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# Incidence and risk factors for acute respiratory illnesses and influenza virus infections in Australian travellers to Asia

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ABSTRACT

*Background:* Respiratory infections including influenza are a common cause of acute short-term morbidity in travellers and yet the risk of these infections is poorly defined.
*Objectives:* To estimate the incidence density of and risk factors for acute respiratory infections (ARIs) and influenza in Australian travellers to Asia.
*Study design:* Travel-clinic attendees were prospectively identified and completed questionnaires (demographic data, travel itinerary, health and vaccination history) and also provided pre and post-travel serological samples for Influenza A and B (complement fixation test). Returned travellers with an ARI provided nasopharyngeal specimens for RT-PCR identification of respiratory viruses.
*Results:* In this cohort ($n = 387$) of predominantly (72%) short-term travellers, 58% were female, the median age was 37 years and 69% were tourists. ARIs occurred in 109 travellers (28%) translating to an incidence of 106.4 ARIs per 10,000 traveller days (95% confidence interval CI 88.6–126.7). The traveller type of missionary or aid worker was a risk factor for acquiring an ARI ($p = 0.03$) and ARIs occurred early (< 30 days) in the travel period ($p = 0.001$). Four travellers (1%) acquired influenza A during travel translating to an incidence density of 3.4 infections per 10,000 days of travel (95% CI 1.4–8.6). Influenza vaccination was reported in 49% of travellers with a 3.5-fold higher incidence of influenza in unvaccinated travellers compared to vaccinated travellers ($p = 0.883$).
*Conclusions:* This is one of the largest prospective studies estimating the incidence of respiratory infections in travellers. These findings have important implications for practitioners advising prospective travellers and for public health authorities.



## 1. Background

The spread of influenza and other viral respiratory tract infections has been at the forefront of public health priorities in recent years. Travel is a key factor in the rapidity and ease of transmission of respiratory viruses across continents as illustrated by the recent H1N1 pandemic and SARS outbreak.

Acute respiratory illnesses (ARIs) are common in international travellers and are diagnosed in up to 20% of febrile travellers who

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attend a health-care facility after travel.[1–3] The infectivity, frequency and high short-term morbidity of ARIs have a significant impact on travellers but they are often overlooked given that the associated mortality is generally low. In particular, influenza virus infections have been observed in up to 5% of returned travellers[1–3] and higher rates have been reported in specific types of travellers.[1,4]

Accurate data about the incidence of and risk factors for developing an ARI during travel is not available.

## 2. Objectives

Our primary objectives were to (i) estimate the overall incidence density of ARIs (ii) estimate the incidence density of confirmed influenza virus infections in Australian Travellers to Asia and (iii) identify the risk factors associated with ARIs.

## 3. Study design

### 3.1. Study population and questionnaires

From August 2007–January 2010, we performed a prospective cohort study involving three travel clinics (Royal Melbourne Hospital [RMH]; The Travel Doctor/Travellers Medication and Vaccination Centre, Melbourne CBD [TMVC]; and Monash Medical Centre [MMC]). Travellers over the age of 16 years and intending to travel to countries within Asia (only) for a minimum duration of 7 days were eligible to participate.

Validated pre and post-travel questionnaires were provided to travellers and blood samples were taken from travellers before travel and after return from travel.[5] The pre-travel questionnaire recorded demographic data including gender, age, ethnicity, traveller type, intended destinations, single or group travel, history of past confirmed influenza infection, and influenza vaccination history. The post-travel questionnaire recorded travel data (countries visited, accommodation, activities) and travel health (symptoms, locations and dates when illness episodes occurred, visits to health care providers, health status on return from travel). Travellers were contacted via phone within 72 h of return from travel by study investigators and travellers who developed respiratory symptoms within 72 h of return were seen within 3–5 days to obtain nasopharyngeal samples.

### 3.2. Serological testing and respiratory virus PCR testing

Paired serum samples (before and after travel) were analysed together for antibodies to Influenza A (subtypes H1–H3) and Influenza B using complement fixation antibody assays.[6] A greater than or equal to 4-fold increase in antibody titres in paired serum samples was defined as seroconversion to influenza virus infection or vaccination. Antibody titres for influenza that were >1:80 in the pre-travel samples were considered to be indicative of previous influenza exposure. Complement fixation antibody assays do not measure antibody responses to vaccination so vaccination history was recorded.

Nose and throat swabs were used to collect samples which were transported in viral culture media for RT-PCR analysis. Detection of respiratory viruses was performed using a nested multiplex PCR, amplifying specific and conserved sequences for viruses including influenza A and B viruses, adenoviruses, RSV, picornaviruses and parainfluenza viruses 1, 2 and 3.[7]

### 3.3. Case definitions

ARIs were defined as illness episodes involving the presence of at least two of fever, cough, sore-throat, coryza, headache, or myalgia with at least one being a respiratory symptom (cough, coryza, sore-throat). Travellers who reported already suffering from an ARI at the time of departure from Australia were not considered as ARIs related to travel. ARIs that were reported up to 72 h after return to Australia were considered as ARIs related to travel.

Influenza Like Illness (ILI) was defined according to the CDC criteria as fever plus either cough or sore-throat.[8]

Confirmed influenza virus infection was defined as seroconversion to influenza A or B (greater than or equal to) and a clinical illness consistent with an ARI or ILI and/or a positive RT-PCR for influenza A or B.

## 4. Statistical analysis

The data were analysed with SPSS statistical software, version 19. Because the periods of travel varied the incidences of respiratory and influenza infections were calculated as incidence densities – the numbers of ARIs/influenza infections per 10,000 traveller days. For assessment of predictors for developing the first ARI, Cox's proportional hazards regression approach was used. In this analysis, subjects are removed from being at risk when they experience their first ARI. The Cox regression was used because it compares incidence rates, and thus allows appropriately for the varying durations of individual travel. Model selection for the Cox model was carried out as follows. Age and gender were included, and two other variables, namely, the country visited, and "recent international travel", defined as an international border crossing in the last five days. These latter two variables are "time-dependent covariates." After the inclusion of these four core variables, forward selection was used to add more variables that were statistically significant, considering all other potential explanatory variables. Dates of illness, travel and days spent in each country were independently collected in different sections of the questionnaires. When there was a discrepancy between the length of travel as determined by the difference between the departure data and return date, and the length of travel determined by summing the days recorded in the travel diaries, the latter was re-scaled to the former so that the totals agreed, with consequent slight adjustments to the numbers of days spent in different countries.

## 5. Results

From August 2007–February 2010, 681 eligible travellers were invited to participate in the study. Of the 467 travellers who agreed to participate, 58 (12.4%) were lost to follow-up, 4 had missing post-travel sera and 18 were later excluded as they did not meet the study criteria at a time after enrolment into the study, leaving 387 travellers with complete demographic data and paired serological assays.

### 5.1. Acute respiratory infections in travellers

Overall, 126 episodes of ARI were reported in 109 travellers (28.1%). One traveller experienced an ARI on departure from Australia and this was not considered to be travel-related. Twenty-nine (7.5%) travellers were ill with an ARI on return to Australia and 12 travellers experienced multiple separate ARIs ($\geq$2 illness episodes) during their trip. Picornavirus was the only virus identified, and was found in 10 of the 29 unwell returned travellers.

The symptoms of the illness episodes reported by travellers who experienced an ARI, ILI and confirmed influenza virus infection are described in Table 2. One hundred and nine travellers experienced at least one illness episode during their travel or immediately after travel translating to an incidence ($n$ = 126) of