

Travellers' Pneumonia – An Unsolicited Accomplice of Travellers

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Received: November 17, 2017; **Published:** January 22, 2018

'The vagabond, when rich, is a tourist' - Paul Richard, The Scourge of Christ, 1929'

Abstract

Travel medicine is relatively new domain of medicine which is still in stage of infancy. Better modes of transport like air travel has led to increased number of international travellers. With travellers, diseases especially infectious diseases also travel. Respiratory illness is quite common in returned travellers. Pneumonia is a rare but an important cause of health care-seeking among travellers. Travellers' pneumonia is an enigmatic condition for general physician as they have little knowledge of global infections and their geographical trends. Age, sex, duration of trip and type of travel are the most important risk factors for acquiring pneumonia during travel. The pathogens causing respiratory infection in travellers are generally speaking the same as those in non-travellers with bacterial pneumonia comprises around 50% of all travel associated pneumonias. Other important causative organisms are parasitic, viral and fungal pathogens that are endemic to destination places. Respiratory infections like H1N1, severe acute respiratory syndrome (SARS), middle-east respiratory syndrome (MERS) have posed a global threat and need constant reconnaissance of travellers especially coming from middle east and endemic areas. Establishment of travel clinics for practising travel medicine and imparting health education to travellers, personal hygiene and vaccination are the important steps needs to be taken to prevent and treat travel related illnesses.

Keywords: Travellers' Pneumonia; Travel Medicine; H1N1; Middle-East Respiratory Syndrome (MERS); Severe Acute Respiratory Syndrome (SARS)

Introduction

Travel medicine is relatively a new yet important domain of medicine requiring specialist knowledge, academic centres and dedicated clinical services to meet the health and medical needs of the increasing number of leisure and business travellers. With travellers diseases travel too and thus, this large group of people who travel between countries each year has a profound effect on the epidemiology of disease- particularly infectious diseases, the environment, facilities and natural resources. The health problems of international migration for both traveller and the country of destination are well known and include epidemics of infectious diseases, malnutrition, physical and psychological trauma, and the introduction of disease into new and vulnerable populations [1]. Military troops movements, healthcare workers and peace corps assignments, refugees movements, mass pilgrimages are the known activities in addition to business and leisure travel that influence the epidemiology of infections and considered as the gateways for the introduction and spread of infections or diseases to new or naive places.

Diarrhoea represents half to two-thirds of health problems in travellers followed by upper respiratory tract infections (14 - 31%), fever (12 - 15%) and skin conditions (12%) [2]. Respiratory tract infections are common in all countries, in both travellers and non-travellers. However, most infections are mild, and unlike travellers' diarrhoea do not interfere with daily activities. For this reason it is very difficult to determine the true burden of respiratory illness in travellers. However, Pneumonia is a rare but an important cause of health care-seeking among travellers. Travellers' pneumonia is an enigmatic condition for general physician as they have little knowledge of global infections and their geographical trends. Literature focussing on pneumonia among travellers is very limited and only few scattered studies have done in this regard, thus, making the prevalence and etiology of travellers' pneumonia highly variable.

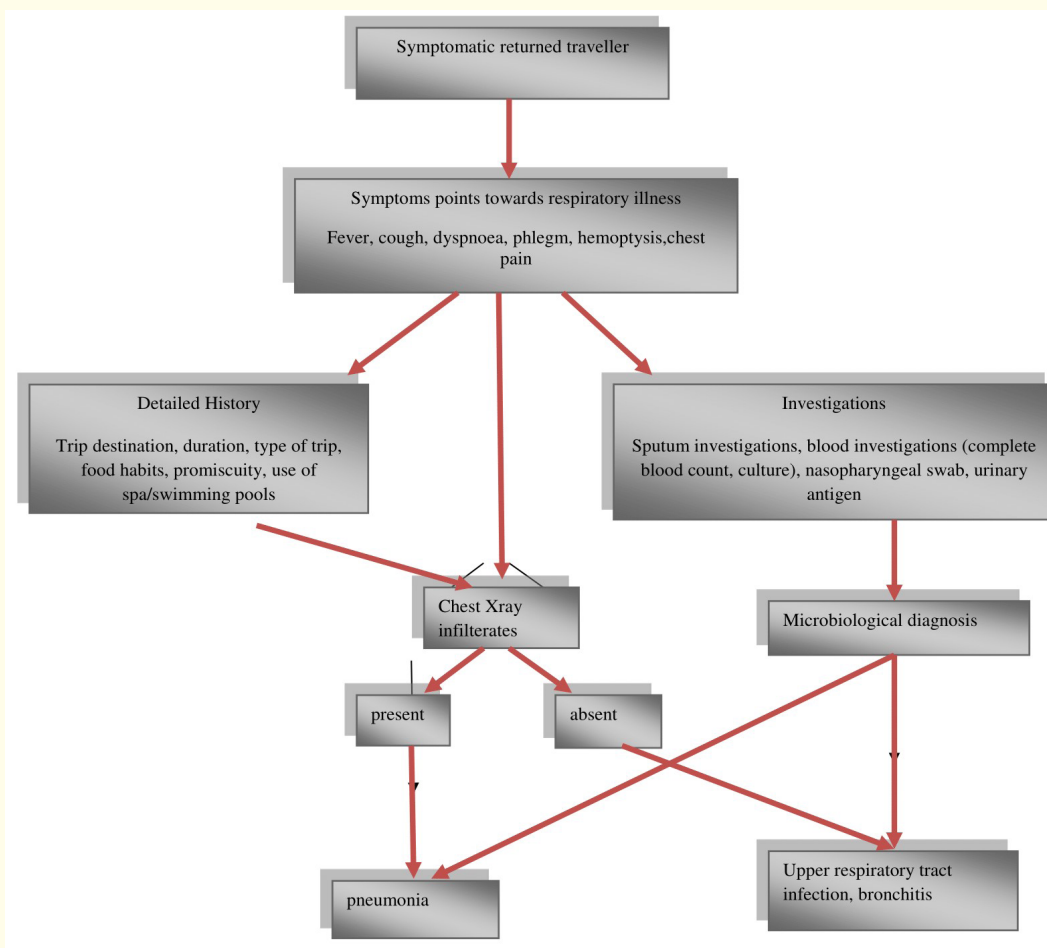


Figure 1: Approach to a returned traveller with respiratory symptoms.

Epidemiology

The epidemiology of infectious diseases in travellers reflects global patterns of infectious disease, and as travel destinations become more exotic, the epidemiology of travel-related disease is also changing. Activities that travellers undertake at their destination - food and alcohol consumption, sexual behaviour, sports, sunbathing- all determine the pattern of disease in returning travellers. It is estimated that

more than 600 million people travel annually with around 30 million people from industrialized countries visiting developing countries and that 15 - 50% of travellers experience health problems related to overseas travel [3]. Steffen., *et al.* estimated the incidence of acute febrile respiratory tract infection in travellers to be 1261 per 100000 travellers for a stay of 1 month in a developing country, i.e. an attack rate of 1.26% [2]. Pneumonia is a rare cause of health care-seeking among travellers. In a study of 838 sick French tourists in Nepal, the prevalence of respiratory tract infections was 17.55%, but pneumonia only accounted for 0.46% of medical consultations [4]. Nevertheless, pneumonia is a frequent cause of fever among returning travellers. O’ Brien., *et al.* studied 232 febrile travellers and found that lower respiratory tract infection was the second most common cause of fever after trips to tropical zones (24%) (Table 1), just after malaria (27%) [5] while Doherty., *et al.* in a study of 195 febrile British travellers showed that respiratory tract infections represented the fourth most common cause of fever, after malaria, viral infections and gastrointestinal disorders [6]. Parola P., *et al.* in a 4 year prospective study of 613 febrile patients found that respiratory infections were the third most common cause of fever in returned travellers [7]. Mortality from pneumonia among travellers is far from negligible; for instance, it was estimated at 1% (3/309 deaths) of global mortality in a Canadian study [8].

Diagnosis	O’Brien., <i>et al.</i> [5] (n = 232)	Parola P., <i>et al.</i> [7] (n = 613)
Respiratory tract infections	56 (24%)	21
Upper respiratory tract infections	28 (12%)	3
Bacterial pneumonia	14 (6%)	4
Influenza	11 (5%)	
Tropical pulmonary eosinophilia	1 (0.4%)	
Tuberculosis	1(0.4%)	
Bronchitis		3
Severe acute respiratory syndrome (SARS)		11

Table 1: Respiratory tract infections among febrile travellers in various studies [5,7].

Geosentinel is a global surveillance network established in 1995 through the International Society for Travel Medicine (Stone Mountain, Georgia) and the Centers for Disease Control and Prevention (CDC; Atlanta) which comprises 25 globally dispersed sentinel clinics [9]. The network carries the burden of providing the global perspective on the spectrum and relative frequency of respiratory infections encountered during travel. During the period of September 1997 through August 2001, 21960 patients presented to the geosentinel site and out of which respiratory tract infection was diagnosed in 1719 persons accounting for 7.8% of all infections in returned travellers reported to GeoSentinel. A lower respiratory tract infection was diagnosed in 680 returned travellers. Bronchitis was present in 349 individuals (20.3%), pneumonia was diagnosed in 232 patients (13.5%), and influenza was diagnosed in 96 patients (5.6%) (Table 2). The majority of cases of pneumonia were reported during the months of November through April, with a peak in November [10].

Diagnosis	N = 1719
URTI	1177
LRTI	693
Bronchitis	349 (20.3)
Pneumonia	232 (13.5)
Influenza	96 (5.6)
Legionnaires disease	2 (0.12)
pleurisy	14 (0.81)
Total for patients with ≥ 1 LRTI diagnosis	680
Total for patients with ≥ 1 URTI diagnosis	1110
Some patients received > 1 diagnosis, and a total of 1870 respiratory diagnoses were given to 1719 patients. A total of 1177 upper respiratory tract diagnoses were made among the 1110 patients with an upper respiratory tract infection (URTI). A total of 693 lower respiratory tract diagnoses were made among the 680 patients with a lower respiratory tract infection (LRTI).	

Table 2: Number of patients reported in Geosentinel surveillance Network database with respiratory diagnosis [10].

Age, sex, duration of trip and type of travel are the most important risk factors for acquiring pneumonia during travel in several studies (Table 3) [5,10]. Age more than 40 years is associated with increased risk of pneumonia and lower respiratory tract infections. Male sex

was associated with a 2-fold increased odds of pneumonia compared with that for female sex and a lower risk of upper respiratory tract infection [10]. Compared with shorter trips, travel duration of more than 30 days was associated with an increased risk of influenza and lower respiratory tract infection. Persons who had visited Central Asia and Indian subcontinent during the autumn months of September through November was significantly associated with acquisition of a lower respiratory tract infection and bronchitis [10]. Acquiring the data and information regarding the factors associated with increased risk of pneumonia in travellers will help in formulation of guidelines for pretravel advice and vaccination in case of high risk travellers, persons visiting during high risk seasons and/or to high risk places.

Factors associated with risk of pneumonia among travellers	
Age	More than 40 years
Sex	Male
Trip duration	prolong duration (more than 30 days)
Type of travel	Peace corps, health care workers
Travel destination	Central Asia, Indian subcontinent
Months of travel	September to November
Comorbidities	Diabetes mellitus, chronic renal disease, immunocompromised state etc

Table 3: Risk factors associated with acquisition of pneumonia in travellers.

Etiology

The pathogens causing respiratory infection in travellers are generally speaking the same as those in non-travellers. Bacterial pneumonia comprises around 50% of all travel associated pneumonias [5,6,10]. Moreover, travellers are also exposed to pulmonary diseases attributed to bacterial, parasitic, viral and fungal pathogens that are endemic to destination places (Table 4). In a prospective 2-year study of 281 adults living in Kenya for more than 3 months including both travellers and residents, Gram-positive bacteria (mainly *Streptococcus pneumoniae*) represented 47.4% of identified etiologic agents of pneumonia, followed by Gram-negative bacilli in 7.1% (*Salmonella* sp. in 2.1%), mycobacteria in 12.5%, *Mycoplasma pneumoniae* in 2.5%, and influenza virus in 5% [10]. Doherty, et al. in his study of 195 febrile travellers diagnosed eight cases of pneumonia which comprised of four cases of bronchopneumonia, three of pulmonary tuberculosis and one of atypical pneumonia [6]. Ansart S., et al. reviewed records of Patients admitted for pneumonia less than 1 month after returning to France and demonstrated a wider range of etiology [11].

Bacterial pneumonia	<i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> including MRSA, <i>Mycoplasma pneumonia</i> , <i>Legionella pneumophila</i> , <i>Coxiella burnetti</i> , <i>Leptospira</i> sp, <i>Mycobacterium tuberculosis</i> , <i>Hemophilus influenza</i> , <i>Kleibsell</i> a, <i>Acinetobacter</i>
Viral pneumonia	<i>Influenza virus</i> , <i>Dengue</i> , <i>SARS-CoV</i> , <i>MERS-CoV</i> , <i>pulmonary renal syndrome (Hanta virus)</i>
Fungal pneumonia	Histoplasmosis (<i>Histoplasma capsulatum</i>), blastomycosis (<i>Blastomyces dermatidis</i>), Coccidiomycosis (<i>Coccidioides immitis</i>), Paracoccidiomycosis (<i>Paracoccidioides brasiliensis</i>), <i>Pneumocystis jiroveci</i>
Parasitic infections	Schistosomiasis (<i>Schistosoma haematobium</i>), tropical pulmonary eosinophilia (<i>Wuchereria</i> , <i>Brugia</i>) paragonimiasis (<i>Paragonimus westermani</i>), strongyloidiasis (<i>strongyloides</i>), Toxocariasis (<i>Toxocara canis</i>), pulmonary hydatid cyst (<i>Echinococcus</i> spp),
Protozoa	Malaria (<i>Plasmodium</i>), amoebiasis (<i>Entamoeba histolytica</i>)

Table 4: Common etiological agents causing travel related pneumonias.

Malaria, dengue and tuberculosis represent the most common imported infections among travellers. Pulmonary infections and eosinophilia are caused by several parasitic infections like tropical pulmonary eosinophilia (TPE), katayama syndrome, loeffler’s syndrome, paragonimiasis, echinococcosis, toxocariasis etc. Endemic fungal infections like histoplasmosis, coccidiomycoses, blastomycoses is a concern for migrants and visitors to America and parts of Africa. Respiratory diseases due to tick bite, chiggers bite and zoonotic infections are also common in tropics. Viral agents causing respiratory diseases and pneumonias have put air travel under scrutiny because of high attack rates. Recently, outbreaks of influenza (H1N1 2009), severe acute respiratory syndrome (SARS) and Middle east respiratory syndrome (MERS) by coronaviruses (2003 and 2012) have raised the issues of global health security and safety of travellers. Non-infectious causes of pulmonary opacities on chest x-ray should also be borne in mind like pulmonary embolism, Acute and chronic eosinophilic pneumonias, hypersensitivity pneumonitis (HP) etc.

Inhalation route is the most important mode of transmission for several infections and is a area of concern due to high attack rate and for spread of airborne infections during air travel. Influenza, tuberculosis, anthrax, histoplasmosis, coccidiomycoses etc are spread through inhalational route. *Legionella* infection is primarily transmitted through aerosols and aspiration of contaminated water while using spas and swimming pools during stay in resorts and hotels or in cruise ships. Transmission of zoonotic diseases occur primarily

through contact with infected animals or their excretions and human to human transmission is rare : pulmonary hanta virus(rodents), tularaemia (rabbits and hares), leptospirosis (rats), Q-fever (sheep and goats), MERS-cov (dromedary camels). Rickettsial infections are transmitted by tick bite while Tsutsugamushi fever is transmitted by chiggers. Detailed history in relation to recent travel along with radiological and microbiological tests are required to reach the diagnosis.

Diagnosis

Diagnosis depends on detailed clinical history regarding travel destination, duration of travel, type of trip (business, leisure, adventurous etc), food habits while on trip, promiscuity or unprotected sex, use of spa/swimming pools during stay apart from age, comorbidity and vaccination status of the returned traveller.

Most common symptoms which lead to visits to travel clinics for respiratory illness are fever, cough, sore throat, shortness of breath, sputum production, hemoptysis [5]. Fever is usually associated with headache and myalgia especially in influenza infection [5]. Cough may be dry or associated with sputum production. Extrapulmonary manifestations like nausea, diarrhoea, abdominal pain (legionella), skin rash/eschar (rickettsiosis/scrub typhus) may be present. Clinical course may be indolent as in mycobacterial infection, histoplasmosis, melioidosis and schistosomiasis or fulminant leading to respiratory failure as in SARS-CoV, MERS-CoV, H1N1 influenza infections.

Thorough clinical examination amalgamated with imaging modalities and laboratory tests are required to find the etiological agent not only for treatment but also for surveillance purposes.

Chest roentgenogram, complete blood count, sputum examination by gram stain/acid fast stain and sputum culture, blood culture, urine culture, nasopharyngeal swab examination, serological studies, urinary antigen tests, stool examination are done to reach the diagnosis. Despite of this, microbiological diagnosis is not possible in all the cases [5].

Specific Infections

Tuberculosis (TB)

About one-third of the world's population is thought to be infected by *Mycobacterium tuberculosis*. The burden of disease is highly disproportionate: with India and China accounting for nearly half of all cases [12]. Surprisingly, countries with high TB incidence are increasingly popular travel destinations, whether to visit family and friends, to work, or for tourism. The risk of an individual developing active TB as a consequence of international travel depends on:- a) the risk of acquiring new TB infection and b) the risk of that infection progressing to active disease.

Acquiring TB infection is usually defined as conversion from a negative to a positive tuberculin skin test (TST), or a positive TST in a child. However, TST interpretation is more difficult in individuals who have had Bacillus Calmette-Guerin (BCG) vaccination [13]. The risk of acquiring new TB infection depends primarily on the probability of contact with a person with infectious TB and is determined by the prevalence of TB in the areas visited, the duration of time spent there and the degree of close contact with infectious individuals. Thus, an individual working in a health care setting in southern Africa will be at far greater risk of acquiring infection than a tourist visiting the same country.

Foreign travel was identified as a risk factor for a positive TST in two studies from the United States, both among mainly Hispanic children. Lobato, *et al.* [14] and Samain, *et al.* [15] found that children in US who had travelled to a country with high TB incidence for more than a week were more likely to have a positive TST. BCG naive status, travel to countries with high incidence of TB, duration of travel and conditions requiring prolonged and close contact with TB infected persons like healthcare workers, peace corps volunteers etc. has been cited as independent risk factors in several studies [16,17]. Infection with TB during air travel has been documented but the overall risk is low, requiring prolonged exposure (greater than 8 hours) and close proximity to the infected person [18]. The lifetime risk of progression from infection to active TB is estimated at around 10% in immunocompetent groups [19]. The risk varies with age [19] and is greatest in

the first few years following infection [20,21]. Individuals with suppressed immune function either secondary to disease (e.g. HIV infection, diabetes mellitus, chronic renal failure) or immunosuppressant medications (e.g. corticosteroids) have a greater risk of progressing to disease. The annual risk of progression to active TB in patients co-infected with HIV and TB (in the absence of antiretroviral therapy) is estimated at around 10% [22] although this varies widely, depending on the degree of immunosuppression.

The World Health Organization guidelines [23] recommend that long-term travellers (greater than three months) travelling from low- to high incidence countries and who are at risk of TB infection (e.g. individuals working in health facilities or prisons) should have TSTs pre- and post-travel. Newly-acquired infection should be treated accordingly. BCG vaccination is considered to be of limited use in travellers with the exception of infants under 6 months and young children, and health care workers. Revaccination is not recommended.

Legionnaire's Disease

Legionella pneumophila is increasingly recognized as a significant cause of sporadic and epidemic community acquired and nosocomial pneumonia. It is estimated that 8000 - 18,000 cases of community-acquired legionellosis occur each year in the United States [24]. Legionellosis classically presents as two distinct clinical entities- Legionnaires' disease (LD) which is a severe multisystem disease involving pneumonia and Pontiac fever (PF), a self-limited flulike illness [25,26]. It is not possible to clinically distinguish patients with Legionnaires' disease from patients with other types of pneumonia [27]. Features of Legionnaires' disease include fever, non-productive cough, headache, myalgias, rigors, dyspnea, diarrhea, and delirium [28]. Although no chest X-ray pattern can separate this infection from other types of pneumonia, alveolar infiltrates are more common with Legionnaires' disease [29]. Legionnaire's disease was first identified as an outbreak among travellers attending the 1976 American Legion convention in Philadelphia [30]. However, outbreaks that occur in travellers are particularly difficult to detect for many reasons: attack rates for Legionnaire's disease are low; the incubation period is long, allowing infected persons to leave the area in which they acquired the infection; and surveillance is poor, making it difficult to link cases epidemiologically. The European Working Group for Legionella Infections (EWGLI) was established in 1986 to better protect the health of travellers by improving the detection and control of infection sources in European countries [31]. EWGLI NET, formed in 2002, is the European union's (EU) surveillance network dedicated to collecting data on cases of LD in the EU, including travel associated LD [32].

When outbreaks of legionellosis are detected, most involve Legionnaire's disease or Pontiac fever exclusively; combined outbreaks of both LD and PF are unusual [33]. Whirlpool spas have been identified as sources of both LD and PF and have been associated with outbreaks in hotels and on cruise ships several studies [33-36]. Because spas are common features of hotels and cruise ships, they may have a significant role in travel-associated legionellosis. Publicly used whirlpool spas may have much heavier use than whirlpool spas in private sites, and a heavy bather load can compromise halogen concentrations [37].

In recent years, our understanding of Legionnaires' Disease (LD) has improved substantially and new diagnostic and treatment strategies have been introduced [38]. Laboratory testing is necessary for confirmation of legionellosis outbreaks. Culture followed by molecular typing is essential for matching environmental isolates to patient isolates for identification of the source of transmission. Both urinary antigen detection and serology testing although rapid detection tests but these tests don't help in isolation. Culture and molecular typing remain essential for tracing a patient isolate to an environmental source.

Influenza

Influenza is a highly contagious acute respiratory disease causing epidemics and pandemics throughout the world. Post-travel monitoring of hospital admissions identified influenza as a common cause of respiratory illness in returned travellers. Primary influenza virus pneumonia is rare but carries a high case fatality rate. Influenza outbreaks have been described frequently in travellers on board ships and aircraft, where conditions are ideal for rapid transmission due to high attack rate. International travel is important in influenza epidemiology, as it is a major factor in the intercontinental spread of new antigenic variants of influenza viruses. Outbreak of A/Sydney/05/97

(H3N2) influenza on a cruise ship, which introduced this antigenic variant to both the USA and Canada in 1997 is a historical example [39]. There are three types of influenza virus, A, B and C. Type A causes widespread epidemics and pandemics, type B is associated with regional and widespread epidemics, and type C is associated with sporadic cases. The clinical picture is of abrupt onset of fever, malaise, headache, sore throat, myalgia, coryza and a dry cough lasting 2 - 5 days. The clinical features in children and in the elderly may differ in some respects and children may present with febrile convulsions, conjunctivitis, croup, otitis media, bronchitis and gastrointestinal symptoms.

Historically, influenza has caused the most pandemics and is expected to cause others in the future [40]. Recent pandemic threats include H5N1 and H7N9, both avian strains of influenza A and the pandemic of H1N1(2009) that happened suddenly and without warning. Because of high attack rate not only tourists and travellers but the health care staff involved in care of infected travellers are also at risk.

SARS and MERS

The emergence of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003 in China [41] and of the Middle East Syndrome Coronavirus (MERS-CoV) in the Kingdom of Saudi Arabia (KSA) in 2012 [42] resurfaced widespread fear and concern for their potential threat to global health security. SARS spreads by droplet transmission or direct person-to-person through close contact [43]. While the pattern of transmission of MERS-CoV remain unclear, hypotheses include frequent zoonotic infections with limited subsequent human-to-human transmission chains. There is growing evidence that the dromedary camel is a reservoir for the MERS-CoV [44]. MERS-CoV has emerged in the Middle East where religious mass gatherings take place in Saudi Arabia every year and potentially may cause severe, life-threatening respiratory disease which may contribute to the international spread of MERS-CoV. Based on the predicted population movements out of Saudi Arabia, a potential for a global spread of MERS-CoV cannot be excluded according to Khan K and colleagues [45]. Breban., *et al.* calculated the risk for MERS-CoV to have a pandemic potential is less than 5% but they didn't take the influence of Hajj mass gathering into account [46].

The clinical picture of SARS and MERS appears to be similar. In 2003, SARS-CoV caused higher rates of infections in healthcare settings, and affected healthier and younger persons [47]. The US CDC does not recommend changing travel plans to the Middle East because of MERS-CoV threat [48]. The CDC travel notice is a Watch (Level 1) which means travellers to the Arabian Peninsula should follow standard precautions, such as hand washing and avoiding contact with people who are ill. The Saudi Ministry of Health (MoH) recommended in 2014 that elderly people, above 65 years of age, and those with chronic diseases, pregnant women and children (under 12) coming for Hajj and Umrah, should postpone the performance of the Hajj and Umrah for their own safety [49].

Infection Control and Personal Protection

Breaking the human to human transmission cycle remains the cornerstone of infection control practices especially infections with high attack rate like viral hemorrhagic fevers (Ebola and Marburg), influenza (H1N1), SARS and MERS. Hand hygiene is a major component of standard precautions and one of the most effective methods to prevent transmission of pathogens associated with health care. It was estimated that the probability of SARS infection was 6% per shift among nurses in Toronto and the risk increases drastically during intubation [50]. In addition to hand hygiene, the use of personal protective equipment should be guided by risk assessment and the extent of contact anticipated with blood and body fluids, or pathogens. Non-pharmaceutical interventions are known to reduce the spread of respiratory viruses from person to person [51]. Thus, people visiting the Middle East at all times of the year and in particular pilgrims of Hajj and Umrah should take precautions such as: avoiding close contact with people suffering from acute respiratory infections, take personal hygiene measures like frequent hand-washing, cough and sneeze etiquette, adhering to food safety and hygiene rules (avoiding unsafe water, undercooked meats, raw fruits and vegetables unless they have been peeled). Personal protection equipment (PPE) must be used after assessment of risk of exposure to body substance, fluids or contaminated surfaces before initiating any health care activity. PPE includes clean non-sterile gloves, clean, non-sterile fluid-resistant gown, mask and eye protection or a face shield. Ensuring safe

waste management of products contaminated with blood, body fluids, secretions and excretions as clinical waste, in accordance with local regulations also plays a significant role in infection control.

Vaccination

The risk of vaccine-preventable illness in travellers depends upon their itinerary, the duration of travel, the style of travel, and the activities engaged in during travel, and it is influenced by the traveller's past medical and vaccination history. Pneumococcal, HiB and influenza vaccines are recommended by the IDSA guidelines in addition to other vaccines recommended for travellers [51].

Conclusion

Globalisation and increase in international travel have drastically changed the epidemiology and geographical patterns of infections. Respiratory infections including pneumonia in returned travellers is an important cause for health care seeking. Risk of contracting the infections depends on destination, trip duration, type of trip etc and the host factors like age, sex, co morbid conditions. Aetiology of pneumonia in returned travellers is diverse and varied. Respiratory infections like H1N1, SARS, MERS have posed a global threat and need constant reconnaissance of travellers especially coming from middle east and endemic areas.

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Volume 7 Issue 2 February 2018

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