Influenza-Like Illness in Travelers to the Developing World

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Abstract. Travelers to developing regions are at risk for development of influenza-like illness (ILI). Little is known of traveler and trip characteristics associated with the development of ILI. TravMil is a prospective observational study, enrolling subjects presenting to six military travel clinics or predeployment-screening sites. We analyzed pre- and post-travel surveys from travelers visiting regions outside of the continental United States, Western or Northern Europe, Canada, Australia, or New Zealand between January 2010 and March 2016. Influenza-like illness was defined as a self-reported fever associated with either sore throat or cough. Trip and traveler characteristics were analyzed to determine risk factors for the development of ILI. Two thousand nine hundred and thirty-two trips were recorded (55% male, median age 45 years, 69% white, 51% on vacation, median travel duration 17 days). The 2,337 trips included the number of self-reported influenza vaccinations in the preceding 5 years (median 5). Eleven percent of the trips were complicated by an ILI lasting a median of 5 days; 70% and 17% of these reported upper and lower respiratory tract infection, respectively, and 12% reported both. On multivariate analysis, increased risk of ILI was associated with female gender (odds ratio [OR]: 1.60 [confidence interval (CI): 1.25–2.05], $P < 0.01$), age (years) (OR: 1.01 [CI: 1.01–1.02], $P < 0.01$); and duration of travel (days) (OR: 1.01 [CI: 1.00–1.01], $P < 0.01$). Influenza-like illness is common in travelers, regardless of traveler characteristics, purpose of travel, destination, or season of year. Female gender, older age, and longer duration of travel were associated with an increased risk of ILI. Additional tools and strategies are needed to prevent ILI in international travelers.

INTRODUCTION

The number of international travelers continues to increase yearly. In 2015, there were 32.7 million trips involving U.S. citizens traveling to regions outside of continental North America, a 15% increase compared with 2010. Of these, 81.9% of trips were to destinations outside of Europe or Oceania.¹ Three of four travelers report the development of some health impairment associated with travel, with many of these being travel-related infections.² A disproportionate number of travel-related infections occur with travel to the developing world.³ In the GeoSentinel network of ill-returning travelers, 93.3% of travel-related infections seen between 2007 and 2011 were subsequent to travel to regions outside of Europe, Australia, New Zealand, or North America.⁴

Much emphasis in travel medicine has been placed on addressing malaria, traveler's diarrhea, and vaccine-preventable diseases, with less emphasis placed on respiratory infections.^{5–7} Despite this, respiratory infections are reported to be the third most common travel-related illness, behind only gastrointestinal and nonspecific febrile illnesses. Respiratory or pharyngeal symptoms were reported in 10.9% of ill-returning travelers in the GeoSentinel population.⁴ Although vaccination, malaria chemoprophylaxis, and antidiarrheal medications may prevent or mitigate a significant number of gastrointestinal and febrile illnesses, there are limited data to support effectiveness of interventions to prevent the development of respiratory infections in travelers to the developing world.⁸

Influenza-like illness (ILI) is defined by the Centers for Disease Control and Prevention as “fever with cough or sore throat.” These symptoms are commonly reported in travelers to the developing world, with 11.2% and 13.1%, respectively, endorsing development of these in one prospective study.⁹ An ILI attack rate of 10.0–11.0% has been documented in Western travelers to Asia and the Middle East.^{8,10,11} Despite this, traveler and trip characteristics associated with ILI are not well characterized.^{12,13}

Military travel presents distinct challenges and opportunities in terms of prevention of travel-related illnesses. Multiple risk factors, including austere or crowded living and working conditions, sleep deprivation, and exposure to dust or smoke may increase the risk for development of respiratory illnesses. Even illnesses with limited morbidity may have an exaggerated impact on mission outcome in military travelers.^{14–18} Despite this, evaluation of military travelers has been limited in large surveillance studies. Less than 1% of enrollees in the GeoSentinel Surveillance Network were military travelers.⁴ The purpose of this study is to determine the attack rate of ILI associated with international travel among Department of Defense (DoD) beneficiaries, describe the morbidity associated with the development of this illness, and determine characteristics and interventions that may be associated with the development of ILI.

MATERIALS AND METHODS

Study design. This study analyzed data from the TravMil study: *Deployment and Travel Related Infectious Disease Risk Assessment, Outcomes, and Prevention Strategies Among Department of Defense Beneficiaries*, approved by the Infectious Disease Institutional Review Board of Uniformed

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Services University of the Health Sciences (Bethesda, MD). TravMil is a prospective observational study that enrolled subjects from six military travel clinics who present for pre-travel counseling. Subjects were also enrolled from operational units who were preparing for deployment. Participating facilities included Landstuhl Regional Medical Center (Landstuhl, Germany), Walter Reed National Military Medical Center (Bethesda, MD), San Antonio Military Medical Center (San Antonio, TX), Naval Medical Center Portsmouth (Portsmouth, VA), Madigan Army Medical Center (Tacoma, WA), and Naval Medical Center San Diego (San Diego, CA). Posttravel enrollment was available to those presenting to travel clinics for possible travel-related illness within 2 months of return. Eligible travelers were limited to adult (> age 18 years) DoD beneficiaries (e.g., active duty military personnel, military retirees, United States Public Health Service, Department of State employees, DoD civilian employees traveling internationally on military orders, and military dependent family members). Travelers were required to be traveling outside of the continental United States, Puerto Rico, Guam, Samoa, the U.S. Virgin Islands, Western or Northern Europe, Canada, Australia, or New Zealand for at least part of their itinerary. Enrollment was between January 2010 and March 2016. Enrollment was limited to a duration of travel less than 6.5 months (to capture most shorter military deployments and to minimize subjects being lost to follow-up).

Survey data. Pretravel enrollees completed a pretravel survey recording their demographics and travel characteristics. Travelers were also provided a diary to record episodes of fever, cough, and sore throat during travel. If a fever with cough or sore throat developed, information on incapacitation, days of symptoms, duration of fever, and whether medical care was required were recorded. Enrollees reported "cold, sore throat, or sinus symptoms" that was recorded as upper respiratory infection, whereas "bronchitis, pneumonia, and cough" was recorded as lower respiratory tract infection. Similarly, post-travel enrollees completed a posttravel survey recording their demographics and travel characteristics. Surveys included the number of self-reported influenza vaccinations received in the prior 5 years. Season of travel was based on the date of travel from the departure location. As travelers were enrolled from sites in the Northern Hemisphere, travel occurring during June, July, or August was recorded as "summer"; if September, October, or November, as "autumn"; if December, January, or February, as "winter"; and if March, April, or May, as "spring."

Statistical analysis. Univariate analysis used Pearson's χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney *U* for continuous variables. Variables with a *P* value of ≤ 0.05 on univariate analysis or suspected clinical significance and without significant correlation with other variables underwent a Poisson regression with robust error variance to assess independent risk factors. Results of multivariate analysis were reported with odds ratio (OR) and 95% confidence intervals (CIs). Statistical significance was defined as a *P* value of ≤ 0.05 . Statistical analysis was performed with SPSS software (IBM SPSS Statistics Version 22, Chicago, IL).

RESULTS

Baseline characteristics. A total of 2,932 separate trips by 2,608 travelers were recorded during the study period (Table 1); 2,817 (96.1%) of these were taken by subjects

TABLE 1

Traveler demographics, purpose and region of travel, and season of departure and return

Characteristic	Number of total travelers (%) (N = 2,932)
Female gender	1,312 (44.7)
Age, median years (IQR)	45 (29, 63)
U.S. born	2,314 (79.1)
Traveler status	
Active duty	1,122 (38.3)
Retiree	778 (26.5)
Family member	1,027 (35.0)
DoD civilian	91 (3.1)
Others	30 (1.0)
Race	
Asian	285 (9.9)
Black	333 (11.4)
White	2,034 (69.4)
Multiracial	148 (5.0)
Others	132 (4.5)
Purpose of travel	
Military	847 (28.9)
Vacation	1,500 (51.2)
Business	105 (3.6)
Visiting friends and relatives	488 (16.6)
Teaching	162 (5.5)
Medical support	182 (6.2)
Missionary	542 (18.5)
Adventure	142 (4.8)
Adoption	15 (0.5)
Others	64 (2.2)
Multipurpose	840 (28.3)
Region of travel	
The Americas	860 (29.3)
Asia	1,004 (34.2)
Africa	940 (32.1)
Others	315 (10.7)
Season of departure	
Winter	640 (21.8)
Spring	732 (25.0)
Summer	901 (30.7)
Autumn	659 (22.5)
Season of return	
Winter	627 (21.4)
Spring	575 (19.6)
Summer	918 (31.3)
Autumn	812 (27.7)
Duration of travel, median days (IQR)	17 (12, 29)

DoD = Department of Defense; IQR = interquartile range.

enrolled pretravel and 115 (3.9%) were enrolled posttravel. Individual subjects could enroll in the study more than once if they had more than one individual periods of travel. Of travelers enrolling pretravel, 88.6% enrolled once/recorded one trip, 7.7% recorded two trips, and 3.8% recorded three or more trips. Less than one-half of travelers were female (44.7%) with median age of 45 years (interquartile range [IQR]: 29, 63). A majority of travelers were U.S. born (79.1%) with a significant proportion either active duty military (38.3%) or retired military (26.5%). More than one purpose could be reported for travel with vacation (51.2%), military purpose (28.9%), missionary purpose (18.5%), and visiting friends and relatives (16.6%) most commonly reported. Multipurpose travel was common, with 28.3% of travelers reporting more than one purpose for their travel.

A traveler's itinerary could include more than one region of travel, with 34.2% reporting travel to Asia (West, South central, and Southeast), 32.1% to Africa (North, North and East, and sub-Saharan), 29.3% to the Americas (noncontinental

North America, Caribbean, Central America, and South America), and 10.7% to “other” regions (Antarctica, Europe excluding Northern or Western Europe, Oceania excluding Australia or New Zealand). The greatest proportion of travel occurred during summer, with 30.7% of departures and 31.3% of returns occurring during this season. Median duration of travel was 17 days (IQR: 12, 29).

Development of ILI. A total of 327 trips were complicated by ILI (Table 2), including 10% of pretravel enrollees (282/2,817) and 39% of posttravel enrollees (45/115). Of these, 112 trips (34.2%) were complicated by some form of self-reported incapacitation. On questioning, 19 (6.7%) pretravel enrollees responded as to whether medical care was sought because of illness either during or after travel. Of those responding, 12 travelers (63.1%) reported seeking medical care with three (25.0%) subsequently required hospitalization.

Factor association analysis. Travelers who engaged in pretravel care and enrolled in the study before travel were included in this analysis ($N = 2,817$). On univariate analysis (Table 3), travelers with ILI were more often female (57.6% versus 43.8%, $P < 0.01$), older (54 versus 45 years, $P < 0.01$), family members of active duty personnel (44.9% versus 34.4%, $P < 0.01$), or with longer duration of travel (21 days [IQR: 14, 39] versus 16 days [IQR: 11, 28], $P < 0.01$). Those with ILI were less often active duty military (25.1% versus 38.6%, $P < 0.01$) or traveling for medical support (3.2% versus 6.5%, $P = 0.03$). The number of self-reported influenza vaccinations in the preceding 5 years was reported in 2,337 (80%) of trip records. On univariate analysis, those without ILI reported a median of five influenza vaccinations in the preceding 5 years (IQR: 2, 5) and those with ILI reported a median of four (IQR: 2, 5), $P = 0.04$. Poisson regression with robust error variance included gender, age, trip duration, and number of influenza vaccinations. Active duty and family member status were excluded from the model because of a moderate correlation between age and status of the traveler. On multivariate analysis, female gender, with an OR of 1.60 (CI: 1.25–2.05, $P < 0.01$), older age (years) (OR: 1.01 [1.01–1.02], $P < 0.01$), and duration of travel (days) with an OR of 1.01 (CI: 1.00–1.01, $P < 0.01$) remained statistically significant as independent predictors of ILI.

DISCUSSION

Our database contains a large sample of travelers to the developing world with 2,932 trips recorded. With an overall attack rate of 10% in travelers, ILI is a frequent complication of travel to the developing world, accounting for 39% of the illness presentations among subjects enrolled posttravel who presented for care. It is a frequent complication, regardless of trip itinerary or traveler demographics, including active duty military personnel and military travel, and a common reason for seeking medical care after travel.

In analyzing our reported attack rate, our data appeared similar to prior studies. As previously noted, GeoSentinel data report respiratory illness in 10.9% of ill-returning travelers, comparable with the “common cold” attack rate of 13.1% reported in a 1997 prospective study of travelers.^{4,9} Prospective studies have similarly documented rates of ILI in approximately 10% of pilgrims returning from the Hajj.^{10,11}

The significant proportion of active duty military travelers and the high degree of influenza vaccine uptake in the preceding 5 years stand out as distinctive demographic features in our study compared with these others. The GeoSentinel survey included < 1% active duty military enrollees compared with 38.3% in our study. To our knowledge, this is the largest prospective study of ILI in international travelers, including military travelers, reported.

Prior studies in active duty military travelers had indicated a higher incidence of respiratory illness. A 2005 study documented respiratory illness in 69.1% of military personnel during deployment, and in 2009, a 40% incidence of self-reported respiratory illness was reported.^{15,16} Those studies required only respiratory symptoms and did not require fever for inclusion. This is in contrast with our definition of ILI as self-reported fever with cough or sore throat. In those studies, the average duration of deployment was 4 months, whereas in ours travel duration was significantly shorter with median of only 17 days. Finally, when comparing the decreased rates of respiratory infection of 40% in 2009 versus 69% in 2005, it was hypothesized that the documented increase in access to flush toilets and hand washing stations in 2005–2006 compared with 2003–2004 may have helped contribute to this decrease in rate of infection. Improved deployment infrastructure for our study population from 2010 to 2016 may have affected the

TABLE 2
Symptoms of ILI and duration reported by international travelers ($N = 327$)

Characteristics	Pretravel enrollees (%)	Posttravel enrollees (%)	Total
Number of trips complicated by ILI	282 (10.0)	45 (39.1)	327
Days of symptoms, composite score (IQR)	5 (3, 9)	5.5 (3.25, 13.75)	5 (3, 10)
Number reporting URI symptoms	205 (72.7)	23 (51.1)	228 (69.7)
Days of URI	5 (3, 8)	5.5 (3, 10.75)	5 (3, 8)
Number reporting LRTI symptoms	43 (15.2)	13 (28.9)	56 (17.1)
Days of LRTI	7 (4, 14)	14 (4, 17.5)	8 (4, 14)
Number with both URI and LRTI symptoms	32 (11.3)	8 (17.8)	40 (12.2)
Number reporting incapacitation	89 (31.6)	23 (69.7)	112
Days 50% incapacitated, median	0 (1.25)	2 (9, 4.5)	0 (0, 2)
Days 100% incapacitated, median	0 (0, 0)	1 (0, 3)	0 (0, 1)
Days of fever, median days (IQR) ($N = 24$)	2 (1, 3)	4 (3, 10)	3 (1.75, 4)
Sought care during travel ($N = 19$)	12/19 (63.1)	0	12 (63.1)
Hospitalized ($N = 12$)	3/12 (25.0)	0	3 (25)

ILI = influenza-like illness; IQR = interquartile range; LRTI = lower respiratory infection; URI = upper respiratory infection.

TABLE 3
Risk factors for ILI in international travelers who engaged in pretravel care (N = 2,817)

Characteristics	Travelers without ILI (%) (N = 2,534)	Travelers with ILI (%) (N = 283)	P value univariate	P value multivariate	Multivariate OR (95% CI)
Female gender	1,109 (43.8)	163 (57.6)	< 0.01	< 0.01	1.60 (1.25–2.05)
Age, median years (IQR)	45 (29, 63)	54 (30, 66)	< 0.01	< 0.01	1.01 (1.01–1.02)
U.S. born	2,006 (79.3)	227 (80.2)	0.72	—	—
Traveler status	—	—	< 0.01	—	—
Active duty	978 (38.6)	71 (25.1)	< 0.01	—	—
Retiree	682 (26.9)	83 (29.3)	0.39	—	—
Family member	870 (34.3)	127 (44.9)	< 0.01	—	—
DoD civilian	79 (3.1)	11 (3.9)	—	—	—
Others	28 (1.1)	1 (0.4)	—	—	—
Race	—	—	0.45	—	—
Asian	252 (9.9)	28 (9.9)	—	—	—
Black	291 (11.5)	21 (7.4)	—	—	—
White	1,755 (69.3)	203 (71.7)	—	—	—
Multiracial	124 (4.9)	18 (6.4)	—	—	—
Others	110 (4.3)	13 (4.6)	—	—	—
Purpose of travel	—	—	—	—	—
Military	735 (29.0)	71 (25.1)	0.17	—	—
Vacation	1,295 (51.1)	146 (51.6)	0.88	—	—
Business	90 (3.6)	10 (3.5)	0.99	—	—
Visiting friends and relatives	417 (16.5)	53 (18.7)	0.33	—	—
Teaching	141 (5.6)	13 (4.6)	0.50	—	—
Medical support	164 (6.5)	9 (3.2)	0.03	—	—
Missionary	465 (18.4)	53 (18.7)	0.88	—	—
Adventure	125 (4.9)	11 (3.9)	0.43	—	—
Adoption	15 (0.6)	0	0.19	—	—
Others	57 (2.2)	5 (1.8)	0.60	—	—
Multipurpose	723 (28.5)	67 (23.7)	0.09	—	—
Region of travel*	—	—	—	—	—
The Americas	747 (29.5)	84 (29.7)	0.94	—	—
Asia	874 (34.5)	91 (32.2)	0.43	—	—
Africa	807 (31.8)	94 (33.2)	0.64	—	—
Season of departure	—	—	0.19	—	—
Season of return	—	—	0.03	—	—
Duration of travel, median days (IQR)	16 (11, 28)	21 (14, 39)	< 0.01	< 0.01	1.01 (1.004–1.01)
Number of flu vaccinations in past 5 years (#, IQR)	5 (2, 5)	4 (2, 5)	0.04	0.06	0.94 (0.88–1.00)

CI = confidence interval; DoD = Department of Defense; ILI = influenza-like illness; IQR = interquartile range; OR = odds ratio.

* Regions of travel included the following: Antarctica, Caribbean, Central America, North America (outside Canada and continental United States), South America, East and North Asia, South Central Asia, Southeast Asia, West Asia, Europe (outside Western or Northern Europe), North Africa, sub-Saharan Africa, Oceania, and others; none were individually statistically significant (data not shown).

rates of development of ILI compared with prior studies, although confirmatory data are lacking.

A correlation between influenza vaccination and prevalence of ILI has been seen in prior studies of Hajj pilgrims. Previously, the largest prospective studies for travelers assessing ILI were targeted at Hajj pilgrims and the largest enrolled 1,600 subjects.^{19–21} One 10-year retrospective analysis of more than 33,000 pilgrims noted a decreased rate of ILI with influenza vaccination.¹³ This is in contrast to our study, where no statistical significance was seen with increased number of self-reported influenza vaccinations in the prior 5 years. One key difference that may account for this discrepancy is the high level of influenza immunization in our population, with the median number of self-reported vaccinations at five in the previous 5 years. In addition, the populations traveling, the reason for travel, and potentially the risk factors are quite different in the Hajj pilgrim studies, compared with these travelers who originated from North America or Germany with various destinations across the globe. Despite much excellent research coming from these prospective studies in pilgrims for the Hajj, the generalizability of the data may be questioned because of such limited diversity in travel destination.²² Differences in circulating influenza strains may limit the effectiveness of vaccination for global travelers as compared with regional travelers in preventing the development of ILI.

Influenza circulates year-round in tropical regions, compared with seasonal circulation in temperate regions.²³ Peak transmission occurs from October to March in the northern hemisphere and from April to October in the southern hemisphere. Cross-hemispheric travel may be a risk factor for acquisition of influenza if there is vaccine mismatch between northern and southern hemisphere strains.²⁴ Although northern hemisphere vaccine was available at our study sites, out-of-season and southern hemisphere strain vaccines were unavailable. Determination of the circulating influenza strain at travel destinations was outside of the scope of our study but may influence the effectiveness of vaccine administered. In addition, given the variability of timing in influenza transmission around the world, our determination of season of travel was not reflective of the likelihood of circulating influenza at travel destinations. Further study acknowledging these issues may help determine influenza vaccine efficacy in prevention of ILI in travelers.

Interestingly, the female gender was associated with an increased risk for development of ILI on multivariate analysis. Female gender has been seen to be a risk factor in several prior studies of ILI in nontravelers.^{25–27} One review of more than 7.5 million individuals in the United Kingdom over an 18-year period saw an increased rate of ILI diagnosis in women compared with men.²⁵ Surveillance of 4,532 United Kingdom-based participants

also saw an increased risk for development of ILI with female gender.²⁶ However, this association with female gender has not been reported in many studies of ILI development in travelers.^{6–8} One of the largest of these studies, the EuroTravNet surveillance study, reviewed 32,136 ill travelers and saw no difference in rates of influenza and ILI based on gender, with a male to female ratio of 51:49 reported.⁶ By contrast to this, increased rates of ILI development have been seen with female deployed U.S. military. One review of respiratory illness among deployed U.S. military reported an association between female gender and self-reported incidence of acute respiratory illness in deployed U.S. military in Iraq and Afghanistan.¹⁶ The reason for this reported association in military travelers as compared with civilian travelers is unclear. In a largely military study population, differences in severity of self-reported symptoms in female versus male patients with ILI has also recently been reported.²⁸ It is unclear whether the increase in reported ILI in our study is due to an increase in severity or other factors. Recall bias, differences in hand hygiene practice, or unmeasured travel characteristics may potentially account for a difference in actual incidence. Increasing age was also associated with increased risk of ILI in this study, although with an OR of only 1.01 on multivariate analysis. We are not aware of a description of increased risk of ILI in older international travelers, although it is possible that this reflects some difference in other unmeasured travel-related variables.

One of the strengths of our study was the large prospective population enrolled. Of our subjects, 2,817 were pretravel enrollees. In addition, our study benefited from diverse travel destinations. Finally, our traveler population uniquely includes a wide variety of travelers: active duty, military retirees and family members, and eligible DoD civilian travelers not seen by many other travel clinics nor examined in prior travel studies.

Several limitations stand out in our study. Foremost, the high influenza immunization rates in our patient population limited our ability to see an effect with this intervention. Annual influenza vaccination is required for active duty members; vaccination is widely available without cost for DoD beneficiaries (and may be administered at their pretravel consultation in many cases). Although self-reported fever with cough or sore throat is appropriate for a clinical diagnosis for ILI, serology or viral polymerase chain reaction may have added further useful information. Although a significant amount of data were collected for our trips, information on hand hygiene and respiratory etiquette counseling were limited. Our data did not allow for calculation of region-specific incidence rates because of missing data on time spent per region in travelers visiting multiple regions. Finally, many patients enrolling in the study before travel had self-selected to make an appointment to be seen in travel clinic, whereas others traveling on military orders were required to seek pretravel evaluation. The fact that these patients were proactively engaging in preventive care may have correlated with a different outcome compared with a less proactive population.

CONCLUSION

Influenza-like illness is a common outcome in travelers to the developing world regardless of traveler characteristics, purpose of travel, destination, or season of year. Travelers may benefit from pretravel counseling explaining this risk and addressing potentially preventive measures and supportive therapies to help mitigate ILI symptoms. Female gender, older

age, and longer duration of travel associated with an increased risk of ILI development in travelers. In addition, although increased number of prior influenza vaccinations was not seen to be statistically significant in reducing the risk of development of ILI in our highly immunized population, further study in a less homogeneously immunized population may be warranted.

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REFERENCES

1. U.S. Department of Commerce ITA, National Travel and Tourism Office (NTTO), 2016. *U.S. Citizen Traffic to Overseas Regions, Canada & Mexico 2015*. Available at: <https://travel.trade.gov/view/m-2015-o-001/index.html>. Accessed June 10, 2018.
2. Freedman DO, Weld LH, Kozarsky PE, Fisk T, Robins R, von Sonnenburg F, Keystone JS, Pandey P, Cetron MS; GeoSentinel Surveillance Network, 2006. Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med* 354: 119–130.
3. Steffen R, deBernardis C, Banos A, 2003. Travel epidemiology—a global perspective. *Int J Antimicrob Agents* 21: 89–95.
4. Leder K et al.; GeoSentinel Surveillance Network, 2013. GeoSentinel surveillance of illness in returned travelers, 2007–2011. *Ann Intern Med* 158: 456–468.
5. Askling HH, Rombo L, 2010. Influenza in travellers. *Curr Opin Infect Dis* 23: 421–425.
6. Schlagenhauf P et al.; EuroTravNet, 2015. Travel-associated infection presenting in Europe (2008–12): an analysis of EuroTravNet longitudinal, surveillance data, and evaluation of the effect of the pre-travel consultation. *Lancet Infect Dis* 15: 55–64.
7. Mutsch M, Tavernini M, Marx A, Gregory V, Lin YP, Hay AJ, Tschopp A, Steffen R, 2005. Influenza virus infection in travelers to tropical and subtropical countries. *Clin Infect Dis* 40: 1282–1287.
8. Ratnam I et al., 2013. Incidence and risk factors for acute respiratory illnesses and influenza virus infections in Australian travellers to Asia. *J Clin Virol* 57: 54–58.
9. Bruni M, Steffen R, 1997. Impact of travel-related health impairments. *J Travel Med* 4: 61–64.
10. Ziyaeyan M, Alborzi A, Jamalidoust M, Moeini M, Pouladfar GR, Pourabbas B, Namayandeh M, Moghadami M, Bagheri-Lankarani K, Mokhtari-Azad T, 2012. Pandemic 2009 influenza A (H1N1) infection among 2009 Hajj Pilgrims from southern Iran: a real-time RT-PCR-based study. *Influenza Other Respir Viruses* 6: e80–e84.
11. Balaban V et al., 2012. Protective practices and respiratory illness among US travelers to the 2009 Hajj. *J Travel Med* 19: 163–168.
12. Leggat PA, Leder K, 2010. Reducing the impact of influenza among travelers. *J Travel Med* 17: 363–366.
13. Alfelali M, Barasheed O, Tashani M, Azeem MI, El Bashir H, Memish ZA, Heron L, Khandaker G, Booy R, Rashid H; Hajj Research Team, 2015. Changes in the prevalence of influenza-like illness and influenza vaccine uptake among Hajj pilgrims: a 10-year retrospective analysis of data. *Vaccine* 33: 2562–2569.
14. Riddle MS, Sanders JW, Putnam SD, Tribble DR, 2006. Incidence, etiology, and impact of diarrhea among long-term travelers (US military and similar populations): a systematic review. *Am J Trop Med Hyg* 74: 891–900.
15. Sanders JW, Putnam SD, Frankart C, Frenck RW, Monteville MR, Riddle MS, Rockabrand DM, Sharp TW, Tribble DR, 2005. Impact of illness and non-combat injury during operations Iraqi freedom and enduring freedom (Afghanistan). *Am J Trop Med Hyg* 73: 713–719.
16. Soltis BW, Sanders JW, Putnam SD, Tribble DR, Riddle MS, 2009. Self reported incidence and morbidity of acute respiratory illness among deployed U.S. military in Iraq and Afghanistan. *PLoS One* 4: e6177.
17. Murray CK, Horvath LL, 2007. An approach to prevention of infectious diseases during military deployments. *Clin Infect Dis* 44: 424–430.
18. Cohen SP, Brown C, Kurihara C, Plunkett A, Nguyen C, Strassels SA, 2010. Diagnoses and factors associated with medical evacuation and return to duty for service members participating in operation Iraqi freedom or operation enduring freedom: a prospective cohort study. *Lancet* 375: 301–309.
19. Gautret P, Vu Hai V, Sani S, Douchi M, Parola P, Brouqui P, 2011. Protective measures against acute respiratory symptoms in French pilgrims participating in the Hajj of 2009. *J Travel Med* 18: 53–55.
20. Gautret P, Yong W, Soula G, Gaudart J, Delmont J, Dia A, Parola P, Brouqui P, 2009. Incidence of Hajj-associated febrile cough episodes among French pilgrims: a prospective cohort study on the influence of statin use and risk factors. *Clin Microbiol Infect* 15: 335–340.
21. Ashshi A et al., 2014. Demographic distribution and transmission potential of influenza A and 2009 pandemic influenza A H1N1 in pilgrims. *J Infect Dev Ctries* 8: 1169–1175.
22. Razavi SM, Sabouri-Kashani A, Ziaee-Ardakani H, Tabatabaei A, Karbakhsh M, Sadeghipour H, Mortazavi-Tabatabaei SA, Salamati P, 2013. Trend of diseases among Iranian pilgrims during five consecutive years based on a Syndromic Surveillance System in Hajj. *Med J Islam Repub Iran* 27: 179–185.
23. Azziz Baumgartner E et al., 2012. Seasonality, timing, and climate drivers of influenza activity worldwide. *J Infect Dis* 206: 838–846.
24. Boggild AK et al.; GeoSentinel Surveillance Network, 2012. Latitudinal patterns of travel among returned travelers with influenza: results from the GeoSentinel Surveillance Network, 1997–2007. *J Travel Med* 19: 4–8.
25. Hardelid P, Rait G, Gilbert R, Petersen I, 2015. Recording of influenza-like illness in UK primary care 1995–2013: cohort study. *PLoS One* 10: e0138659.
26. Adler AJ, Eames KT, Funk S, Edmunds WJ, 2014. Incidence and risk factors for influenza-like-illness in the UK: online surveillance using Flusurvey. *BMC Infect Dis* 14: 232.
27. Ross AM, Kai J, Salter R, Ross J, Fleming DM, 2000. Presentation with influenza-like illness in general practice: implications for use of neuraminidase inhibitors. *Commun Dis Public Health* 3: 256–260.
28. Deiss R et al., 2016. Differences in self-reported severity of symptoms between women and men experiencing influenza-like illness. *Open Forum Infect Dis* 3 (Suppl1): 1271.