Travellers and influenza: risks and prevention

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Abstract

Background: Influenza viruses are among the major causes of serious human respiratory tract infection worldwide. In line with the high disease burden attributable to influenza, these viruses play an important, but often neglected, role in travel medicine. Guidelines and recommendations regarding prevention and management of influenza in travellers are scarce. Of special interest for travel medicine are risk populations and also circumstances that facilitate influenza virus transmission and spread, like travel by airplane or cruise ship and mass gatherings.

Methods: We conducted a PUBMED/MEDLINE search for a combination of the MeSH terms Influenza virus, travel, mass gathering, large scale events and cruise ship. In addition we gathered guidelines and recommendations from selected countries and regarding influenza prevention and management in travellers. By reviewing these search results in the light of published knowledge in the fields of influenza prevention and management, we present best practice advice for the prevention and management of influenza in travel medicine.

Results: Seasonal influenza is among the most prevalent infectious diseases in travellers. Known host-associated risk factors include extremes of age and being immune-compromised, while the most relevant environmental factors are associated with holiday cruises and mass gatherings.

Conclusions: Pre-travel advice should address influenza and its prevention for travellers, whenever appropriate on the basis of the epidemiological situation concerned. Preventative measures should be strongly recommended for travellers at high-risk for developing complications. In addition, seasonal influenza vaccination should be considered for any traveller wishing to reduce the risk of incapacitation, particularly cruise ship crew and passengers, as well as those participating in mass gatherings. Besides advice concerning preventive measures and vaccination, advice on the use of antivirals may be considered for some travellers.

Keywords: Travel medicine, influenza, vaccination, mass gatherings, seasonality

Introduction

Influenza viruses, members of the Orthomyxoviridae family, are among the most diverse emerging infectious agents and cause predominantly respiratory disease in humans. Of the three influenza virus types (A, B and C), influenza A is the best known for its ability to drift, re-assort and cause yearly seasonal outbreaks in the temperate regions of the world. There are three presentations of human influenza: seasonal, avian and pandemic. Seasonal influenza is caused by influenza A or B viruses and affects 5–15% of the human population every year. Symptoms
vary from mild respiratory complaints to fatal respiratory distress syndrome, while subclinical infections may also occur. Severity of infection and outcome of disease depend largely on the influenza virus involved and the immune and health status of the infected individual. Most seasonal influenza virus infections are self-limiting and patients do not need to seek medical care. However, in most years, seasonal influenza does cause a considerable burden of disease, especially in individuals at high-risk for complications.\(^2\) Sporadic infections of humans with avian influenza A viruses may occur causing serious and even fatal disease, but these viruses are not efficiently transmitted among humans. However, an avian virus that, by mutation and/or re-assortment, acquires the capacity to be transmitted efficiently from human-to-human, could be the basis of an emerging pandemic. Four major influenza pandemics have occurred in the past century: in 1918–1920 (Spanish Flu), 1957–1958 (Asian Flu), 1968–1970 (Hong Kong Flu) and recently in 2009–2010 (Mexican or ‘swine’ Flu). Some avian strains pathogenic to humans may be directly transmitted from birds to humans and may also adapt to human-to-human transmissibility by mutation or re-assortment.\(^3,4\) Avian influenza viruses should be considered a major global health threat.\(^5\)

Several reviews have recently addressed influenza virus epidemiology, high-risk groups, vaccination strategies, and treatments.\(^6–10\) However, one fast-growing risk group—travellers—is largely missing from these overviews. Several changes in our globalizing world contribute to the growing importance of this group: (i) steady increase in total travel volume worldwide, (ii) advent of mass-tourism and (iii) increasing numbers of immune-compromised and elderly travellers. These changes highlight the importance of harmonized international and national guidelines for influenza prevention and treatment in travel medicine. For example, it is easy to imagine how large pan-national religious gatherings like the Hajj and Umrah, or international sporting events and festivals could facilitate global spread of influenza. Modern means of transport that gather large numbers of people in relatively small spaces, like cruise ships and airplanes or airports, may also require special attention from a public health perspective. Herein, we summarize existing guidelines and discuss recommendations dealing with the prevention and management of influenza from a traveller’s perspective including the use of vaccines and antivirals as well as hygienic and societal measures. Special attention is given to implications of air and cruise-ship travel, travel to tropical regions and between hemispheres, mass gatherings, necessary actions and directions for future research.

Methods

A PUBMED/MEDLINE search was performed using a combination of the MeSH terms Influenza virus, travel, mass gathering, cruise ships and large-scale events up to June 2016. Only articles written in English were included. In addition, we gathered guidelines and recommendations from selected countries and public health organizations, associated with the International Society of Travel Medicine with online accessible travel medicine guidelines. Finally, we compared and evaluated these search results in the light of currently published knowledge in the fields of influenza prevention and management. PUBMED/MEDLINE search resulted in 828 articles of which after screening for relevance by the authors 73 were included.

Results

Epidemiology of Seasonal Influenza in Travellers

Seasonal influenza is the most frequent vaccine preventable disease in travellers,\(^11\) with the risk of infection beginning upon start of travel, i.e. gathering for transportation (i.e. busses, trains and airports), when increased direct and indirect human-to-human contacts take place. Influenza virus may be transmitted by aerosol/droplet transmission, and through contact with contaminated surfaces, like touching door handles and subsequently touching mucosal membranes.\(^3\) Most likely seasonal influenza viruses first replicate in the columnar epithelial cells of the upper respiratory tract. From there the virus can spread throughout the respiratory tract. Shedding of the seasonal strains from the upper respiratory tract can be highly efficient and virus can be readily recovered in respiratory secretions before symptom onset and for 5–8 days after the symptoms become apparent.

Environmental Factors and Influenza Virus Infection Risk during Travel

Among the challenging epidemiological aspects of seasonal influenza in travellers are differences in seasonality and virus strains between climate zones and between northern and southern hemispheres. In tropical areas, influenza viruses may circulate throughout the year with several seasonal peaks, whereas in the moderate climate zones, circulation is largely limited to one or two peaks in the fall and winter months.\(^12\) Recent data have revealed interesting patterns of emergence and spread of antigenic drift variants, showing the global circulation of the different seasonal influenza viruses. These observations have major implications for selection of viruses that should be represented in the seasonal vaccines, which from time to time results in different strains being represented in seasonal influenza vaccines for the northern and southern hemispheres.\(^13,14\)

Several studies have attempted to estimate the effectiveness of influenza transmission during travel; especially air transportation. For instance, a study on four north American flights carrying ill passengers with confirmed pandemic H1N1 (2009) infection calculated overall attack rates for acute respiratory infection and influenza-like illness (ILI). In the 1–7 days following travel, passenger attack rates were 5.2 and 2.4%, respectively, of which a significant proportion were confirmed to be influenza by serology.\(^15\) These results were in line with a retrospective study on in-flight transmission of pandemic H1N1 (2009) infection in which 3% of exposed passengers developing ILI in the days following the flight. Being placed in the same area (up to two rows apart) as an index case with ILI, resulted in a significantly increased risk.\(^16\) Other studies using contact tracing,\(^17\) mathematical modelling and an experimental air cabin setting, all confirmed the predisposing conditions of influenza droplet transmission during flights.\(^18–21\)

The increased risk of being infected with seasonal influenza appears not to be limited to the period directly before and during the actual flight, but continues after leaving the aircraft. Several studies have shown high incidence rates of confirmed infection with
seasonal influenza viruses during travel with the most recent analysis documenting a rate of 8.9 (95% CI 7.1–10.9) per 100 person-months. However, only ~10% had ILL. Among Dutch long-term travellers, the influenza attack rate of seroconverters confirmed infection during travel was 15%, and of symptomatic infection was 6.3% (fever alone) and 2% (ILI), respectively. Results from a GeoSentinel Surveillance Network study showed that persons who travel to East and Southeast Asia have a 7-fold higher risk of acquiring influenza compared with those who travel to other destinations. Influenza virus infection in travellers largely occurs outside the epidemic season in the country of departure, and especially at risk are those visiting family and relatives or those staying abroad for >30 days. GeoSentinel and EuroTravNet act as surveillance networks that monitor all travel-related illnesses reported to any of their clinics worldwide. Data collected from these organisations indicate that in 2008, prior to the H1N1 pandemic, the number of influenza confirmed cases was at just 0.1%. During 2009, however the number of confirmed influenza cases rose to prevalence figures of 11, 12, 18, and as high as 32% with the majority of these attributable to pH1N1. Close human-to-human contact may also occur at mass-gatherings or on board cruise ships, as discussed below.

**Host Factors**

High morbidity and mortality in influenza are seen especially among those at the extremes of age (elderly and very young), those with underlying health conditions and pregnant women. Underlying health conditions especially associated with an increased risk for complicated influenza are immunocompromised individuals, either due to the underlying disease, or to immunomodulatory treatment, like organ transplant recipients and those taking medication for autoimmune conditions. Furthermore, chronic pulmonary disease, diabetes mellitus, cardiovascular disease and malignancies are also considered risk factors for developing severe influenza or complications.

**Impact on Travellers**

Even a relatively mild, self-limiting seasonal influenza virus infection can have drastic impact on the success of a holiday or business trip. Furthermore, travel of athletes to international contests and artists to performances abroad or social gatherings like weddings can be ruined by influenza. Among the well-recognized examples spread through the media are the German national football team and coach during the 2010 World Cup in South Africa and a famous rock star of a concert that had to be cancelled as he got influenza. A large study of influenza virus infection in persons travelling to tropical and sub-tropical countries found that 1.1% of the travellers enrolled in the study seroconverted and that 40% of those who seroconverted had sought medical attention during their travel: a highly significant number. Influenza virus infections were acquired largely from Asia (47.5%), Africa (27.5%) and Latin America (25%).

It is important to note that, independent of travel, seasonal influenza outbreaks have been repeatedly associated with poor outcomes even in patients without co-morbidities: including small numbers who develop severe and even lethal influenza as well as life-threatening complications. Examples include patients with severe viral pneumonia, acute respiratory distress syndrome (ARDS), post-influenza Staphylococcus aureus infection with a potential Methicillin-resistant S. aureus infection or rare examples of myocarditis and encephalitis. It is now generally accepted that even healthy individuals have a low but important risk of developing severe influenza-associated disease. Furthermore, there is a significant economic burden of seasonal influenza due to sick leave, medical care and medication. Unexpected medical events while travelling can be particularly expensive.

**Preventive Measures and Treatment Options**

There are several ways to decrease the risk of catching influenza. First of all hygienic measures, including active ventilation of crowded places, hand sanitation and (possibly) wearing a face mask can reduce the risk of spreading influenza. Influenza prevention by vaccination and specific problems associated with vaccinating travellers against influenza, are discussed in more detail below. As an adjunct to vaccination, the value of early antiviral therapy or prophylactic antiviral usage is also discussed.

**Hygienic Measures**

Several studies have addressed the effectiveness of non-pharmaceutical interventions (NPIs) in reducing influenza virus spread, especially in the case of a pandemic. For seasonal influenza, most attention has been focused on hand hygiene and the use of facemasks. These NPI’s may be especially important when someone in the immediate environment or a travel companion is infected. For instance, careful hand hygiene and the use of facemasks appear to reduce household transmission of influenza virus when implemented within 36 h of symptom onset of the index patient. The general utility of hand hygiene and facemasks in reducing influenza spread has been confirmed by a recent meta-analysis although the quality of the data in many studies, particularly when children are involved, is relatively poor. Furthermore, in studies that focus on scenarios in which there is active, on-going influenza transmission in the population, like during a pandemic, large variation in effectiveness of these NPIs has been observed. Despite these limitations, there seems to be sufficient evidence to conclude that facemasks, hand hygiene and reduced crowding are effective in reducing the spread of influenza. Hand hygiene would be relatively simple for travellers to implement and several studies suggest that the use of alcohol based sanitizers and hand washing after touching contaminated surfaces can be effective.

However, these trials were not conducted in travellers. Facemask usage in travellers is particularly controversial and may only have measurable impact when a close companion (i.e. shared living quarters) is infected. In mass gatherings, there seems to be a (very) modest decrease in risk of infection in persons using facemasks. Furthermore, the overall effectiveness of masks and respirators is likely dependent on consistent and correct usage. In this light, it is important to note that up to 40% of influenza cases may be transmitted prior to the onset of symptoms.

**Antiviral Options for Travellers**

Another potential preventive strategy for influenza is the use of antivirals either prophylactically or for early treatment. Currently, the most effective anti-influenza drugs are the
neuraminidase inhibitors (NIs: oseltamivir, zanamivir and peramivir). M2 inhibitors (amantadine and rimantadine) are rarely used since they suffer from rapid development of virus resistance and virtually all currently circulating seasonal influenza A viruses have pre-existing resistance. Furthermore, M2 inhibitors do have considerable side effects and are not effective against influenza B viruses. Although influenza viruses can develop resistance to individual NIs quite rapidly, the risk of resistance development to the whole class of drugs is unlikely and lower than with M2 inhibitors, illustrated by the fact that virtually no cross resistance to oseltamivir and zanamivir has been identified. For travellers, the NIs may play a role in both pre- and post-exposure prophylaxis, with confirming data coming from both animal models (mouse and ferret) and human trials. NIs provide protective efficacy when used preventively in an outbreak situation, or soon after the first clinical symptoms, by reducing the duration and severity of symptomatic influenza. Furthermore, several 2009 pandemic period observational studies suggest that early treatment can reduce rates of hospitalisation and in-hospital mortality. Some consider the use of NIs controversial because almost all published studies have been industry-funded, and the reported effects are generally minor and there have been no large randomized control trials proving efficacy for post-exposure treatment. However, a recent independent meta-analysis showed that oseltamivir in adults with influenza accelerates clinical symptom alleviation, reduces risk of lower respiratory tract complications, and admission to hospital, while increasing the occurrence of nausea and vomiting.

Although NIs have relatively mild side effects, their cost and modest efficacy suggest they should play only a limited role in routine pre-travel advice. However, elderly or other high-risk groups in which vaccine efficacy can be low, could be advised to consider bringing a NI for influenza early treatment, if access to medical care at the destination will be limited. Especially since in many countries NI requires a medical script to be purchased and may not be readily available resulting in an unnecessary delay. These drugs could also play a role in mass transportation settings like cruises or group travel. The use of NIs does lead to reduction in disease duration—if used within 48 h after first symptoms—about 1 day—and to reduction in disease severity, although this has been also a matter of debate. In specific cases, such reductions may be crucial: e.g. athletes, politicians, scientists and those travelling for business. The prophylactic use of NI decreases the chance of being infected. To our knowledge, and in light of the recent Olympics in Rio de Janeiro and upcoming sport events, NIs are not currently listed as prohibited substances by the World Anti-Doping Agency (WADA) [https://www.wada-ama.org/en/what-we-do/prohibited-list (26 October 2016, date last accessed)].

The CDC currently suggests that patients infected with avian influenza should be treated with oseltamivir or zanamivir. Furthermore, the curative use of NIs is recommended as early as possible, preferably within 48 h, for patients hospitalized with confirmed or suspected influenza, with severe, complicated, or progressive illness or at high risk for influenza-associated complications (e.g. children <2years, adults ≥65years, nursing home residents, individuals with major co-morbidities) according to CDC guidelines (www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm). Currently, oseltamivir is FDA registered for influenza treatment for any age and as chemoprophylaxis from 3 months of age. Age cut-offs for zanamivir use are currently 7 and 3 years, respectively. Prophylactic dosing with chloroquine—known to have some non-specific antiviral efficacy in vitro—did not translate into clinical protection in a large randomized controlled community trial during the H1N1 outbreak in 2009 and therefore does not seem to have a role in travel medicine regarding influenza prevention.

**Vaccination of the Healthy, ‘Low Risk’ Traveller**

Currently, seasonal influenza vaccination in most guidelines is only advised for healthy travellers if they plan to attend large events or to travel by cruise ship. This is mainly because influenza is widely considered a relatively mild and self-limiting disease in most healthy individuals. However, over the past decade, reports of patients without co-morbidities who develop severe and even lethal influenza with apparently ‘normal’ seasonal influenza viruses, have steadily accumulated. Since seasonal influenza is the most frequent vaccine preventable infectious disease in travellers, influenza vaccination should be part of regular pre-travel advice for all travellers. This raises the more general question about what burden of expected disease during the envisaged travel would justify inclusion of vaccination advice in travel guidelines. The probability of acquiring influenza, severity of disease, expected effectiveness of the vaccine and cost are among the factors that should be taken into account. One could argue that the a priori chances of developing typhoid fever, hepatitis A or tetanus during a two and half week trip to an Asian destination are much lower than being infected with an influenza virus. However, at least according to most guidelines issued in industrialized nations, these three immunizations are usually recommended for most travellers going to many developing countries while influenza vaccination is often not even considered.

**Vaccination of Travellers Belonging to High-Risk Groups**

The majority of elderly individuals (≥60 or ≥65 years old) and those with serious co-morbidities would be candidates for influenza vaccination even without travel plans. However, it remains important to assess vaccination status and to evaluate whether or not the strains the individual has been vaccinated against are appropriate for the geographic area and season of the travel plans (see below). Recommendations for the elderly are not only based on the inevitably growing number of co-morbidities in this age group, but also on immune-senescence. Unfortunately, the effectiveness of influenza vaccines is often impaired in individuals who could benefit most from vaccination: immune-compromised and elderly individuals, as well as patients in the other high-risk groups mentioned in virtually all recommendations. Limited data are available about the added value of recently introduced adjuvanted, high-dose (HD) and quadrivalent vaccines (for review see Reperant et al.85). To date, strong RCT data providing evidence of superiority are only available for the HD formulation in the elderly and the effect was modest.

Although in the past one has been reluctant to immunize pregnant women, currently vaccination of pregnant women against seasonal influenza is incorporated in most guidelines and recommendations. This is based on the real risks of influenza during pregnancy that far outweighs the risks associated with vaccination. During the H1N1 (2009) pandemic, influenza...
vaccines proved to be safe and effective for pregnant women and their unborn babies; findings very similar to studies of seasonal influenza vaccination in this high risk group. In line with these recommendations, the advice might be broadened to pregnant women travelling to influenza endemic areas and possibly to persons in close contact with pregnant women or other high-risk individuals, like partners and close family members.

Influenza vaccination status of travellers in defined risk categories should be checked and either vaccination or additional vaccination against influenza should be recommended on the basis of the epidemiological situation in the area of intended travel. The relatively limited effectiveness of influenza vaccination in most of the high-risk groups and the value of newer generations of vaccines that might overcome these problems are important topics for future study. Finally, for very frail patients, the advice not to travel to certain areas should always be considered during pre-travel consultation, although risk assessment in these cases should obviously not be limited to the threat posed by influenza.

Mass Gatherings

The Hajj is undoubtedly among of the most challenging large-scale events as regards infectious disease control. Every year more than 10 million pilgrims from all over the world visit the holy places of Islam in the Kingdom of Saudi Arabia. Almost one-third of these pilgrims will perform this religious obligation during a 6-day fixed period, called the Hajj. The remaining two-thirds will perform the Umrah, which can be done at any time in the year with peak incidence of visitors during Ramadan. The number of Hajj pilgrims has increased by a factor of 5 from 1920 to 2012 and, at specific pilgrimage ‘bottlenecks’, crowding can be as high as 3–4 persons/square meter. In a recent extensive review covering 31 Hajj-associated studies, respiratory tract infections were by far the most common infections among pilgrims with 60% of ill Hajjis presenting with respiratory tract infections were by far the most common infections among pilgrims with 60% of ill Hajjis presenting with respiratory tract complaints. After rhinovirus, influenza viruses are the most common cause of these respiratory complaints. The rapid increase in case numbers during the 6-day Hajj confirms the predisposing conditions for influenza transmission during this pilgrimage. Given the severe consequences that influenza can have for high-risk groups and since influenza is currently the only vaccine preventable respiratory virus infection in pilgrims, the Ministry of Health of the Kingdom of Saudi Arabia recommends that international pilgrims be vaccinated against seasonal influenza with the most recently available vaccines. The need to aim for optimal vaccination coverage of pilgrims during the Hajj is further confirmed by studies showing that almost 50% of the pilgrims in the 2009 Hajj had at least one risk factor for the development of severe influenza. Despite the Saudi government requirement, a recent cross-sectional study showed vaccination coverage in Malaysian pilgrims to be only 65.2%. Of course, non-pharmaceutical measures (e.g. hand hygiene, wearing face masks and social distancing) could further reduce influenza transmission during the Hajj, although effectiveness outcomes have not always been convincing. However, combined data from multiple studies suggest that the prevalence of ILI has decreased among Hajj pilgrims as vaccine coverage increased over the last decade. Influenza outbreaks are not recorded very often at other large-scale religious and sporting or cultural events, but reported examples include the religious World Youth Day in Sydney, Australia 2008, outbreaks at musical events in 2009 in Belgium, Hungary and Serbia, and at the winter Olympics in Salt Lake City in 2002.

Cruise Ship Holidays

Special attention should be given to the prevention and management of influenza during cruise ship holiday travel. Some modern cruise ships carry over 5000 passengers served by more than 2000 crew-members, who may come from and, during the cruise, may also visit several geographical areas or even travel between the hemispheres. Often, at least some of the passengers originate from a part of the world where there is an influenza epidemic. Crews of these ships may function as reservoirs for influenza viruses between trips, since they often work long periods throughout the season, while having contact with the changing groups of passengers. In the last two decades, multiple reports have described influenza outbreaks on cruise ships. Most were seasonal influenza outbreaks, that occurred outside the ‘traditional’ influenza seasons characteristic of the temperate regions. A recent systematic review of 41 studies of respiratory virus propagation during transportation and in transportation hubs found that cruise ship influenza outbreaks typically affect 2–7% of the passengers. After acute gastroenteritis, influenza is the most common communicable ship-board illness. In most cruise ship influenza outbreaks, crew members are at the highest risk of infection, probably because their living quarters are more crowded, facilitating spread. Although an influenza outbreak can occur on any cruise worldwide, outbreaks were most frequently reported from cruises travelling to Alaska, Australia/Trans-Tasman and South America.

Increased Influenza vaccination coverage of passengers and crew would logically be expected to result in decreasing disease burden. However, mismatches between circulating and vaccine strains, in part based on differences between the vaccines for the respective hemispheres, may reduce the effectiveness of this strategy. Together with the reduced response of elderly and immune-compromised individuals, the level of protection afforded by increased vaccination coverage may be insufficient to prevent outbreaks and implementation of other prevention strategies should be considered. In 2009, a previously established European Union project (SHIPSAN) actively promoted measures to prevent communicable disease outbreaks on passenger ships, with special emphasis on the H1N1 influenza pandemic. There have been reports describing successful interruption of influenza transmission on cruise ships through the introduction of a combination of measures including surveillance, isolation, and vaccination of crew, complemented with antiviral chemoprophylaxis for both crew and passengers.

Avian Influenza and Travel Medicine

Although human cases of severe avian influenza virus infections have been reported in Asia since 1997 when a highly pathogenic (for poultry) avian influenza A H5N1 infection affected 18
people in Hongkong, 6 of whom died,91–93 there have not yet been many reports of avian influenza in travellers. Recently, a case report was published of an otherwise healthy Canadian 28-year-old woman who returned from China with a fatal pneumonia and meningoencephalitis due to highly pathogenic (for poultry) avian influenza A H5N1 infection.94 Another case report described a 59-year-old woman who visited a poultry market in South China as a tourist and developed dyspnea and haemoptysis due to highly pathogenic (for poultry) avian influenza virus strains is rare, and therefore prevention should focus predominantly on avoidance of traveller contact with poultry and uncooked poultry products.

Preventive Measures and Treatment Options for Avian Influenza

Although avian influenza only sporadically occurs in humans with limited bird-to-human transmission, preventive measures do play a role in dealing with traveller’s risk. Currently, no vaccines for avian influenza in humans are commercially available. Therefore, prevention of infection with avian influenza viruses should concentrate on raising awareness of travel medicine professionals and adjusting traveller’s behaviour through pre-travel advice. Particular attention should be given to travellers planning to visit areas endemic for avian influenza in poultry and where human cases have occurred. Such areas are currently found in Asia, Africa and the Middle East. Advice should focus on avoiding contacts with patients suffering from respiratory

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Table 1. Summary of available guidelines regarding influenza vaccination in travel medicine

| Authority                     | High-risk          | Normal risk          | Source                                                                 |
|-------------------------------|--------------------|----------------------|----------------------------------------------------------------------|
| Australia                     | Recommended        | Consider             | http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part3~handbook10-3-2 (26 October 2016, date last accessed) |
| Austria Government            | not mentioned      | not mentioned        | https://www.gesundheit.gv.at/Portal.Node/gph/public/content/Reiseimpfungen_LN.html (26 October 2016, date last accessed) |
| Austria Travel Medicine       | Recommended        | Recommended          | http://www.reisemed.at/krankheiten/influenza-echte-grippe (26 October 2016, date last accessed) |
| France                        | Recommended        | Not mentioned        | http://www.invs.sante.fr/beh/2015/reco/pdf/2015_reco.pdf |
| Germany CRM                   | Recommended        | Mentioned            | https://www.crm.de/krankheiten/krankheiten.asp?Domain=CRM&Spraech=de&Bereich=krankheiten&Klientel laic&Auspraegung=kurz&HTML.fragmente=no&Auswahl=A-Z (26 October 2016, date last accessed) |
| Germany DTG                   | Recommended        | Useful               | http://www.dg.org/influenzasaisonal.html (26 October 2016, date last accessed) |
| Switzerland                   | Recommended        | Not mentioned        | http://www.safetravel.ch/safetravel2/servlet/ch.ofac.wv204j.pages.Wv204ConselsSanteListeCtrl?action=afficheDetail&elementCourant=0 (26 October 2016, date last accessed) |
| The Netherlands               | Recommended        | Not recommended      | http://www.mijnlcr.nl (26 October 2016, date last accessed) |
| United Kingdom                | Southern hemisphere vaccine not available. Consult health-care provider for advice. | Not recommended | (no influenza page on NaTHNaC site) |
| Canada                        | Not recommended    | Not recommended      | http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-10-eng.php (26 October 2016, date last accessed) |
| United States                 | Recommended        | Recommended          | http://www.cdc.gov/travel/diseases/influenza-seasonal-zoonotic.html# (26 October 2016, date last accessed) |
| World Health Organization     | Should be vaccinated | not mentioned        | http://www.who.int/ith/vaccines/seasonal_influenza/en/ (26 October 2016, date last accessed) |
| Kingdom of Saudi Arabia       | Must be vaccinateda | Should be vaccinateda | http://www.moh.gov.sa/en/Hajj/Pages/HealthRegulations.aspx (26 October 2016, date last accessed) |
| Brazil                        | Refer to WHO guidelines | Refer to WHO guidelines | http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/leia-mais-o-ministerio/440-secretaria-svs/viajante/viajante-en/9654-brazilians-abroad (26 October 2016, date last accessed) |
| South Africa                  | No travel guidelines | No travel guidelines | http://travelhealthpro.org.uk/olympic-and-paralympic-games-2016-brazil/ (26 October 2016, date last accessed) |

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*aMinistry of health of Saudi Arabia have made influenza vaccination compulsory for Hajj and Umrah related visa applications.

*bSouth African ministry of health recommend a yearly flu vaccine for everyone 6 months of age and older.
disease, and contacts with birds and their excreta at live bird markets or farms, as well as avoiding contacts with, and consumption of insufficiently cooked poultry products. Since consumption of poultry blood and uncooked poultry meat has been associated with bird-to-human transmission, poultry products for human consumption should be fully cooked, and should therefore preferably not be purchased from street vendors. Visits to live-bird markets in endemic areas should be discouraged, as aerosol transmission has been shown to be a risk factor (i.e. contamination with aerosolized poultry faeces). General hygiene measures like washing and disinfecting hands may limit avian influenza virus transmission but only limited data are available about direct and indirect bird-to-human transmission and prevention in travellers going to areas endemic for avian influenza in poultry. A questionnaire-based study among Australian backpackers going to areas with outbreaks of avian H5N1 virus in poultry suggests an overall poor knowledge of this infection. While currently relying on such generic preventive measures, vaccine development efforts for H5N1 and H7N9 viruses are on-going. This effort is not directed towards the development of travel vaccines however, but rather for pandemic preparedness, since the avian viruses may cause a future pandemic through mutation or re-assortment. In view of the risk posed by avian influenza viruses, the early or, in specific cases, even preventive use of antivirals like oseltamivir and peramivir may be live saving. Since the availability of potent NIs may be limited in some areas, travellers with a high likelihood of exposure, like poultry workers, veterinarians or medical doctors should consider bringing these drugs with them.

Pandemic Influenza and Travel Medicine
Data and recommendations summarized for seasonal influenza and travel medicine also apply to an influenza pandemic. During a pandemic however, guidelines and recommendations will be issued by international and national health authorities largely based on the knowledge available regarding the influenza strain as it spreads. As we have also learned from the 2009 influenza pandemic, vaccination advice, antiviral use and target groups will likely differ between pandemics and therefore tailor-made advice should be provided. Strain-specific travel advice may also be appropriate in this setting to reduce spreading of the pandemic virus through air travel, in order to buy time for the development and implementation of intervention and mitigating strategies.

Availability of Effective Influenza Vaccines — Action Needed
WHO recommends that “high-risk individuals travelling from one hemisphere to the other shortly before or during the other hemisphere’s influenza season should obtain the vaccination recommended for the opposite hemisphere two weeks before travel” [http://www.who.int/ith/vaccines/seasonal_influenza/en/ (26 October 2016, date last accessed)]. However, compliance with this recommendation depends largely on availability of the appropriate vaccine in the country of residence. Unfortunately, even in years when the northern and southern hemisphere vaccines contain identical strains, the shelf life of the local ‘winter influenza vaccine’ has typically expired when travel is considered and neither the following winter season vaccine nor the opposite hemisphere vaccine are available (i.e. licensed in the country of departure). Thus, when no suitable influenza vaccine is available locally, the traveller should arrange vaccination as soon as possible after arriving at the travel destination, bearing in mind that vaccine-induced protection may take 1–2 weeks to develop. Furthermore, the likelihood of travellers on short-term holidays seeking out influenza vaccination in the country they are visiting is highly unlikely to happen. This approach may be particularly important in years with a significant change in formulation between northern and southern hemisphere vaccines. In some years, simply increasing the shelf-life of seasonal influenza vaccine would improve this situation. Commercial vaccines often maintain acceptable potency for many months after they have ‘expired’. In addition, efforts should be made by pharmaceutical industry and regulatory bodies to make opposite hemisphere influenza vaccines available at least for travel clinics. Obviously, success in the development of more universal influenza vaccines that would induce longer lasting and increased effectiveness would bring great benefits for the combat of influenza not only in high-risk groups but also for travellers.

Future Studies
Given the impact and burden of disease caused by travel-related influenza, the prevention and management of influenza before and during travel is a field of travel medicine that deserves more attention than it gets today. Current data show that vaccine coverage among travellers can be greatly improved. Future studies should focus on both a better understanding of the epidemiological aspects of seasonal influenza and optimization of vaccination strategies. Although the WHO advises travellers going to the opposite hemisphere to be vaccinated with a vaccine containing strains circulating at their destination [http://www.who.int/ith/ITH2010chapter6 (26 October 2016, date last accessed)], this advice is currently almost impossible to implement except by advising travellers to seek vaccination immediately upon arrival at their destination. Increasing the shelf-life of seasonal influenza vaccines could improve the situation in years when the strains do not change between northern and southern formulations but other strategies should also be pursued, like ensuring global licensure of seasonal vaccines and development of more universal vaccines. Improvement in the effectiveness of seasonal influenza vaccines would especially benefit the very young and old as well as the immune-compromised since vaccine efficacy continues to be far from satisfactory in these high-risk groups. Although only sporadic cases of travel-related avian influenza have been reported to date, these infections are usually severe and often fatal. In the absence of registered vaccines for avian influenza and, in view of their sporadic and geographically restricted nature, preventive measures should focus on adequate pre-travel advice to reduce exposure. Finally, the availability of specific antivirals for early treatment or prevention of seasonal and avian influenza in travellers needs to be given more attention and should be covered in (inter)national guidelines.

Conclusions
Seasonal influenza is a significant problem for travellers that should be routinely addressed in pre-travel counselling and in the differential diagnosis of any returning traveller with fever.
We have aimed to provide an overview of the available literature and guidelines. Potential limitations of this overview might come from guidelines not available in English or accessible by our search strategy. However, based on the available literature we believe prevention and management of influenza before and during travel is a field of travel medicine that deserves more attention than it gets today. Expert advice about preventive hygienic and behavioural measures, vaccination and options for antiviral treatment should become routine elements of pre-travel counselling. Seasonal influenza vaccination should be strongly recommended for people in high-risk groups such as the elderly, and the immune compromised, for whom such protective measures are already part of standard advice for non-travellers in most jurisdictions (Table 1). Routine immunization should also be considered for the healthy travel partners of these high-risk individuals. Many would also recommend influenza vaccination for all cruise ship travellers and crew, as well as for travellers going to major religious gatherings and other mass gathering events. In addition, influenza immunization can be considered in any international traveller wishing to reduce the personal risk of being incapacitated by influenza during travel. Besides vaccination against influenza, tourists can be informed about other means to reduce the risk of influenza and its transmission, such as implementing hygienic and behavioural measures and options for rapid antiviral treatment.

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References

1. Clark NM, Lynch JP. Influenza: epidemiology, clinical features, therapy, and prevention. Semin Respir Crit Care Med 2011; 32: 373–92.
2. Nicholson KG, Wood JM, Zambon M. Influenza. Lancet 2003; 362: 1733–45.
3. Herfst S, Schrauwen EJ, Linster M et al. Airborne transmission of influenza A/HSN1 virus between ferrets. Science 2012; 336: 1534–41.
4. Imai M, Watanabe T, Hatta M et al. Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. Nature 2012; 486: 420–8.
5. Liem NT, Tung CV, Hien ND et al. Clinical features of human influenza A (H5N1) infection in Vietnam: 2004–2006. Clin Infect Dis 2009; 48: 1639–46.
6. Lazarus R, Lim PL. Avian influenza: recent epidemiology, travel-related risk, and management. Curr Infect Dis Rep 2015; 17: 456.
7. Bautista E, Chotprayasunondh T, Gao Z et al. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med 2010; 362: 1708–19.
8. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions. Cochrane Database Syst Rev 2016; 6: CD005187.
9. Remschmidt C, Wichmann O, Harder T. Vaccines for the prevention of seasonal influenza in patients with diabetes: systematic review and meta-analysis. BMC Med 2015; 13: 53.
10. Beck CR, McKenzie BC, Hashim AB et al. Influenza vaccination for immunocompromised patients: summary of a systematic review and meta-analysis. Influenza. Other Respir Viruses 2013; 7: 72–9.
11. Steffen R, Behrens RH, Hill DR et al. Vaccine-preventable travel health risks: what is the evidence—what are the gaps?. J Travel Med 2015; 22: 1–12.
12. Hirve S, Newman LP, Paget J et al. Influenza seasonality in the tropics and sub tropics—when to vaccinate? PLoS One 2016; 11: e0153003.
13. Bedford T, Riley S, Barr IG et al. Global circulation patterns of seasonal influenza viruses vary with antigenic drift. Nature 2015; 523: 217–20.
14. Russell CA, Jones TC, Barr IG et al. The global circulation of seasonal influenza A (H3N2) viruses. Science 2008; 320: 340–6.
15. Neatherlin J, Cramer EH, Dubray C et al. Influenza A (H1N1)pdm09 during air travel. Travel Med Infect Dis 2013; 11: 110–8.
16. Foxwell AR, Roberts L, Lokuge K et al. Transmission of influenza on international flights, May 2009. Emerg Infect Dis 2011; 17: 1188–94.
17. Kim JH, Lee DH, Shin SS et al. In-flight transmission of novel influenza A (H1N1). Epidemiol Health 2010; 32: e020006.
18. Leitmeyer K, Adlhoch C. Influenza transmission on aircraft: a systematic literature review. Epidemiology 2016; 27: 743–51.
19. Baker MG, Thornley CN, Mills C et al. Transmission of pandemic A/H1N1 2009 influenza on passenger aircraft: retrospective cohort study. BMJ 2010; 340: c2424.
20. Gupta JK, Lin CH, Chen Q. Risk assessment of airborne infectious diseases in aircraft cabins. Indoor Air 2012; 22: 388–95.
21. Khan K, Arino J, Hu W et al. Spread of a novel influenza A (H1N1) virus via global airline transportation. N Engl J Med 2009; 361: 212–4.
22. Belderkor SM, Rimmelzwaan GF, van den Hoek A et al. Effect of travel on influenza epidemiology. Emerg Infect Dis 2013; 19: 925–31.
23. Whelan J, Rimmelzwaan GF, van den Hoek A et al. Influenza in long-term Dutch travelers in the tropics: symptoms and infections. BMC Infect Dis 2016; 16: 158.
24. Bogdil AK, Castelli F, Gautret P et al. Latitudinal patterns of travel among returned travelers with influenza: results from the GeoSentinel Surveillance Network, 1997–2007. J Travel Med 2012; 19: 4–8.
25. Mutsch M, Tavernini M, Marx A et al. Influenza virus infection in travelers to tropical and subtropical countries. Clin Infect Dis 2005; 40: 1282–7.
26. Follin P, Lindqvist A, Nystrom K et al. A variety of respiratory viruses found in symptomatic travelers returning from countries with ongoing spread of the new influenza A(H1N1)v virus strain. Euro Surveill 2009; 14: E3–1.
27. Jaureguberry S, Boutolleau D, Grandsire E et al. Clinical and microbiological evaluation of travel-associated respiratory tract infections in travelers returning from countries affected by pandemic A(H1N1)2009 influenza. J Travel Med 2012; 19: 22–7.
28. Odolini S, Parola P, Gkrania-Klotsas E et al. Travel-related imported infections in Europe, EuroTravNet 2009. Clin Microbiol Infect 2012; 18: 468–74.
29. Costantino C, Vitale F. Influenza vaccination in high-risk groups: a revision of existing guidelines and rationale for an evidence-based preventive strategy. J Prev Med Hyg 2016; 57: F13–8.
30. Ison MG. Influenza prevention and treatment in transplant recipients and immunocompromised hosts. Influenza. Other Respir Viruses 2013; 7: 60–6.
31. Samei F, Wilkinson T. Influenza vaccination for patients with chronic obstructive pulmonary disease: understanding immunogenicity, efficacy and effectiveness. Thor Adv Respir Dis 2016; 10: 349–67.
32. Seki M, Fuke R, Oikawa N et al. Association of influenza with severe pneumonia/empyema in the community, hospital, and healthcare-associated setting. Respirology Case Rep 2016; 19: 1–4.
33. http://www.bbc.com/sport/football/28150945 (26 October 2016, date last accessed).
34. http://www.chartattack.com/news/2003/12/10/david-bowie-down-with-the-flu-canadian-shows-still-on/ (26 October 2016, date last accessed).
35. https://bowiesongs.wordpress.com/2015/03/11/the-last-tour/.
36. Tomas J, Macario MC, Gaspar E et al. Severe post-influenza (H1N1) encephalitis involving pulvinar nuclei in an adult patient. BMJ Case Rep 2015; 22: 2015.
37. Shah NS, Greenberg JA, McNulty MC et al. Bacterial and viral co-infections complicating severe influenza: Incidence and impact among 507 U.S. patients, 2013–14. J Clin Virol 2016; 80: 12–9.
38. Sues T, Remschmidt C, Schink SB et al. The role of facemasks and hand hygiene in the prevention of influenza transmission in households: results from a cluster randomised trial; Berlin, Germany, 2009–2011. BMC Infect Dis 2012; 12: 26.
39. Cowling BJ, Chan KH, Fang VJ et al. Facemasks and hand hygiene to prevent influenza transmission in households: a cluster randomised trial. Ann Intern Med 2009; 151: 437–46.
40. Wong VW, Cowling BJ, Aiello AE. Hand hygiene and risk of influenza virus infections in the community: a systematic review and meta-analysis. Epidemiol Infect 2014; 142: 922–32.
41. Willmott M, Nicholson A, Busse H et al. Effectiveness of hand hygiene interventions in reducing illness absence among children in educational settings: a systematic review and meta-analysis. Arch Dis Child 2016; 101: 42–50.
42. Aiello AE, Coulborn RM, Aragon TJ et al. Research findings from nonpharmaceutical intervention studies for pandemic influenza and current gaps in the research. Am J Infect Control 2010; 38: 251–8.
43. Godoy P, Castilla J, Delgado-Rodríguez M et al. Effectiveness of hand hygiene and provision of information in preventing influenza cases requiring hospitalization. Prev Med 2012; 54: 434–9.
44. Torner N, Soldevila N, Garcia JJ et al. Effectiveness of non-pharmaceutical measures in preventing pediatric influenza: a case-control study. BMC Public Health 2015; 15: 543.
45. Aiello AE, Murray GF, Perez V et al. Mask use, hand hygiene, and seasonal influenza-like illness among young adults: a randomized intervention trial. J Infect Dis 2010; 201: 491–8.
46. Barasheid O, Alfelali M, Mushita S et al. Uptake and effectiveness of facemask against respiratory infections at mass gatherings: a systematic review. Int J Infect Dis 2016; 47: 105–11.
47. Bin-Reza F, Lopez Chavarrias V, Nicoll A et al. The use of masks and respirators to prevent transmission of influenza: a systematic review of the scientific evidence. Influenza Other Respir Viruses 2012; 6: 257–67.
48. Fraser C, Riley S, Anderson RM et al. Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci USA 2004; 101: 6146–51.
49. Loregian A, Mercorelli B, Nannetti G et al. Antiviral strategies against influenza virus: towards new therapeutic approaches. Cell Mol Life Sci 2014; 71: 3659–83.
50. Glezen WP. Clinical practice. Prevention and treatment of seasonal influenza. N Engl J Med 2008; 359: 2579–85.
51. Spanakis N, Patiriga V, Gennimata V et al. A review of neuraminidase inhibitor susceptibility in influenza strains. Expert Rev Anti Infect Ther 2014; 12: 1325–36.
52. Oh DY, Lowther S, McCaw JM et al. Evaluation of oseltamivir prophylaxis regimens for reducing influenza virus infection, transmission and disease severity in a ferret model of household contact. J Antimicrob Chemother 2014; 69: 2458–69.
53. Jefferson T, Jones M, Doshi P et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev 2010; CD001265.
54. Jefferson T, Jones MA, Doshi P et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev 2014; CD008965.
55. Beck CR, Sokal R, Arunachalam N et al. Neuraminidase inhibitors for influenza: a review and public health perspective in the aftermath of the 2009 pandemic. Influenza Other Respir Viruses 2013; (Suppl 1): 14–24.
56. Dobson J, Whitley RJ, Pocock S et al. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet 2015; 385: 1729–37.
57. Heneghan CJ, Onakpoya I, Jones MA et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess 2016; 20: 1–242.
58. Paton NI, Lee L, Xu Y et al. Chloroquine for influenza prevention: a randomised, double-blind, placebo controlled trial. Lancet Infect Dis 2011; 11: 677–83.
59. Alqahtani AS, Alfelali M, Arbon P et al. Burden of vaccine preventable diseases at large events. Vaccine 2015; 33: 6552–63.
60. Botelho-Nevers E, Gautret P. Outbreaks associated to large open air festivals, including music festivals, 1980 to 2012. Euro Surveill 2013; 18: 20426.
61. Freedman D, Chen LH, Kozarsky P. Medical considerations before international travel. N Engl J Med 2016; 375: 247–60.
62. Gnanasekaran G, Biedenbender R, Davidson HE et al. Vaccinations for the older adult. Clin Geriatr Med 2016; 32: 609–25.
63. McElhaney JE, Kuchel GA, Zhou X et al. T-cell immunity to influenza in older adults: a pathophysiological framework for development of more effective vaccines. Front Immunol 2016; 7: 41.
64. Dominguez A, Soldevila N, Toledo D et al. Factors associated with influenza vaccination of hospitalized elderly patients in Spain. PLoS One 2016; 11: e0147931.
65. Reperant LA, Rimmelzwaan GF, Osterhaus AD. Advances in influenza vaccination. F1000Prime Rep 2014; 6: 47.
66. DiazGranados CA, Dunning AJ, Kimmel M et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med 2014; 371: 635–45.
67. Mutsaerts E, Madhi SA, Cufland CL et al. Influenza vaccination of pregnant women protects them over two consecutive influenza seasons in a randomized controlled trial. Expert Rev Vaccines 2016; 6: 1–8.
68. Omer SB, Bednarczyk R, Madhi SA et al. Benefits to mother and child of influenza vaccination during pregnancy. Hum Vaccin Immunother 2012; 8: 130–7.
69. Memish ZA, Zumla A, Alhakeem RF et al. H1N1: infectious disease surveillance and control. Lancet 2014; 383: 2073–82.
70. Gautret P, Benkouten S, Al-Tawfiq JA et al. Hajj-associated viral respiratory infections: a systematic review. Travel Med Infect Dis 2016; 14: 92–109.
71. Memish ZA, Ahmed QA. Mecca bound: the challenges ahead. J Travel Med 2002; 9: 202–10.
72. Benkouten S, Charrel R, Belhouchat K et al. Circulation of respiratory viruses among pilgrims during the 2012 Hajj pilgrimage. Clin Infect Dis 2013; 57: 992–1000.
73. Annan A, Owusu M, Marfo KS et al. High prevalence of common respiratory viruses and no evidence of Middle East respiratory syndrome coronavirus in Hajj pilgrims returning to Ghana, 2013. Trop Med Int Health 2015; 20: 807–12.
74. Health conditions for travelers to Saudi Arabia for the pilgrimage to Mecca (Hajj), 2015. Wky Epidemiol Rec 2015; 90: 381–4.
75. Gautret P, Benkouten S, Al-Tawfiq JA et al. The spectrum of respiratory pathogens among returning Hajj pilgrims: myths and reality. Int J Infect Dis 2016; 47: 83–5.
76. Gautret P, Parola P, Brouqui P. Risk factors for H1N1 influenza complications in 2009 Hajj pilgrims. Lancet 2010; 375: 199–200.
77. Hashim S, Ayub ZN, Mohamed Z et al. The prevalence and preventive measures of the respiratory illness among Malaysian pilgrims in 2013 Hajj season. J Travel Med 2016; 23: tav019.
78. Benkouiten S, Brouqui P, Gautret P. Non-pharmaceutical interventions for the prevention of respiratory tract infections during Hajj pilgrimage. Travel Med Infect Dis 2014; 12: 429–42.
79. Alfelali M, Barasheed O, Tashani M et al. Changes in the prevalence of influenza-like illness and influenza vaccine uptake among Hajj pilgrims: a 10-year retrospective analysis of data. Vaccine 2015; 33: 2562–9.
80. Gautret P, Steffen R. Communicable diseases as health risks at mass gatherings other than Hajj: what is the evidence? Int J Infect Dis 2016; 47: 46–52.
81. Millman AJ, Kornylo DK, Lafond K et al. Influenza B virus outbreak on a cruise ship—Northern Europe, 2000. MMWR Morb Mortal Wkly Rep 2001; 50: 137–40.
82. Fernandes EG, de Souza PB, de Oliveira ME et al. Influenza B outbreak on a cruise ship off the Sao Paulo Coast, Brazil. J Travel Med 2014; 21: 298–303.
83. Browne A, Ahmad SS, Beck CR et al. The roles of transportation and transportation hubs in the propagation of influenza and coronaviruses: a systematic review. J Travel Med 2016; 23: tav002.
84. Marshall CA, Morris E, Unwin N. An epidemiological study of rates of illness in passengers and crew at a busy Caribbean cruise port. BMC Public Health 2016; 16: 314.
85. Influenza in travellers to Alaska, the Yukon Territory, and on west coast cruise ships, summer of 1999. Can Commun Dis Rep 1999; 25: 137–9.
86. Ferson M, Paraskevopoulos P, Hatzi S et al. Presumptive summer influenza A: an outbreak on a trans-Tasman cruise. Commun Dis Intell 2000; 24: 45–7.
87. Ward KA, Armstrong P, McAnulty JM et al. Outbreaks of pandemic (H1N1) 2009 and seasonal influenza A (H3N2) on cruise ship. Emerg Infect Dis 2010; 16: 1731–7.
88. Ward KA, Armstrong P, McAnulty JM et al. A large outbreak of influenza A and B on a cruise ship causing widespread morbidity. Epidemiol Infect 2003; 130: 263–71.
89. Mouchtouri V, Black N, Nichols G et al. Preparedness for the prevention and control of influenza outbreaks on passenger ships in the EU: the SHIPSAN TRAINET project communication. Euro Surveill 2009; 14: 1–4.
90. Claas EC, Osterhaus AD, van BR et al. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. Lancet 1998; 351: 472–7.
91. Claas EC, Osterhaus AD. New clues to the emergence of flu pandemics. Nat Med 1998; 4: 1122–3.
92. Subbarao K, Klimov A, Katz J et al. Characterization of an avian influenza A (H5N1) virus isolated from a child with a fatal respiratory illness. Science 1998; 279: 393–6.
93. Rajabali N, Lim T, Sokolowski C et al. Avian influenza A (H5N1) infection with respiratory failure and meningoencephalitis in a Canadian traveller. Can J Infect Dis Microbiol 2015; 26: 221–3.
94. To KK, Ng KH, Que TL et al. Avian influenza A H5N1 virus: a continuous threat to humans. Emerg Microbes Infect 2012; 1: e25.
95. Leggat PA, Mills D, Speare R. Hostellers’ knowledge of transmission and prevention of avian influenza when travelling abroad. Travel Med Infect Dis 2007; 5: 53–6.
96. Di GG, Abbate R, Albano L et al. A survey of knowledge, attitudes and practices towards avian influenza in an adult population of Italy. BMC Infect Dis 2008; 8: 36.
97. Houser K, Subbarao K. Influenza vaccines: challenges and solutions. Cell Host Microbe 2015; 17: 295–300.
98. Bednarczyk RA, Chu SL, Sicking H et al. Low uptake of influenza vaccine among university students: evaluating predictors beyond cost and safety concerns. Vaccine 2015; 33: 1659–63.
99. Khan NM, Jentes ES, Brown C et al. Pre-travel medical preparation of business and occupational travelers: an analysis of the Global TravEpiNet Consortium, 2009 to 2012. J Occup Environ Med 2016; 58: 76–82.
100. Pfeil A, Mutsch M, Hatz C et al. A cross-sectional survey to evaluate knowledge, attitudes and practices (KAP) regarding seasonal influenza vaccination among European travellers to resource-limited destinations. BMC Public Health 2010; 10: 402.