Respiratory Syndrome and Respiratory Tract Infections in Foreign-Born and National Travelers Hospitalized with Fever in Italy

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Background: We measured frequency and epidemiologic, clinical, and hematochemical variables associated with respiratory tract infections (RTIs) in foreign-born and national patients hospitalized with fever with a history of international travel, and compared the final diagnosis of RTI with the presence of a respiratory syndrome (RS) at presentation.

Methods: A prospective, multicenter, observational study was conducted at tertiary care hospitals in Northern Italy from September 1998 to December 2000.

Results: A final diagnosis of RTI was obtained in 40 cases (7.8%), 27 (67.5%) with lower RTI and 13 (32.5%) with upper RTI. The most common RTIs were pneumonia (35%) and pulmonary tuberculosis (15%). A white blood cell count $\geq$ 10,000 and an erythrocyte sedimentation rate $\geq$ 20 mm/h were independently associated with a final diagnosis of RTI; onset of symptoms at $\geq$ 16 days and $\geq$ 75% neutrophils were independently associated with lower RTI. An RS was identified in 51 (9.9%) of 515 travelers. Sensitivity, specificity, and positive and negative predictive values of a diagnosis of RS for a final diagnosis of RTI were 67.5%, 94.9%, 52.9%, and 97.2%, respectively.

Conclusions: Pneumonia and pulmonary tuberculosis were frequent among foreign-born and national travelers with fever admitted to a tertiary care hospital. Half of the pneumonia cases did not present with an RS at first clinical examination.

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International travels are becoming more frequent, and an estimated 30 million people move from industrialized to developing countries annually.[1] At the same time, the importance of travel medicine, the discipline that deals with health problems associated with travel, is progressively increasing.

Respiratory tract infections (RTIs) are a frequent, potentially life-threatening health problem in travelers and a reason for concern because of the possibility of importation of infections such as influenza, diphtheria, and tuberculosis.[2–6] The epidemic of severe acute respiratory syndrome became a worldwide pandemic over a period of a few months owing to the movements of patients.[7] Steffen has estimated the monthly incidence of acute febrile RTIs to be 1,261 in 100,000 travelers.[2] In his analysis, RTI ranked third after travelers' diarrhea and malaria among all infectious problems of the travelers.

The frequency and nature of RTIs vary according to the sampled populations; as most RTIs, especially those of the upper tract, are mild and not incapacitating, they are less likely to be sampled in series of patients passively recruited at clinical sites. Little information has been published on RTIs among migrants, despite the abundant literature that is available on tuberculosis and migration. The types of RTIs affecting travelers are usually similar to those observed in the autochthonous population, and exotic causes of RTIs are considered a rare event.

RTIs represent a significant diagnostic challenge for physicians. An optimal sequence of diagnostic procedures and reliable indications for presumptive treatment has not been defined, mainly because of the incomplete understanding of the frequency of underlying etiologies. It is not known whether the absence of a respiratory syndrome (RS) at presentation reliably excludes a final diagnosis of RTI.

We present here the analysis of foreign-born and national travelers admitted to tertiary care hospitals in Northern Italy with fever, to describe the frequency of RTIs, the spectrum of underlying diagnoses, clinical and epidemiologic factors associated with the diagnosis, the presence of an RS at first presentation of cases with RTI, and the diagnostic procedures implemented.

Methods

A prospective, observational, multicenter study was conducted from September 1998 to December 2000 in a network of 12 centers in the North of Italy (belonging to the Lombardy Region clinical network for International Health, SIRL). All the centers are referral hospitals for infectious diseases. Only inpatients were considered in this study. Criteria for eligibility included the presence of temperature above 37.5°C at the time of the clinical evaluation, a history of international travel in the subtropical belt within 18 months since onset of symptoms, and the clinical judgment that the disease was related to travel.

RS was defined as the presence of cough, dyspnea/polypnea, or hemoptysis accompanying fever.

Cases of RTI were identified according to the final diagnosis reported on the discharge document (gold standard). RTIs were further classified as upper (URTI) and lower (LRTI). URTIs included infections of the nose, pharynx, larynx, facial sinuses, and influenza, whereas LRTIs included bronchitis, pneumonia, and other lung parenchymal infections. Clinical diagnoses were accepted such as bronchitis or pharyngitis. The diagnosis of pneumonia always required an abnormal finding on a chest radiograph. Etiologic diagnoses, when available, were based on the demonstration of a microorganism in a clinically relevant specimen or on seroconversion to an infectious agent. Investigators did not follow prospectively designed, standardized, diagnostic procedures to manage patients with RS. Because of the observational nature of the study, there was no standardization of any procedure of diagnostic evaluation.

Data were collected on specifically designed data collection sheets. Patients were classified as immigrants, travelers, foreign visitors, or expatriates. Regarding the reason for travel, cases were classified as involving immigrants (foreign-born persons arriving for the first time into Italy), foreign-born persons visiting relatives and friends, tourists, businessmen, expatriates, soldiers, or missionaries.

Areas where the infection likely originated were broadly classified as Africa (the African continent), Asia and the Pacific (Southeast Asia, Indian subcontinent, the South Pacific, Australia, New Zealand, and Papua New Guinea), and Latin America (Central and South Americas).

Statistical Methods

Microsoft Access 97 was used for data storage and management. Statistical analyses were performed with SPSS 10.0 for Windows (SPSS, Inc.). The association of sociodemographic, epidemiologic, and clinical categoric variables with RTI or LRTI was assessed using the chi-square test or Fisher's exact test, as appropriate. The crude and adjusted odds ratios (ORs) with their respective 95% CI are presented. The chosen level of significance was 5% and the p values described are two-tailed. Logistic regression models to identify the variables independently associated with RTI and LRTI were constructed using the variables that were statistically significant in the univariate analysis ($p \leq .05$) controlled by sex and age.

Results

A total of 540 travelers who matched the inclusion criteria were observed. We present the results of an analysis conducted on 515 cases (95%) for whom information on the syndrome at presentation was available.

The baseline demographic data of the 515 patients, the characteristics of their travel, and the laboratory test results at entry are summarized in Table 1. Patients were predominantly males (72.0%), with a median age of 34 years (range 1–79 yr). There were 295 foreign-born persons (accounting for 57.3% of all cases), 80.3% of whom were residents in Italy visiting relatives and friends. Italian tourists and businesspeople still accounted for 36.1% of all the cases described here. The probable origin of the infection was Africa in 80.6% of the cases, which reflects both the pattern of immigration in Italy and the origin of malaria in both foreign-born persons and national tourists. The duration of travel was shorter than 30 days for 196 patients (38.1%). The median number of days between arrival in Italy and admission to hospital was 11 (range 1–540 d); it was < 2 weeks in 61.8%, and longer than 6 months in 5.3%.

Malaria was by far the single most common disease, diagnosed in 305 (59.2%) patients. A final diagnosis of RTI was obtained in 40 cases (7.8%). Among the cases with RTI, 27 (67.5%) had an LRTI and the remaining 13 (32.5%) had a URTI. The frequency of diagnosed conditions is presented in Table 2. All 6 patients with pulmonary tuberculosis were foreign-born persons; 2 were immigrants at first arrival, and 4 had traveled to visit relatives and friends.

At first clinical examination, RS was identified in 51 of 515 travelers (9.9%) and ranked third among all syndromes, following fever without organ involvement (44.3%) and enteric syndrome (29.9%). Among 51 cases with RS at entry, 27 had a conclusive diagnosis of RTI. The remaining 24 cases involved malaria (14), typhoid fever (2), and other diagnoses (8 conditions, 1 case each). In this series 4.6% (14 of 305) of malaria cases presented with an RS, and malaria was the final diagnosis of 27.5% (14 of 51) of the cases with a diagnosis of RS at entry. Among 464 patients with no RS at entry, 13 had a final diagnosis of RTI: 9 had pneumonia (including 1 tuberculosis case), 1 influenza, 2 tonsillitis, and 1 sinusitis. The sensitivity, specificity, and positive and negative predic-

Table 1 Baseline Demographic Data and Travel Characteristics of 515 Travelers and Immigrants with Fever

Characteristics and Test Results	n	*%*
Gender		
Male	371	72.0
Female	144	28.0
Age		
< 30 yr	168	32.6
30–60 yr	317	61.6
> 60 yr	30	5.8
Type of traveler		
Migrant	295	57.3
Traveler	150	29.1
Foreign visitor/expatriate	70	13.6
Reason for travel		
Immigration	62	12.0
Visiting relatives and friends	237	46.0
Tourism	129	25.0
Business	57	11.1
Student/volunteer/unknown	30	5.8
Area of infection		
Africa	415	80.6
America	28	5.4
Asia/Pacific	72	14.0
Duration of travel		
< 30 d	196	38.1
≥ 30 d	319	61.9
Time before admission*		
< 14 d	302	61.8
15–180 d	161	32.9
> 180 d	26	5.3
Laboratory tests		
WBC > 10,000†	70	13.7
Neutrophils > 75%‡	120	24.0
Platelets < 130,000†	239	46.7
LDH > 400§	248	62.5
ESR > 20‖	313	68.6

ESR = erythrocyte sedimentation rate; LDH = L-lactate dehydrogenase; WBC = white blood cell count.
*n = 489.
†n = 512.
‡n = 500.
§n = 397.
‖n = 456.

Table 2 Specific Diagnoses among 40 Patients with Respiratory Tract Infections after International Travel

Infection	n *(%)*
URTI	13 (32.5)
Pharyngotonsillitis	5 (12.5)
Sinusitis	3 (7.5)
Influenza	1 (2.5)
Nonspecified	4 (10.0)
LRTI	27 (67.5)
Pneumonia	14 (35.0)
Pneumococcal	1 (2.5)
Nonspecified	13 (32.5)
Pulmonary tuberculosis	6 (15.0)
Interstitial pneumonia	4 (10.0)
Pneumocystis carinii	1 (2.5)
Mycoplasma	1 (2.5)
Nonspecified	2 (5.0)
Tracheobronchitis	2 (5.0)
Pulmonary hydatidosis	1 (2.5)

LRTI = lower respiratory tract infection; URTI = upper respiratory tract infection.

tive values of a diagnosis of RS at entry for a final diagnosis of RTI were 67.5, 94.9, 52.9, and 97.2, respectively.

After excluding 305 patients with malaria (including 3 patients that also had a final diagnosis of RTI other than malaria), we studied the remaining 210 cases to evaluate the association of epidemiologic and hematochemical variables with RTI (Table 3). White blood cell count ≥ 10,000 and erythrocyte sedimentation rate (ESR) ≥ 20 mm/h were both independently associated with a final diagnosis of RTI (see Table 3). On the other hand, the variables independently associated with a diagnosis of LRTI were onset of symptoms ≥ 16 days and a neutrophil percentage ≥ 75% (Table 4).

The diagnostic procedures adopted by the attending clinicians on cases presenting with an RS included a chest radiograph in 43 (84.3%) and a sputum examination in 20 (39.2%). The latter examination gave positive results in 6 cases (30%), allowing for the identification of *Mycobacterium tuberculosis* in 4 cases and *Pneumocystis carinii* and *Streptococcus pneumoniae* in 1 case each. A chest radiograph was performed in 153 cases (50.2%) with uncomplicated malaria and without an RS. Other diag-

Table 3 Crude and Adjusted ORs and CIs for a Diagnosis of an RTI according to Epidemiologic and Hematochemical Variables among 210 Travelers and Immigrants*

Variable	n *(%) with RTI*	*Crude OR (95% CI)*	p *Value*	*Adjusted OR (95% CI)*	p *Value*
Sex					
Male	24/127 (18.9)	1	.58	1	.98
Female	13/83 (15.7)	0.80 (0.38–1.67)		0.99 (0.39–2.49)	
Age					
< 30 yr	15/84 (17.9)	1	1.0	1	.41
≥ 30 yr	22/126 (17.5)	0.97 (0.47–2.01)		0.69 (0.28–1.68)	
Category of patient					
Other	19/146 (13.0)	1	.01	1	.59
Migrant	18 /64 (28.1)	2.62 (1.26–5.41)		1.47 (0.35–6.17)	
Reason for travel					
Miscellaneous	23/163 (14.1)	1	.02	1	.49
Visiting relatives and friends	14/47 (29.8)	2.58 (1.20–5.55)		1.60 (0.42–6.17)	
Country of infection					
Not Africa	11/78 (14.1)	1	.35	NA	NA
Africa	26/132 (19.7)	1.53 (0.71–3.30)			
Duration of travel†					
< 30 d	14/122 (11.5)	1	.009	1	.36
≥ 30 d	22/84 (26.2)	2.74 (1.31–5.73)		1.60 (0.59–4.34)	
Time before admission‡					
< 14 d	14/120 (11.7)	1	.01	1	.35
≥ 14 d	22/86 (25.6)	2.60 (1.24–5.45)		1.56 (0.61–4.0)	
WBC‡					
< 10,000	20/160 (12.5)	1	.003	1	.01
≥ 10,000	15/47 (31.9)	3.28 (1.52–7.10)		3.29 (1.29–8.39)	
Neutrophils§					
< 75%	19/141 (13.5)	1	.06	NA	NA
≥ 75%	15/60 (25.0)	2.14 (1.00–4.57)			
Platelets‡					
≥ 130,000	30/179 (16.8)	1	.79	NA	NA
< 130,000	5/28 (17.9)	1.08 (0.38–3.07)			
LDH‖					
< 400 IU/L	14/87 (16.1)	1	.38	NA	NA
≥ 400 IU/L	13/57 (22.8)	1.54 (0.66–3.58)			
ESR#					
< 20	4/69 (5.8)	1	.001	1	.02
≥ 20	28/112 (25.0)	5.42 (1.81–16.22)		3.83 (1.18–12.43)	

ESR = erythrocyte sedimentation rate; IU/L = international units per liter; LDH = L-lactate dehydrogenase; NA = not applicable; OR = odds ratio; RTI = respiratory tract infection; WBC = white blood cell count.

*These 210 travelers and immigrants had fever but a diagnosis of malaria had been excluded.

†n = 206.

‡n =207.

§n = 201.

‖n = 144.

#n = 181.

Table 4 Crude and Adjusted ORs and CIs for a Diagnosis of an LRTI according to Epidemiologic and Hematochemical Variables among 210 Travelers and Immigrants*

Variable	n *(%) with LRTI*	*Crude OR (95% CI)*	p *Value*	*Adjusted OR (95% CI)*	p *Value*
Sex					
Male	16/127 (12.6)	1	.83	1	.86
Female	9/83 (10.8)	0.84 (0.35–2.01)		0.91 (0.33–2.50)	
Age					
< 30 yr	10/84 (11.9)	1	1	1	.88
≥ 30 yr	15/126 (11.9)	1.00 (0.43–2.35)		1.10 (0.40–1.89)	
Category of patient					
Other	15/146 (10.3)	1	.35	NA	NA
Migrant	10/64 (15.6)	1.62 (0.68–3.82)			
Reason for travel					
Miscellaneous	19/163 (11.7)	1	.80	NA	NA
Visiting relatives and friends	6/47 (12.8)	1.11 (0.42–2.96)			
Country of infection					
Not Africa	7/78 (9.0)	1	.43	NA	NA
Africa	18/132 (13.6)	0.62 (0.22–1,70)			
Duration of travel†					
< 30 d	11/122 (9.0)	1	.19	NA	NA
≥ 30 d	13/84 (15.5)	1.85 (0.78–4.35)			
Onset of symptoms‡					
< 16 d	8/120 (6.7)	1	.01	1	.004
≥ 16 d	16/86 (18.6)	3.20 (1.30–7.87)		4.43 (1.60–12.24)	
WBC‡					
< 10,000	13/160 (8.1)	1	.02	1	.19
≥ 10,000	10/47 (21.3)	3.06 (1.24–7.51)		2.05 (0.70–5.99)	
Neutrophils§					
< 75%	10/141 (7.1)	1	.006	1	.01
≥ 75%	13/60 (21.7)	3.62 (1.49–8.82)		3.96 (1.36–11.50)	
Platelets‡					
≥ 130,000	20/179 (11.2)	1	1.0	NA	NA
< 130,000	3/28 (10.7)	0.95 (0.26–3.45)			
LDH‖					
< 400 IU/L	7/87 (8.0)	1	.11	NA	NA
≥ 400 IU/L	10/57 (17.5)	2.43 (0.87–6.82)			
ESR#					
< 20	4/69 (5.8)	1	.09	NA	NA
≥ 20	16/112 (14.3)	2.71 (0.87–8.47)			

ESR = erythrocyte sedimentation rate; IU/L = international units per liter; LDH = L-lactate dehydrogenase; LRTI = lower respiratory tract infection; NA = not applicable; OR = odds ratio; WBC = white blood cell count.

*These 210 travelers and immigrants had fever but a diagnosis of malaria had been excluded.

†$n = 206$.

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nostic procedures targeting agents of RTI were done sporadically, including pharyngeal swab (9) and serology for *Legionella* spp (6), *Mycoplasma* spp (4), and *Chlamydia* spp (3). Rapid, bedside diagnostic tests, including antigen detection for influenza, *Streptococcus* spp, or *Legionella* spp, were used in only 2 (3.9%) RS cases.

Discussion

We present the results of a prospective investigation on hospitalized foreign-born and national travelers with fever and respiratory symptoms. Our network is likely to have captured the large majority of occurring cases because in Italy most foreign-born and national travelers with fever are admitted to infectious diseases departments of the public health sector, being that the private sector is extremely poorly developed in this regard. RTIs were common and accounted for 7.8% of the cases. Most such infections were indeed represented by pneumonia or other LRTIs (5.2% of the total).

Our data confirm that the importance of RTIs among causes of fever after international travel is increas-

ing. Incidence rates were recently reviewed by Denny and Kallings, ranging from 4 to 42%.[8] In a more recent report, Evans showed that among 1,469 British package-holiday tourists, 7.6% had respiratory infection; this condition was outnumbered by travelers' diarrhea only.[9] Respiratory illness occurred in 26% of 748 travelers from the United States in another study, second only to diarrhea.[10] We observed a relatively high proportion of LRTIs, most likely because we missed mild infections (which do not require hospital care) and those with very short incubation periods, which resolve before the travel is over. The hospital setting we investigated is similar to that of a recent study from Australia: in a group of 232 sick travelers mainly from Asian destinations, RTIs were second after malaria in prevalence, accounting for 24% of the cases.[11] In that series LRTIs accounted for 50% of all RTIs and were almost equally distributed between bacterial pneumonia and influenza.[11]

The spectrum of specific RTIs identified in this series confirms that exotic imported infections are rare, and most cases are caused by cosmopolitan infections. Diagnostic procedures and treatment should therefore primarily be directed toward the latter agents. Remarkably, we observed 6 cases of pulmonary tuberculosis, which accounted for 1.2% of all cases and 25% of cases with pneumonia. A similar result was reported by Doherty and colleagues in London.[12] The importance of tuberculosis as a travel-related disease is debated and still not fully recognized. The high proportion of foreign-born persons in our sample and the study design allowing for a period of 18 months from the last reported travel made it possible for us to "capture" these cases. Tuberculosis has a specific importance among RTI because it can spread through respiratory contact and requires strict isolation conditions in hospitals, and because there is an important threat of resistant cases.

Risk factors for the acquisition of RTIs during international travel are not clearly identified. Unlike a large study that recently reported on the data in the GeoSentinel Network,[13] we could not identify any role of age, gender, trip duration, or reason for travel as a predictor for developing respiratory infections. We had a much smaller data set than that of the GeoSentinel Network, which may account for our failure to identify risk factors. However, O'Brien and colleagues reported a five times higher risk of pneumonia among travelers > 40 years of age in a series of the same magnitude as ours.[11] The destination of travel was Africa in 80% of our cases; in series from the United States and Australia,[10,12] most travelers had visited Central and South America or Southeast Asia, which may also account for some differences in the results.

We also studied the association of hematochemical variables and RTI, which may be useful in the clinical diagnosis of individual patients. Patients with an RTI had higher leukocyte counts and higher ESR values; patients with an LRTI presented significantly longer "incubation" periods and a higher neutrophil percentage. However, there was a significant overlap of patients with and without LRTI, and the predictive value of these two variables, alone or combined, remained low. Still, leukocyte count (particularly with a high neutrophil percentage), ESR, and latency period may play a role in the decision to administer early antibiotic treatment in travelers with fever since a significant proportion of LRTIs are caused by bacterial agents.

Our case definition for RS consisting of cough or dyspnea/polypnea or hemoptysis accompanying fever was insensitive for a final diagnosis of RTI as it was unable to identify as much as one-third of all true cases of RTI. It actually failed to recognize 9 cases of pneumonia; a chest radiograph should be performed routinely in travelers with fever and no obvious diagnosis. Interestingly, most cases of RS and a diagnosis other than RTI were affected by malaria. In our study sample, almost 5% (14 of 305) of all malaria cases presented with an RS, although respiratory signs and symptoms are not usually included in signs and symptoms of uncomplicated malaria.

A few diagnostic procedures other than chest radiography were adopted by clinicians in this series. The usefulness of sputum Gram stain is debated: it is a simple procedure that is quick and inexpensive, but it is insensitive since only half of patients with pneumonia may produce sputum, and contamination occurs in one-third of the patients. In our series etiologic diagnosis was obtained in only 1 of 14 patients with lobar pneumonia. The high proportion of tuberculosis cases among foreign-born travelers with fever may support the need for sputum examination for acid-fast bacilli in patients with an abnormal chest radiograph.

The use of rapid, bedside, diagnostic techniques was limited, despite the potential benefit of these procedures. Among other tests, the value of pharyngeal detection of streptococcal and influenza antigens from nasopharyngeal samples would need to be assessed. Among cases of pharyngitis, a rapid test would be of value to identify patients deserving antibiotic treatment to prevent complications. The occurrence of influenza might be underestimated among travelers. Although this disease represented 20% of diagnoses in another study,[11] only 1 case of influenza was identified in our series, most likely because diagnostic tests for influenza were rarely used. The importance of the diagnosis of influenza is twofold. First, selected patients with an increased risk of developing complications may require antiviral treatment, which is now available. Second, the recognition of the true proportion of influenza cases among travelers with fever may cause current prevention strate-

gies for this vaccine-preventable disease to be reconsidered.

There are a number of limitations of this study. First, the relatedness between travel and pulmonary disease remains unproven, as it is in other published studies; however, our findings describe what clinicians have to manage in patients with fever and a history of travel at tertiary care hospitals in Italy. Second, results apply to travelers from the subtropical belt; the number of people moving between Eastern and Western Europe is increasing, and this phenomenon may have an epidemiologic impact. Third, the inclusion of pulmonary tuberculosis cases in the series is controversial. This is due to the prospective design of the study, which enforced us to keep in the case list all enrolled patients, regardless of the final diagnosis. Despite the fact that tuberculosis may present with a variety of clinical conditions, persons with fever, respiratory signs, and history of travel should undergo diagnostic procedures to rule it out.

Conclusions

In conclusion, our prospective investigation on hospitalized foreign-born and national travelers with fever confirms that RTIs are common and account for up to 8% of such cases. Exotic infections were rare. Most cases were represented by community-acquired pneumonia and pulmonary tuberculosis among foreign-born patients. Half of the patients with pneumonia did not present with an RS at first clinical examination.

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Declaration of Interests

The authors state they have no conflicts of interest.

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