MAJOR ARTICLE

Influenza Virus Infection in Travelers to Tropical and Subtropical Countries

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Background. Influenza outbreaks have been reported among travelers, but attack rates and incidence are unknown.

Methods. A cohort study was conducted. Travelers to subtropical and tropical countries recruited at the University of Zurich Travel Clinic (Switzerland), January 1998 to March 2000, were investigated with pre- and posttravel assessment of hemagglutination inhibition and by questionnaire.

Results. Among 1450 travelers recruited who completed questionnaires and provided serum samples before departure, 289 (19.9%) reported febrile illness during or after traveling abroad; of these, 211 (73.0%) provided paired serum samples. Additionally, paired serum samples were collected from 321 frequency-matched afebrile control subjects among the remaining 1161 subjects of the study population. Seroconversion for influenza virus infection was demonstrated in 40 (2.8%) of all travelers; 18 participants (1.2%) had a $\geq$4-fold increase in antibody titers. This corresponds to an incidence of 1.0 influenza-associated events per 100 person-months abroad. Among the 211 febrile participants, 27 (12.8%) had seroconversion, 13 (6.2%) with a $\geq$4-fold increase; among the 321 afebrile control subjects, 13 (4.0%) had seroconversion, 5 (1.6%) with a $\geq$4-fold increase. Twenty-five seroconverters (62.5%; $P = .747$) acquired influenza outside of the European epidemic season. Sixteen patients (40.0%) sought medical attention either abroad or at home, and 32 (80.0%) were asymptomatic at the time of completion of the survey.

Conclusions. This survey indicates that influenza is the most frequent vaccine-preventable infection among travelers to subtropical and tropical countries. Infections occur mainly outside the domestic epidemic season, and they have a considerable impact. Pretravel vaccination should be considered for travelers to subtropical and tropical countries.

Epidemiological investigations of health risks in travelers have thus far concentrated on infections perceived as specific for this population, such as travelers' diarrhea, malaria, hepatitis, and other travel-related vaccine-preventable diseases. Hepatitis A appeared to be the most common vaccine-preventable infection [1–4]. Earlier reports indicate that fever, often of undetermined origin, affects 11% of travelers while abroad [5]. Anecdotal reports of outbreaks of influenza associated with travel by air or ship, also reported after military exercises abroad, indicate that international travelers are at risk of acquiring this infection [6–11].

Posttravel monitoring of hospital admissions identified respiratory tract infections, including influenza, as a common cause of illness in returned travelers, but thus far, the attack rate and incidence of influenza in travelers have not been assessed [12–14]. Thus, we performed a seroepidemiological cohort study to determine the attack rate and incidence of influenza virus infection among Swiss residents traveling to subtropical and tropical countries, the proportion of symptomatic and asymptomatic cases, and geographic areas and seasons with particular risk.

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METHODS

Participants. After receipt of approval by our institutional ethics committee, persons aged ⩾12 years who attended the University of Zurich Travel Clinic (Switzerland) were invited from 1 January 1998 to 31 March 2000 to participate in the study if they were planning travel to subtropical and tropical countries for ⩽6 months, had not traveled to these destinations during the preceding 2 months, reported no febrile illness at the date of enrollment, were able to understand a written German-language questionnaire, and resided in German-speaking Switzerland. They were selected regardless of their vaccination status against influenza, and each participant received travel advice in accordance with World Health Organization (WHO) recommendations of that time [15].

Recruited volunteers were then invited to sign a written informed consent form and to provide demographic (i.e., age, sex, place of residence, and date of enrollment) and basic travel data (i.e., travel destinations and dates and duration of stay), as well as a first blood sample. To include a posttravel follow-up time, a structured questionnaire was mailed to the volunteers 2 weeks after their return, followed by a reminder, if necessary. They were asked to report travel history, type of travel, visits to health care providers, fever and other health problems, impact of illness on travel plans, and their actual health status. Those who had experienced a "febrile illness" (measured temperature or just subjective fever) were invited to return to our travel clinic to provide a second blood sample. Additionally, a control sample from members of the same study population who did not experience fever abroad was frequency-matched with samples from those with fever by travel region and travel season and was similarly followed up.

Serological testing and case definitions. Paired serum samples were collected at intervals of ⩾3 weeks but ⩽50 weeks and were analyzed together for antibodies to influenza A virus subtypes H1N1 and H3N2 and for influenza B virus by the hemagglutination inhibition assay (HI) [16]. Selection of contemporary reference strains was based on data from global influenza surveillance [17–19]. Serum samples were tested in 2 batches. The first batch consisted of samples collected from 1 January to 16 October 1998, with use of reference strains and antibodies against A/Bayern/7/95 (H1N1), A/Beijing/262/95(H1N1), A/Wuhan/359/95(H3N2), A/Sydney/5/97(H3N2), B/Beijing/184/93, and B/Shandong/7/97. The second batch consisted of samples collected subsequently until 31 March 2000, with use of reference strains and antibodies against A/Bayern/7/95(H1N1), A/New Caledonia/20/99(H1N1), A/Sydney/5/97(H3N2), A/Nanchang/933/95(H3N2), B/Yamanashi/166/98, and B/Shandong/7/97. Because we did not expect acute influenza, no virus isolation or PCR was done on respiratory tract specimens.

Confirmed cases of influenza virus infection were defined by a ⩾4-fold increase above pretravel titer, and probable cases of influenza were defined by a 2.0- to 3.9-fold increase in serum antibody titer, compared with the first sample. Because we were interested in determining the ratio of clinically apparent to inapparent infections on the basis of the HI assay, no clinical symptoms of influenza-like illness were included in the case definitions. To avoid a misclassification of influenza virus infections, cases for which pretravel or posttravel blood sampling intervals exceeded 30 days and, at the same time, occurred during the northern epidemic season (December–March) were excluded (17 cases total). Probable cases of influenza were included to avoid the loss of potential cases due to such factors as asymptomatic infection or repeated exposure.

Travelers with pretravel HI antibody titers of ⩾1:20 for all 3 subtypes included in the then-contemporary vaccine of the Northern Hemisphere were considered to be immune against the corresponding vaccine strains and were termed immune. No influenza vaccine history was established, but at that time, neither we in Switzerland nor others specifically recommended this vaccine to travelers.

Statistical analysis. Data were analyzed with Stata statistical software, version 7 (Stata). Statistical significance for the crude analysis of the independent variables assessed by the questionnaires was determined by 2-sided χ^2 and Fisher's exact tests and by logistic regression with calculation of risk ratios and 95% confidence intervals. All covariates with a P value of <.1 at the univariate analysis were included in multivariate logistic regression analyses. We checked for confounding and colinearity whenever the β estimate or the standard error were disparate for the crude and adjusted OR estimate. To assess potential classification biases, sensitivity analyses were done to compare the population who provided paired serum samples with the residual study population, as well as to compare confirmed influenza virus infections with probable ones.

RESULTS

Overall, 1999 persons were recruited, of whom 506 (25.3%) did not provide an informed consent or were lost to follow-up; 43 (2.2%) did not correspond to the inclusion and exclusion criteria. Thus, a total of 1450 travelers (738 men [50.9%] and 712 women [49.1%]) completed questionnaires and provided a serum sample before departure. They had a median age of 31 years (range, 12–83 years); 54 (3.7%) were aged ⩾65 years. Both sexes had a comparable age distribution. As presented in table 1, the median duration of travel was 21 days (range, 7–182 days). Among 289 persons (19.9%) who reported febrile illness during or after traveling abroad, 211 provided second serum samples; additionally, 321 control subjects without fever provided a second serum sample. Among the total of 532 vol-

Table 1. Demographic characteristics of the total population in a study of influenza among Swiss travelers to tropical and subtropical areas.

Characteristic	Patients with confirmed influenza (n = 18)	Patients with probable influenza (n = 22)	Immune traveler[a] (n = 64)	All travelers (n = 1450)
Age, median years (range)	29 (20–68)	34 (22–59)	31 (20–72)	31 (12–83)
Sex, percentage of female/male subjects	44/56	36/64	52/48	49/51
Travel destination, no. (%) of subjects				
Africa	5 (27.8)	6 (27.3)	7 (10.9)	447 (30.8)
Asia excluding India	7 (38.9)	4 (18.2)	18 (28.1)	436 (30.1)
Indian subcontinent	2 (11.1)	6 (27.3)	7 (10.9)	130 (9.0)
Latin America	4 (22.2)	6 (27.3)	21 (32.8)	393 (27.1)
Other[b]	0 (0)	0 (0)	1 (1.6)	44 (3.0)
Duration of stay, median days (range)	28 (14–168)	28 (14–168)	25 (7–175)	21 (7–182)

[a] Subjects with pretravel hemagglutination inhibition antibody titers of ⩾1:20 for all 3 subtypes included in the then-contemporary vaccine of the Northern Hemisphere were considered to be immune against the corresponding vaccine strains.
[b] The Middle East and the Caribbean.

unteers with 2 samples, the median interval between collection of the first and second serum specimen was 109 days (range, 31–331 days).

Overall, 40 travelers tested positive for influenza virus infection. Infections were rated as confirmed for 18 subjects (45.0%) and as probable for 22 subjects (55.0%); 27 (67.5%; 14 men and 13 women) had reported fever episodes while abroad or shortly after return, whereas 13 (32.5%) remained asymptomatic throughout (10 men and 3 women). Thus, subjective fever was significantly associated with influenza virus infection ($P < .001$), and symptomatic patients reported visits to health care practitioners more frequently than did asymptomatic patients ($P < .001$); there were no significant differences between them with regard to demographic or travel characteristics. The median age of the 40 subjects who tested positive by HI was 33 years (range, 20–68 years), and the age distributions were slightly different between men and women (table 1). The largest proportion (26 [65.0%] of 40 cases) of influenza virus infections occurred in travelers aged 20–39 years ($P = .818$).

The total attack rate was 2.8% for all travelers in the study, and it was 1.2% when only confirmed influenza virus infections were taken into account. The incidences were 2.3 influenza-associated events per 100 person-months abroad for all influenza infections and 1.0 for those with confirmed infections. Among the 532 subjects who underwent serological analysis, 64 (12.0%) were classified as immune. A minority of subjects in this group had fever.

Influenza virus infections were acquired during travel to Asia (47.5%), Africa (27.5%), and Latin America (25.0%); this reflects the distribution of destinations among all travelers enrolled in the study—that is, 39.1%, 30.8%, and 27.1%, respectively ($P = .626$). Participants visiting the Indian subcontinent were more often affected (table 2). None of the other variables tested, such as demographic data and travel characteristics, were associated with a significantly increased risk of acquiring influenza virus infection. Additionally, there was no indication that persons with preexisting illness were more often affected.

Table 2. Factors associated with detecting influenza virus infections in travelers.

Type of analysis, risk factor	Odds ratio (95% CI)	P
Univariate analysis		
Sex, female/male	0.68 (0.36–1.30)	.244
Age, by decade	0.95 (0.74–1.21)	.651
Travel destination		
Hemisphere, Northern/Southern	0.95 (0.51–1.79)	.886
Africa	0.85 (0.42–1.71)	.640
Asia	1.28 (0.70–0.35)	.422
Indian subcontinent	2.61 (1.18–5.79)	.018
Southeast Asia	0.98 (0.46–2.09)	.965
Latin America	0.85 (0.41–1.77)	.672
Travel duration of >28 days	1.46 (0.72–2.95)	.297
Type of travel, individual/with others	1.76 (0.92–3.37)	.086
Season of travel, Dec–Mar/Apr–Nov	0.92 (0.48–1.77)	.808
Year of travel, 1998/1999	1.09 (0.54–2.17)	.817
Multivariate analysis		
Sex, female/male	0.70 (0.36–1.34)	.280
Age, by decade	1.01 (0.77–1.31)	.956
Indian subcontinent	2.76 (1.24–6.16)	.013
Type of travel	1.93 (0.95–3.92)	.067

NOTE. Multivariate analysis corresponds to multivariate logistic regression analyses.

Table 3. Influenza virus subtypes and symptoms reported by travelers to tropical and subtropical countries.

Characteristic	Patients with confirmed influenza (n = 18)	Patients with probable influenza (n = 22)	Immune traveler[a] (n = 64)	All travelers (n = 1450)
Influenza subtype				
A (H1N1)	2 (11.1)	1 (4.5)	…	…
A (H3N2)	14 (77.8)	16 (72.7)	…	…
B	0 (0)	3 (13.6)	…	…
A or B[b]	2 (11.1)	2 (9.1)	…	…
Symptom				
Fever				
Subjective	13 (72.2)	14 (63.6)	21 (32.8)	289 (19.9)
Temperature of ⩾38°C	9 (50.0)	9 (40.9)	8 (12.5)	154 (10.6)
Sore throat and/or cough	13 (72.2)	11 (50.0)	22 (34.4)	249 (17.2)
Aches[c]	11 (61.1)	13 (59.1)	30 (46.9)	455 (31.4)
No fever	5 (27.8)	8 (36.4)	43 (67.2)	1161 (80.1)

[a] Subjects with pretravel hemagglutination inhibition antibody titers of ⩾1:20 for all 3 subtypes included in the then-contemporary vaccine of the Northern Hemisphere were considered to be immune against the corresponding vaccine strains.
[b] Four persons tested positive for >1 influenza virus subtype.
[c] Headache, myalgia, and/or arthralgia; multiple answers were possible.

The most frequent symptoms included subjective fever, respiratory symptoms (such as sore throat or cough), diarrhea, headache, and myalgia (table 3). Exanthema, arthralgia, coryza, fatigue, and otitis media were reported less frequently. Only 57.4% of those with fever had measured their temperature; the median temperature reported was 38.5°C (range, 37.5°C–40.5°C). Influenza A (H3N2) virus was the most commonly detected subtype, followed by influenza A (H1N1) virus and, less frequently, influenza B virus. Four (10.0%) of the 40 travelers with positive HI results tested positive for >1 influenza virus subtype. Fifteen travelers (37.5%) acquired influenza virus infection during the main epidemic season in Europe (i.e., December–March). Figure 1 shows a considerable exposure to influenza throughout the year, including months when influenza was not prevalent in Switzerland.

Three patients (7.5%) among the 40 who had seroconversion to influenza virus had to change their itinerary because of illness, and 16 (40.0%) sought medical attention either abroad or after returning to Switzerland or both. Thirty-two subjects (80.0%) with positive HI results felt healthy again at the time of completion of the survey; the others had mostly minor residual illness or relapses of influenza-like illness, including fever, cough, headache, or otitis media.

The sensitivity analysis showed that subjects with confirmed and probable influenza were comparable and did not differ significantly with respect to reported symptoms of influenza-like illness (e.g., subjective fever, temperature of ⩾38.0°C, sore throat, cough, headache, and myalgia), demographic characteristics, and travel characteristics.

Demographic and travel-related variables showed similar distributions in the subpopulation from whom paired serum samples were collected and in the whole study population. The only exception was the Indian subcontinent with regard to travel destination, which was significantly overrepresented in the subgroup providing paired serum samples, compared with the whole study population ($P < .05$).

DISCUSSION

This cohort study demonstrates that influenza is a frequent health problem among travelers to subtropical and tropical countries and that the risk is far from limited to cruises. The attack rate of 1.2%–2.8% and the monthly incidence of influenza-associated febrile events of 1.0%–2.3% in confirmed and probable infections, respectively, make this clearly the most frequent vaccine-preventable infection in travelers to tropical or subtropical countries. The risk of influenza virus infection is ⩾3-fold greater than the risk of clinical hepatitis A virus infection [1]. The impact of influenza is considerable; of all travelers recruited, >1% required medical attention abroad or after return, and 0.2% had to change their travel plans. The distribution of the destinations reflects the travel pattern for Swiss visitors to subtropical and tropical countries between 1998 and 2000: Asia, 40%; Africa, 35%; and Latin America, 25% [20]. Thus, we believe that we enrolled a representative sample in that respect.

In the search for particular risk groups, the GeoSentinel surveillance network [13] found travel duration of >30 days to be

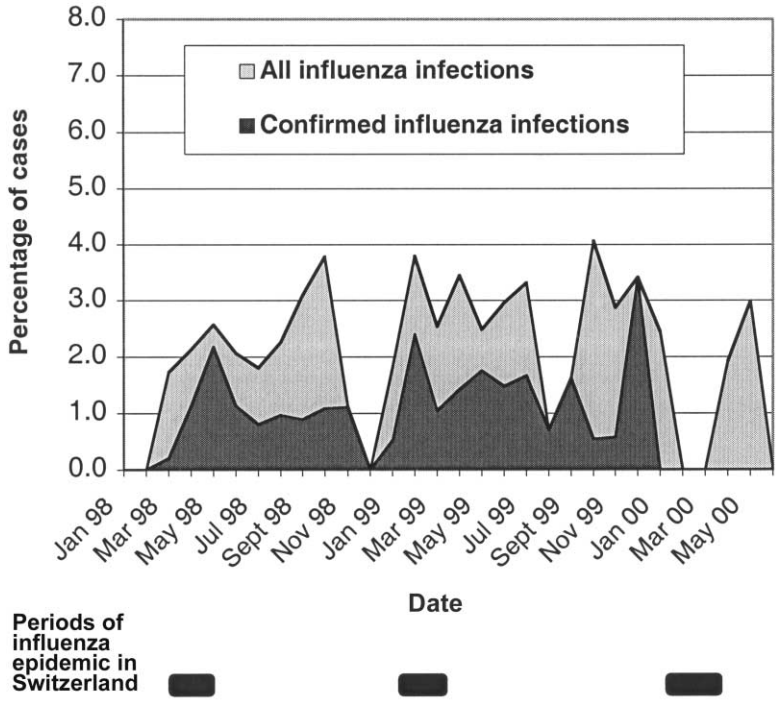

Figure 1. Proportion of influenza virus infections per month of travel, January 1998 to May 2000

a risk factor for influenza virus infection. We were unable to confirm this finding, possibly because of the small number of cases detected. We found the Indian subcontinent to be a higher-risk area.

The WHO rated the investigated 3 influenza seasons as moderate to severe in the Northern Hemisphere, whereas activity was reported to be less extensive in the Southern Hemisphere. The majority of infections were reported outside the traditional influenza epidemic season in the Northern Hemisphere between December and March (figure 1). We cannot, however, differentiate whether influenza virus infection occurred just before departure at home, en route, abroad, or shortly upon return. For affected travelers, this is presumably of limited relevance, because the impact of influenza may be equally important whether it infects a traveler just before departure or upon resumption of normal activities shortly after return.

Because confirmed and probable cases were comparable with respect to influenza-like symptoms, the 2 groups were subsequently combined. Approximately 30% of influenza virus infections remained clinically undetected, and this estimate is consistent with field studies in which proportions of asymptomatic infections of 15%–42% were reported [21, 22]. Such persons are also relevant, because they could unwittingly contribute to the spread of influenza. The higher attack rate of febrile illness compared with that seen in previous surveys (11%–13%) [5, 23] could be explained by the fact that surveillance was extended for 2 weeks after return.

Eight antigenically distinguishable reference strains were used to detect infections due to the prevailing influenza A and B viruses during the study period. The frequency of detection reflected the relative prevalence of the A (H3N2), A (H1N1), and B viruses—in particular, the worldwide predominance of A (H3N2) viruses during January 1998 and March 2000 [24–26]. The HI assay is the method of choice for epidemiological surveys of influenza because it is easy to use, it can be performed late in the course of infection or after recovery, and the determination of the seroconversion rate shows a good specificity [27, 28]. On the other hand, the accuracy of our results may be limited by several factors. First, the sensitivity of the laboratory case definition: mixed or multiple infections occurred, and other infections might have been the origin of fever, resulting in an overestimation of influenza-related fever cases or an underestimation of afebrile influenza virus infections, respectively. Second, we included subjective fever, because many subjects do not carry thermometers. We calculated all rates for the total number of travelers recruited, although only 73% of the febrile patients had provided second serum samples and had the chance to be detected by seroconversion; this may have resulted in an underestimation of the risk of influenza. In addition, the present 13 asymptomatic influenza cases (4.0%) were found among only 321 healthy travelers. When referring to the overall population of 1161 healthy travelers, a total of 47 asymptomatic cases can be estimated.

In conclusion, the importance of influenza in travelers to

subtropical and tropical countries has thus far been neglected. Influenza is the most frequent vaccine-preventable infection among this population, and it has a considerable impact. Influenza vaccination should certainly be recommended to the traditional at-risk groups, such as senior travelers and those with various preexisting illnesses, during pretravel health advice. Beyond those, it should be considered for others who are willing to take the expense to increase the chance of remaining healthy while abroad. The most recently licensed influenza vaccines, including those for the opposite hemisphere, would need to be available at least to travel clinics to reduce the risk of vaccine failure [29, 30]. Alternatively, in cases in which influenza vaccines are unavailable or contraindicated, guidelines for administering and using antiviral medications should be established.

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