Clinical and Microbiological Evaluation of Travel-Associated Respiratory Tract Infections in Travelers Returning From Countries Affected by Pandemic A(H1N1) 2009 Influenza

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Background. Although acute respiratory tract infections (RTI) have been recognized as a significant cause of illness in returning travelers, few studies have specifically evaluated the etiologies of RTI in this population.

Methods. This prospective investigation evaluated travelers returning from countries with endemic influenza A(H1N1) 2009, and who were seen in our department at the onset of the outbreak (April–July 2009). Patients were included if they presented with signs of RTI that occurred during travel or less than 7 days after return from overseas travel. Patients were evaluated for microbial agents with RespiFinder plus assay, and throat culture according to clinical presentation.

Results. A total of 113 travelers (M/F ratio 1.2:1; mean age 39 y) were included. They were mainly tourists (n = 50; 44.2%) mostly returning from North America (n = 65; 58%) and Mexico (n = 21; 18.5%). The median duration of travel was 23 days (range 2–540 d). The median lag time between return and onset of illness was 0.2 days (range 10 d prior to 7 d after). The main clinical presentation of RTI was influenza-like illness (n = 76; 67.3%). Among the 99 microbiologically evaluated patients, a pathogen was found by polymerase chain reaction (PCR) or throat culture in 65 patients (65.6%). The main etiological agents were influenza A(H1N1) 2009 (18%), influenza viruses (14%), and rhinovirus (20%). A univariate analysis was unable to show variables associated with influenza A(H1N1) 2009, whereas rhinorrhea was associated with viruses other than influenza (p = 0.04).

Conclusion. Despite the A(H1N1) 2009 influenza pandemic, rhinovirus and other influenza viruses were also frequent causes of RTI in overseas travelers. Real-time reverse transcription-PCR and nasopharyngeal swab cultures are useful diagnostic tools for evaluating travelers with RTI.

Respiratory tract infections (RTIs) are a significant cause of health problems, accounting for 7%–11% of consultations in returning travelers. The prevalence of RTI is invariably higher in travelers presenting with fever, as RTIs account for 14%–24% of the etiologies of fever. However, the spectrum of microbial agents causing RTI in travelers has been investigated in only limited circumstances or selected populations.

Influenza is recognized as a significant cause of fever and RTI infections in travelers. An Australian study found that influenza was responsible for 5% of the 56 RTIs diagnosed in 232 returning travelers and immigrants/refugees presenting with fever. Seroconversion for influenza virus was confirmed in 12% of 211 febrile Swiss travelers compared with 2.8% for all Swiss travelers surveyed; the incidence was estimated to be around one influenza-associated event per 100 person-months abroad. However, a high number of RTIs remain unexplained, mostly owing to a lack of evaluation and the rapid, spontaneous recovery of patients.

At the end of April 2009, a new influenza virus A(H1N1) outbreak was identified in Mexico and spread.
rapiddly to North America then to Europe and the rest of the world through international travelers.6,7 The rapid progression of the disease led the WHO to declare a phase 6 pandemic on June 11, 2009.8 During the first months of the outbreak in France, travelers were given particular attention and those with presumed signs of influenza were advised to immediately consult dedicated infectious disease units until July 17, 2009.9 This gave us an opportunity to evaluate the microbiological etiologies of RTI in travelers during the first months of the new Influenza virus A(H1N1) 2009 outbreak (April–July 2009).

Although cell culture is the “gold standard” for the detection of respiratory viruses, it is impractical for general use in travelers, so, we evaluated the use of a multiplex polymerase chain reaction (PCR) assay in this setting.

Patients and Methods

In a consecutive manner, adult (>17 y old) patients, returning from abroad and who consulted within our department in Paris, from April 27, 2009 to July 17, 2009 were enrolled in the study. No informed consent was required because clinical management was as per routine pandemic protocol. Patients were included if they presented with signs suggestive of RTI that had occurred during travel or <7 days after their return from countries endemic for influenza virus A(H1N1) 2009. RTIs were classified as upper RTI [tonsillitis, otitis, sinusitis, laryngitis, or influenza-like illness (ILI)] and lower RTI (bronchitis, lobar pneumonia, or diffuse pneumonia). ILI was defined as the presence of the following signs: temperature >37.5°C with respiratory (eg, cough, sore throat, rhinorrhea) and/or constitutional symptoms (eg, headache, myalgia, arthralgia, fatigue, chills) according to previously established criteria for respiratory illnesses.10 ILI and bronchitis were clinically diagnosed. Lobar pneumonia was diagnosed on chest X-ray. Endemic countries were those which declared outbreaks of new influenza virus A(H1N1) in their territories according to weekly published WHO bulletins. Following admission, patients were isolated either in hospital or at home.

The following epidemiologic data were collected: demographic findings (age and sex), travel history (destination and duration), and purpose of travel (tourism, business, or immigrants visiting friends and relatives). Travel destination was classified according to the country visited. The time between return and symptom onset was also recorded. The following signs and symptoms were assessed: temperature, sore throat, rhinorrhea, cough, dyspnea, headache, myalgia, arthralgia, fatigue, chills, gastrointestinal signs (eg, diarrhea, vomiting), urinary tract symptoms, and cutaneous symptoms. The following biological data were recorded: serum creatinine, liver function tests, blood cell count, platelets count, and C-reactive protein.

The different presentations of RTI were classified according to clinical signs and the results of chest X-ray performed when pneumonia was clinically suspected. Pneumococcal pneumonia was presumed if the patient presented with typical clinical signs, a compatible chest X-ray, and a favorable outcome with amoxicillin. No diagnostic confirmation, such as urinary pneumococcal or Legionella pneumophila 1 antigen was performed. Nasopharyngeal specimens were collected by trained nurses upon admission.

At the virology laboratory, the first step of the diagnostic evaluation was to identify influenza A(H1N1) 2009 virus infection by means of real-time reverse transcription-PCR (RT-PCR), as previously described11 to assess whether or not the patient should remain isolated. In addition, blood cultures were performed in cases with fever and those patients with tonsillitis received a pharyngeal swab for streptococcal evaluation. The second step of the etiologic diagnosis entailed an investigation for other respiratory viruses and intracellular bacteria potentially associated with RTI. The following viral and bacterial assays were performed to detect a broad spectrum of microorganisms. RespiFinder plus (PathoFinder, Maastricht, The Netherlands), a multiplex PCR assay12, is able to detect 15 viruses and 4 bacteria in a single reaction: influenza A virus (InfA), influenza B virus (InfB), influenza A (H5N1) virus (InfA H5N1), respiratory syncytial virus (RSV; types A and B), parainfluenza virus (PIV; types 1–4), human metapneumovirus (hMPV), rhinovirus, coronavirus (types OC43, 229E, NL63), adenovirus, Chlamydophila pneumoniae, Mycoplasma pneumoniae, L. pneumophila, and Bordetella pertussis. Furthermore, human bocavirus (hBoV) DNA was detected using the Bocavirus r-gene kit (Argène, Varilhes, France), and enterovirus RNA was evaluated following the method previously described.13 All assays were performed using the remaining nasopharyngeal specimen frozen at −80°C in the virology laboratory.

Variables were collected using Microsoft Excel 2002 software (Microsoft Windows XP Professional, Microsoft Corp., Redmond, WA, USA). The relative frequency of the diagnoses and their association with biological and clinical findings were analyzed. The statistical significance of differences in dichotomous variables was determined using chi-square tests with the Fisher two-tailed exact test. All variables correlated in a univariate analysis with influenza were included in a stepwise backward regression model (significance level for exclusion was $p \geq 0.25$) to identify predictors of the disease. Statistical analyses were performed by SPSS statistical software 17.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 113 travelers with signs of RTI were included. The M/F ratio was 1.2:1, and the mean age was 39 years old. The reason for travel was mainly tourism ($n = 50$;
upper RTI and 2 (10%) of the 20 patients with
by RT-PCR in 16 (20.2%) of the 79 patients with
agent was influenza A(H1N1) 2009 which was found
patients with mixed infection. The main etiological
throat culture in 65 patients (65.6%), including three
were detected in 32 patients. Results of the biological
to be critically ill, and 17% (17) were hospitalized. 54
symptoms were fever, sore throat, and cough, found in
median lag time between symptoms onset and return
– 0.2 d after return (Table 1). The most common symptoms
were respiratory tract infections. Among the 99 patients
and cough, found in more than 65% of the 113 patients
median duration of travel was 23 days (range 2–540 d). The
Reason for travel
Unknown
VFR
Tourism
Business
Area of travel∗
North America
Central America
South America
Africa
Europe
Asia/Pacific
Location of travel∗∗
Nomurban
Urban
Duration of travel∗∗∗
Median (range)
<15 d
≥15 d
Time of illness∗
Median (range)
Before return
0–5 d after return
>5 d after return
Table 1 Demographic data and travel characteristics of 113 travelers with respiratory tract infections

| Characteristics | n  | %    |
|-----------------|----|------|
| Gender          |    |      |
| Male            | 61 | 54   |
| Female          | 52 | 46   |
| Age             |    |      |
| Median (range)  | 39.01 (19–79 y) | |
| <30 y           | 38 | 33.6 |
| 30–60 y         | 63 | 55.8 |
| >60 y           | 12 | 10.6 |
| Reason for travel|    |      |
| Unknown         | 22 | 19.5 |
| VFR             | 11 | 9.7  |
| Tourism         | 50 | 44.2 |
| Business        | 30 | 26.5 |
| Area of travel* |    |      |
| North America   | 65 | 58.0 |
| Central America | 28 | 25.0 |
| South America   | 4  | 3.6  |
| Africa          | 3  | 2.7  |
| Europe          | 4  | 3.6  |
| Asia/Pacific    | 8  | 7.1  |
| Location of travel∗∗ |    |      |
| Nomurban        | 14 | 13.9 |
| Urban           | 87 | 86.1 |
| Duration of travel∗∗∗ | Median (range) | |
| 23.42 (2–540)   | |
| <15 d           | 81 | 82.7 |
| ≥15 d           | 17 | 17.3 |
| Time of illness* | Median (range) | |
| 0.26 (–10;7)    | |
| Before return   | 61 | 54.5 |
| 0–5 d after return | 46 | 41.1 |
| >5 d after return | 5  | 4.5  |

North America: Canada, USA; Central America: Mexico, Dominican Republic; South America: Brazil, Argentina.
VFR = visiting friends and relatives.
∗n = 112; ∗∗n = 101; ∗∗∗n = 98.

44.2%) to the United States (n = 59; 52.2%), Canada
(n = 6; 5.3%), and Mexico (n = 21; 18.5%). The median
duration of travel was 23 days (range 2–540 d). The
median lag time between symptoms onset and return
was 0.2 days (10 d before return to 7 d after) (Table 1).
The most common symptoms were fever, sore throat,
and cough, found in more than 65% of the 113 patients
(Table 2). A total of 89 patients were diagnosed with
an upper RTI, including 76 ILI, whereas 24 patients
were diagnosed with a lower RTI (Table 3). Of the 41
patients who had a chest X-ray performed, four had
interstitial infiltrates, two had bronchiolar infiltrates,
and three had lobar infiltrates, while no abnormalities
were detected in 32 patients. Results of the biological
data are shown in Table 2.

Among the 99 patients with microbiological
evaluations, at least one pathogen was found by PCR or
throat culture in 65 patients (65.6%), including three
patients with mixed infection. The main etiological
agent was influenza A(H1N1) 2009 which was found
by RT-PCR in 16 (20.2%) of the 79 patients with
upper RTI and 2 (10%) of the 20 patients with

Table 2 Presenting signs, symptoms, and laboratory tests in 113 travelers with respiratory tract infections

| Symptoms          | n   | %   |
|-------------------|-----|-----|
| Dry cough         | 100 | 88.5|
| Sore throat       | 79  | 69.9|
| Fever (>38°C)     | 75  | 66.4|
| Myalgia           | 65  | 57.3|
| Rhinorrhea        | 56  | 49.6|
| Headache          | 44  | 38.9|
| Asthenia          | 26  | 23.0|
| Chills            | 26  | 23.0|
| Arthralgia        | 11  | 9.7 |
| Diarrhea          | 8   | 7.1 |
| Lung crackles     | 6   | 5.3 |
| Dyspnea           | 5   | 4.4 |
| Nasal obstruction | 5   | 4.4 |
| Urinary tract symptoms | 3 | 2.7 |
| Abdominal pain    | 2   | 1.8 |
| Otopathia         | 2   | 1.8 |
| Epistaxis         | 1   | 0.9 |
| Vomiting          | 1   | 0.9 |
| Conjunctivitis    | 0   | 0.0 |
| Rash              | 0   | 0.0 |

Laboratory tests (n)

| Symptom            | Mean | Range |
|--------------------|------|-------|
| CRP (50)           | 29   | 0–173 |
| WBC (66)           | 7,796| 3,000–22,200 |
| Neutrophils (34)   | 5,813| 1,141–18,850 |
| Lymphocytes (34)   | 1,554| 550–2,850  |
| Platelets (66)     | 226,190| 120,000–391,000 |
| Serum creatinine (62) | 72 | 42–106 |
| ASAT (54)          | 23   | 12–44  |
| ALAT (55)          | 22   | 8–45   |

CRP = C-reactive protein; WBC = white blood cell count; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase.

Table 3 Clinical forms of respiratory tract infections among 113 travelers

| Clinical presentation | n   | (%)   |
|-----------------------|-----|-------|
| URTI                  | 89  | 78.7  |
| Tonsillitis           | 10  | 8.8   |
| ILI                   | 76  | 67.3  |
| Sinusitis             | 2   | 1.8   |
| Laryngitis            | 1   | 0.9   |
| LRTI                  | 24  | 21.3  |
| Tracheobronchitis     | 20  | 17.7  |
| Lobar pneumonia       | 3   | 2.7   |
| Interstitial pneumonia| 1   | 0.9   |
| Total LRTI and URTI   | 113 | 100.0 |

ILI = influenza-like illness; LRTI = lower respiratory tract infection; URTI = upper respiratory tract infection.

lower RTI (18% of the microbiologically evaluated
cases). Aside from influenza A(H1N1) 2009, the
most common viruses detected were other influenza
virus (14%) and rhinovirus (20%). Beta-hemolytic
Streptococcus sp. was cultured from four pharyngeal
swabs in eight patients with tonsillitis. Of the three
Discussion

This study provides a prospective and solid evaluation of etiological causes of RTI in a population of returning travelers with RTI regardless of intensity. The unusual situation surrounding the H1N1 pandemic allowed us to access a general population, accustomed to mild RTI symptoms for which they do not usually consult. This was illustrated in a study of 779 American travelers visiting developing countries where 75 patients (10%) presented symptoms of RTI after return but only 22 (3%) sought medical consultation for RTI. In France, at the beginning of the flu pandemic, travelers with any sign of RTI were advised to promptly consult a clinician. Therefore, we were able to test most, if not all, our patients with RTI, providing an accurate evaluation of the spectrum of respiratory pathogens that may target travelers.

The age distribution in our study (>60% of our cases are more than 30 y old) is consistent with that found in a Japanese study during the same outbreak. Indeed the median age of confirmed cases of influenza A(H1N1) 2009 in Japanese travelers (ie, 25 y old) was older than the median age of influenza confirmed cases who did not travel (ie, 15 y old). Older adults tend to travel more often than younger and therefore are perhaps more at risk of contracting respiratory disease.

The clinical spectrum of RTI in travelers is broad. In the Geosentinel study in which RTI was diagnosed in 1719 returning travelers (7.8% of all returning travelers), the main clinical presentations of RTI were “nonspecified” upper RTI (diagnosed in 47% of the patients), bronchitis (20%), pneumonia (13%), pharyngitis (13%), and ILI (5%). In an Italian series of 540 hospitalized patients with a history of travel and fever, RTI was diagnosed in 40 patients (7% of the febrile patients) and the most common RTIs were pneumonia (35%) and tuberculosis (15%), whereas ILI was found in 2.5% of the patients. In contrast to previously reported literature and as an illustration of the inclusion bias discussed above, most (67%) of our patients had ILI, a situation that does not routinely lead to a consultation.

Table 4 Specific diagnosis among 99 patients with respiratory tract infections after travel, according to clinical presentation and microbiological evaluation

| Pathogens                        | Tonsillitis (n = 8) | ILI (n = 68) | Sinusitis (n = 2) | Laryngitis (n = 1) | Tracheobronchitis (n = 17) | Lobar pneumonia (n = 3) | Total (n = 99) |
|----------------------------------|---------------------|-------------|------------------|--------------------|---------------------------|------------------------|--------------|
| InfA (H1N1) 2009                 | 1                   | 14          | 1                | 0                  | 2                         | 0                      | 18           |
| Other influenza viruses          | 1                   | 7           | 0                | 1                  | 5                         | 0                      | 14           |
| Undetermined subtype InfA        | 1                   | 2           | 0                | 1                  | 0                         | 0                      | 4            |
| InfA (H1N1)                      | 0                   | 1           | 0                | 0                  | 3                         | 0                      | 4            |
| InfA (H3N2)                      | 0                   | 2           | 0                | 0                  | 1                         | 0                      | 3            |
| InfB                             | 0                   | 2           | 0                | 0                  | 1                         | 0                      | 3            |
| Other viruses                    | 0                   | 25          | 0                | 0                  | 5                         | 1                      | 31           |
| Rhinovirus                       | 0                   | 15          | 0                | 0                  | 4                         | 1                      | 20           |
| Coronavirus*                     | 0                   | 3           | 0                | 0                  | 0                         | 0                      | 3            |
| hMPV                             | 0                   | 1           | 0                | 0                  | 0                         | 0                      | 1            |
| PIV-3                            | 0                   | 5           | 0                | 0                  | 1                         | 0                      | 6            |
| RSV-A                            | 0                   | 1           | 0                | 0                  | 0                         | 0                      | 1            |
| Bacteria                         | 4                   | 1           | 0                | 0                  | 0                         | 3                      | 8            |
| Streptococcus A                  | 3                   | 0           | 0                | 0                  | 0                         | 0                      | 3            |
| Streptococcus G                  | 1                   | 0           | 0                | 0                  | 0                         | 0                      | 1            |
| M pneumonia                      | 0                   | 1           | 0                | 0                  | 0                         | 0                      | 1            |
| Presumed pneumococcus            | 0                   | 0           | 0                | 0                  | 0                         | 3                      | 3            |
| Mixed infections†                | 1                   | 2           | 0                | 0                  | 0                         | 1                      | 4            |
| Negative result                  | 3                   | 23          | 1                | 0                  | 5                         | 0                      | 32           |

ILI = influenza-like illness; InfA = influenza virus A; InfB = influenza virus B; hMPV = human metapneumovirus; PIV-3 = parainfluenza virus type 3; RSV-A = respiratory syncytial virus type A.

*Coronavirus includes 229E and NL63.
†One patient with tonsillitis with undetermined subtype InfA + Streptococcus G; one patient with ILI with InfA (H1N1) 2009 + coronavirus C229E; one patient with ILI with undetermined subtype InfA + PIV-3; and one patient with lobar pneumonia with presumed pneumococcus + rhinovirus.
Research for influenza A(H1N1) virus, adenovirus, human bocavirus (hBoV), enterovirus, Chlamydia pneumoniae, Legionella pneumophila, and Bordetella pertussis were negative.
The spectrum of microbial agents causing RTI had been previously described and include numerous viruses (eg, influenza, parainfluenza, respiratory syncitial virus, metapneumovirus, adenovirus, rhinovirus, and coronavirus) as well as some bacteria (eg, Streptococcus sp., M. pneumoniae, L. pneumophila). In the subset of our 99 patients evaluated with RT-PCR and a throat swab, an infectious agent was found in 65.6%. This is much higher than that observed in many other studies performed in travelers or during influenza season. In a series of 500 Hajj pilgrims presenting with upper RTI, 54 (10%) had a positive viral throat culture. Of these 54 positive cultures, 27 (50%) were due to influenza B, 7 (12%) due to RSV, 4 (7%) due to parainfluenza, and 3 (5%) due to influenza A. In another study of 255 Iranian pilgrims with RTI, 83 (32%) had a viral pathogen isolated by throat culture. Of these 83 positive throat cultures, influenza was diagnosed in 25 (9.8%), followed by parainfluenza in 19 (7.4%), rhinovirus in 15 (5.9%), adenovirus in 14 (5.4%), enterovirus in 5 (2%), and RSV in 4 (1.6%); coinfection with two viruses was observed in one patient (0.4%). Of 67 German travelers that fulfilled the WHO case definition of suspected or probable severe acute respiratory syndrome (SARS) during the 2003 outbreak, influenza and PIVs accounted for 14.2 and 15.5% of the viral etiologies, respectively. Otherwise viruses identified and rhinovirus accounting for 30.9 and 19.6% of the ILI cases respectively. In the subset of patients did not undergo PCR evaluation because of various reasons such as technical issues on assays on weekends or nights. Fourth, bronchoalveolar lavage was not performed due to lack of severity or treatment failure in case of pneumonia. Finally it was impossible to have a denominator (ie number of air travelers) during this period. Therefore incidence rate could not be assessed.

These study findings demonstrate that, even at the onset of the influenza A(H1N1), rhinovirus and other influenza viruses were common. Therefore, these viral infections should always be considered in the diagnosis of RTI in returning travelers. Systematic research of pathogens by RT-PCR and culture of nasopharyngeal swab lead to almost 70% diagnoses and could therefore be considered for use in travelers with RTI.

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Declaration of Interests

The authors state they have no conflicts of interest to declare.

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