associated cases (and 994 clusters) and 105 ship-associated cases of legionnaires disease (with 366 deaths) were reported by ELDSNET.<sup>40</sup> For 2015, 1141 travel-associated legionnaires disease cases were reported through ELDSNET, 20% more than in 2014. A total of 167 new travel-associated clusters were detected in 33 countries, compared with 132 in 2014, 110 in 2013, and 99 in 2012. In 2015, 60% of the detected clusters of travel-associated legionnaires disease were characterized by initial cases from several different countries.<sup>41</sup> 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.<sup>42</sup>

Transmission is airborne, 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 large outbreak in the Netherlands reported incubation periods >10 days.<sup>43</sup> 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.<sup>44</sup> 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, with 80% sensitivity and 99% specificity). Culture can also be employed. Where available, PCR can be used to identify *L. pneumophila* from bronchoalveolar lavage fluid and other clinical specimens. 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.<sup>45</sup> *B. pseudomallei* was one of the more frequent isolates from travelers and patients affected by the 2005 Asian tsunami.<sup>46</sup> Risk factors for clinical disease include diabetes, chronic alcoholism, chronic lung disease, and chronic renal disease.

Septicemia, pneumonia, cellulitis, and abscess formation are the most frequent manifestations. Lung involvement consists of acute necrotizing pneumonia or chronic granulomatous or fibrosing lung disease mimicking TB. The diagnosis of pulmonary melioidosis is difficult. Physicians in western countries should be aware of the possibility of melioidosis not only in patients originating from endemic areas but

also in patients returning from travel in those regions. Because it can manifest months or years after leaving the endemic area, patients may not remember the exposure event and its potential relationship to their symptoms. 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 indirect hemagglutination assay (IHA) or enzyme-linked immunosorbent assay (ELISA) serology in the appropriate clinical setting.<sup>47–49</sup> IHA titers above 1:80 are suggestive of active infection, but can also be seen in asymptomatic subjects in endemic regions.<sup>48</sup> Treatment of patients with melioidosis usually involves meropenem or ceftazidime plus trimethoprim-sulfamethoxazole or doxycycline for a period of at least 2–6 weeks. Therapy should be guided by antimicrobial susceptibility tests. For severe disease, prolonged treatment for 2–6 months is recommended to prevent relapses. A vaccine against melioidosis is not commercially available; the best way to prevent infection is by avoiding contact with contaminated soil or water; travelers should be advised to always wear shoes.<sup>45</sup>

### 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,<sup>50</sup> and leptospirosis with pulmonary hemorrhage has been noted with increasing frequency.<sup>51,52</sup> 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 acute respiratory distress syndrome (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 nonspecific, with mild fever, malaise, and a nonproductive 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 reemerging 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 United States). The most heavily affected African countries are Madagascar, Democratic Republic of Congo, Uganda, the United Republic of Tanzania, and Mozambique. 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 since the 1990s. Permanent plague foci exist in the Americas among native rodent and flea populations in Bolivia, Brazil, Ecuador, Peru, and the United States.<sup>53</sup> 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.<sup>54</sup> Travelers are rarely affected by plague while visiting endemic areas (e.g., 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 airborne 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.<sup>55</sup> Serologic tests to detect antibodies to the F1 antigen by passive HAI or ELISA method 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 *Paragonimus westermani*. Humans become infected through the ingestion of undercooked or raw crabs, crayfish, or their juices. The infection is endemic in Southeast Asia (including Thailand, the Philippines, Vietnam, China, and Taiwan),

South and North America,<sup>56</sup> and Africa, with most cases being reported in Asia. The disease is well described, although rare in travelers to endemic regions.<sup>57</sup> 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 and 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 semiarid regions of the Americas. Symptomatic disease develops in approximately 40% of individuals infected by *C. immitis*, presenting as a flulike 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.<sup>58</sup> The diagnosis is serologic, and 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 United States. Outbreaks of acute histoplasmosis among travelers have been repeatedly reported.<sup>59–61</sup> The disease may evolve as a mild, spontaneously resolving condition, but severe and systemic disease may develop in immunocompromised patients. Acute pulmonary histoplasmosis (APH) in returning travelers typically presents as a flulike illness with high-grade fever, chills, headache, nonproductive cough, pleuritic chest pain, and fatigue. Symptom onset is usually 1–3 weeks following exposure and most individuals recover spontaneously within 3 weeks. 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 and serum antigen assay, or comparison of acute-phase and convalescent-phase serum specimens. Antifungal treatment is not usually indicated for mild to moderate APH in immunocompetent persons. For patients who continue to have symptoms for >1 month, itraconazole is recommended. Patients with moderately severe to severe APH should receive liposomal amphotericin B followed by itraconazole.

### Tuberculosis

TB is a widely distributed infection and a leading cause of human morbidity and mortality. Travel can increase the risk of TB, especially among individuals traveling to high burden countries, those visiting friends and relatives, those performing health care or service work overseas, and those traveling for extended periods. Most individuals who become infected with *Mycobacterium tuberculosis* do not develop the disease and are diagnosed as having latent TB infection (LTBI), often on the basis of a skin test or interferon-gamma-based assays. Multidrug-resistant tuberculosis (MDR TB) is now present in many regions, including a number of sites in Eastern Europe and parts of Southeast Asia popular with travelers.<sup>62</sup>

### TB Among Travelers From Low-Endemic to High-Endemic Areas.

There is evidence of an 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.<sup>62</sup> Cobelens et al. estimated the risk of acquiring *M. tuberculosis* infection among long-term ( $\geq 3$  months) Dutch travelers to Africa, Asia, and Latin America as 3.3% per year.<sup>63</sup> Abubakar et al. provided the first evidence in the United Kingdom that travel to countries with high levels of TB infection may be an independent risk factor for acquiring LTBI.<sup>64</sup> A systematic review using tuberculin skin testing (TST) conversion as a surrogate for LTBI calculated the cumulative incidence of LTBI in long-term travelers to be 2%.<sup>65</sup> Other factors identified for increased TB risk among travelers were being a health care worker, a longer cumulative duration of travel, and a longer total time spent in TB-endemic countries.<sup>63</sup>

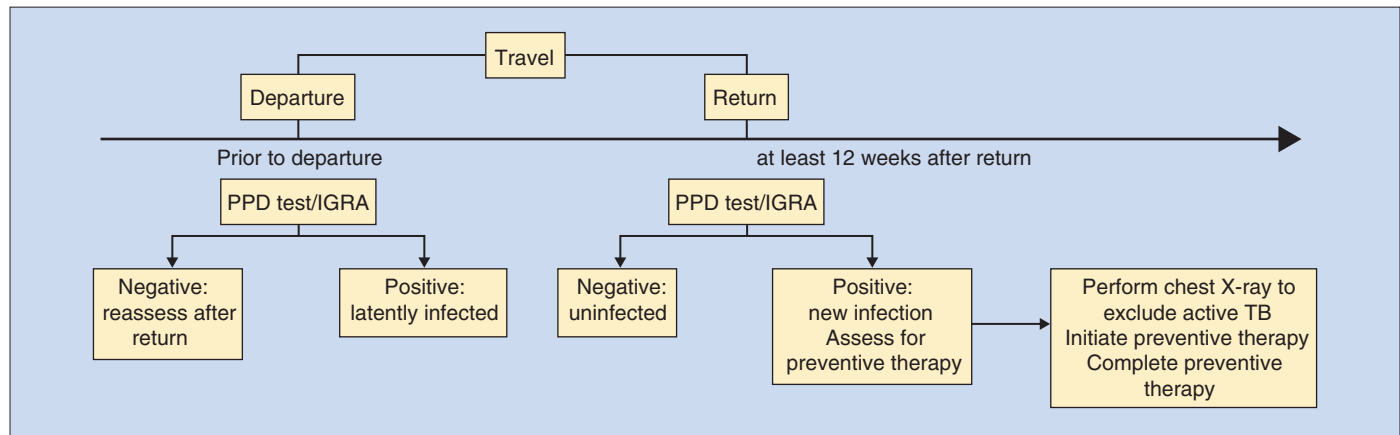
Air travel itself is not considered a major risk factor for transmission of TB.<sup>66</sup> The risk of TB transmission on ships and trains has also been described but is similarly of little epidemiologic importance.

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.<sup>66</sup> Despite this, the evidence of association between actual travel (as opposed to demographics of travels) and active TB (as opposed to LTBI) is sparse. Where overall risk is judged to be sufficiently high, pretravel testing for LTBI (TST or interferon-gamma release assays) may be indicated. Travelers to high TB-endemic areas can employ behavioral modifications (i.e., individuals traveling to provide health care should use personal protective equipment in caring for patients with probable TB). Following travel, assessment should focus on establishing whether a significant risk of exposure to TB occurred, and on any signs or symptoms that may suggest active infection (Fig. 59.3). Asymptomatic individuals who are considered at sufficient risk of exposure (or where direct contact with TB is known to have occurred) should be tested for LTBI. Symptomatic individuals should be evaluated for active TB.<sup>62</sup>

A vaccine (Bacillus Calmette-Guérin [BCG]) is available in many countries and many national guidelines recommend vaccination for children <5 years old traveling to TB-endemic countries for 1 month or longer.

## CONCLUSION

Respiratory infections represent a 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 antiinfluenza 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 RTI, and consider the travel itinerary, exposure history, clinical manifestations, incubation period, and host-specific conditions.



**FIG. 59.3** Prevention of tuberculosis (TB) disease in long-term travelers: identification and treatment of new infections. IGRA, Interferon-gamma release assay; PPD, purified protein derivative tuberculosis skin test.

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