

## Review

## 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.

**Key words:** 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.<sup>1</sup> 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.<sup>2</sup> 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,<sup>3,4</sup> avian influenza viruses should be considered a major global health threat.<sup>5</sup>

Several reviews have recently addressed influenza virus epidemiology, high-risk groups, vaccination strategies, and treatments.<sup>6–10</sup> 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 immunocompromised 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 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,<sup>11</sup> 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.<sup>3</sup> 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.<sup>12</sup> 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.<sup>13,14</sup>

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.<sup>15</sup> 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.<sup>16</sup> Other studies using contact tracing,<sup>17</sup> mathematical modelling and an experimental air cabin setting, all confirmed the predisposing conditions of influenza droplet transmission during flights.<sup>18–21</sup>

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.<sup>11,12</sup> However, only ~10% had ILI. Among Dutch long-term travellers, the influenza attack rate of serologically confirmed infection during travel was 15%, and of symptomatic infection was 6.3% (fever alone) and 2% (ILI), respectively.<sup>23</sup> 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.<sup>24</sup> 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.<sup>22,23,25</sup> 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.<sup>24,26–28</sup> 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.<sup>29</sup> Underlying health conditions especially associated with an increased risk for complicated influenza are immune-compromised individuals, either due to the underlying disease, or to immunomodulatory treatment, like organ transplant recipients and those taking medication for autoimmune conditions.<sup>30</sup> Furthermore, chronic pulmonary disease<sup>31</sup>, diabetes mellitus, cardiovascular disease and malignancies are also considered risk factors for developing severe influenza or complications.<sup>32</sup>

#### 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.<sup>33–35</sup>

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.<sup>25</sup> Influenza virus infections were acquired largely from Asia (47.5%), Africa (27.5%) and Latin America (25%).<sup>25</sup>

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.<sup>32,36,37</sup> It is now generally accepted that even healthy individuals have a low but important risk of developing severe influenza-associated disease.<sup>2</sup> 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 in 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 NPIs may be especially important when someone in the immediate environment or a travel companion is infected.<sup>38</sup> 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.<sup>39</sup> The general utility of hand hygiene and facemasks in reducing influenza spread has been confirmed by a recent meta-analysis<sup>40</sup> although the quality of the data in many studies, particularly when children are involved, is relatively poor.<sup>41</sup> 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.<sup>42</sup> 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.<sup>43,44</sup>

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.<sup>45</sup> In mass gatherings, there seems to be a (very) modest decrease in risk of infection in persons using facemasks.<sup>46</sup> Furthermore, the overall effectiveness of masks and respirators is likely dependent on consistent and correct usage.<sup>47</sup> In this light, it is important to note that up to 40% of influenza cases may be transmitted prior to the onset of symptoms.<sup>48</sup>

#### 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).<sup>49</sup> 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.<sup>50</sup> 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.<sup>51</sup> 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.<sup>52</sup> 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.<sup>53,54</sup> Furthermore, several 2009 pandemic period observational studies suggest that early treatment can reduce rates of hospitalisation and in-hospital mortality.<sup>55</sup> 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.<sup>53,54</sup> 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.<sup>56</sup>

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.<sup>46</sup> In specific cases, such reductions may be crucial: e.g. athletes, politicians, scientists and those travelling for business.<sup>57</sup> The prophylactic use of NI decreases the chance of being infected.<sup>57</sup> 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](http://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 5 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.<sup>58</sup>

### *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.<sup>2</sup> 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.<sup>7,32,36,37,59,60</sup> 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.<sup>61</sup>

### *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.<sup>62–64</sup> 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.*<sup>65</sup>). To date, strong RCT data providing evidence of superiority are only available for the HD formulation in the elderly and the effect was modest.<sup>66</sup>

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 by 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.<sup>67,68</sup> 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 [CDC guideline: [http://www.cdc.gov/h1n1flu/clinician\\_pregnant.htm](http://www.cdc.gov/h1n1flu/clinician_pregnant.htm) (26 October 2016, date last accessed)] or travel partners.

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.<sup>69</sup> The number of Hajj pilgrims has increased by a factor of 5 from 1920 to 2012<sup>70</sup> and, at specific pilgrimage ‘bottlenecks’, crowding can be as high as 3–4 persons/square meter.<sup>71</sup> 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 complaints.<sup>70</sup> After rhinovirus, influenza viruses are the most common cause of these respiratory complaints.<sup>72,73</sup> The rapid increase in case numbers during the 6-day Hajj confirms the predisposing conditions for influenza transmission during this pilgrimage.<sup>73</sup> 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.<sup>70,74,75</sup> 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.<sup>76</sup> Despite the Saudi government requirement, a recent cross-sectional study showed vaccination coverage in Malaysian pilgrims to be only 65.2%.<sup>77</sup> 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.<sup>78</sup> 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.<sup>79</sup> 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.<sup>59,60,80</sup>

### 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,<sup>81</sup> 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.<sup>82,83</sup> 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.<sup>84</sup> After acute gastroenteritis, influenza is the most common communicable ship-board illness.<sup>85</sup> 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.<sup>85</sup> 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.<sup>86–98</sup>

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<sup>89</sup> 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.<sup>90</sup> 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.<sup>81</sup>

Most likely due to the relatively slow speed of sea travel compared with airplane travel, there are no indications to date that sea transport accelerates global influenza spread.<sup>84</sup>

### 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

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

Authority	High-risk	Normal risk	Source
Australia	Recommended	Consider	<a href="http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part3~handbook10-3-2">http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part3~handbook10-3-2</a> (26 October 2016, date last accessed)
Austria Government	not mentioned	not mentioned	<a href="https://www.gesundheit.gv.at/Portal.Node/ghp/public/content/Reiseimpfungen_LN.html">https://www.gesundheit.gv.at/Portal.Node/ghp/public/content/Reiseimpfungen_LN.html</a> (26 October 2016, date last accessed)
Austria Travel Medicine	Recommended	Recommended	<a href="http://www.reisemed.at/krankheiten/influenza-echte-grippe">http://www.reisemed.at/krankheiten/influenza-echte-grippe</a> (26 October 2016, date last accessed)
France	Recommended	not mentioned	<a href="http://www.invs.sante.fr/beh/2015/reco/pdf/2015_reco.pdf">http://www.invs.sante.fr/beh/2015/reco/pdf/2015_reco.pdf</a>
Germany CRM	Mentioned	Mentioned	<a href="https://www.crm.de/krankheiten/krankheiten.asp?Domain=CRM&amp;Sprache=de&amp;Bereich=krankheiten&amp;Klientel=laie&amp;Auspraegung=kurz&amp;HTMLfragmente=no&amp;Auswahl=A-Z">https://www.crm.de/krankheiten/krankheiten.asp?Domain=CRM&amp;Sprache=de&amp;Bereich=krankheiten&amp;Klientel=laie&amp;Auspraegung=kurz&amp;HTMLfragmente=no&amp;Auswahl=A-Z</a> (26 October 2016, date last accessed)
Germany DTG	Recommended	Useful	<a href="http://www.dtg.org/influenzasaisonal.html">http://www.dtg.org/influenzasaisonal.html</a> (26 October 2016, date last accessed)
Switzerland	Recommended	Not mentioned	<a href="http://www.safetravel.ch/safetravel2/servlet/ch.ofac.wv.wv204j.pages.Wv204ConseilsSanteListeCtrl?action=afficheDetail&amp;elementCourant=0">http://www.safetravel.ch/safetravel2/servlet/ch.ofac.wv.wv204j.pages.Wv204ConseilsSanteListeCtrl?action=afficheDetail&amp;elementCourant=0</a> (26 October 2016, date last accessed)
The Netherlands	Recommended	Not recommended	<a href="http://www.mijnlcr.nl">http://www.mijnlcr.nl</a> (26 October 2016, date last accessed)
United Kingdom	Southern hemisphere vaccine not available. Consult health-care provider for advice.	Not mentioned (no influenza page on NaTHNaC site)	<a href="http://travelhealthpro.org.uk/olympic-and-paralympic-games-2016-brazil/">http://travelhealthpro.org.uk/olympic-and-paralympic-games-2016-brazil/</a> (26 October 2016, date last accessed)
Canada	Not recommended	Not recommended	<a href="http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-10-eng.php">http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-10-eng.php</a> (26 October 2016, date last accessed)
United States	Recommended	Recommended	<a href="http://www.nnc.cdc.gov/travel/diseases/influenza-seasonal-zoonotic-and-pandemic">http://www.nnc.cdc.gov/travel/diseases/influenza-seasonal-zoonotic-and-pandemic</a> (26 October 2016, date last accessed)
World Health Organization	Should be vaccinated	not mentioned	<a href="http://www.who.int/ith/vaccines/seasonal_influenza/en/">http://www.who.int/ith/vaccines/seasonal_influenza/en/</a> (26 October 2016, date last accessed)
Kingdom of Saudi Arabia	Must be vaccinated <sup>a</sup>	Should be vaccinated <sup>a</sup>	<a href="http://www.moh.gov.sa/en/Hajj/Pages/HealthRegulations.aspx">http://www.moh.gov.sa/en/Hajj/Pages/HealthRegulations.aspx</a> (26 October 2016, date last accessed)
Brazil	Refer to WHO guidelines	Refer to WHO guidelines	<a href="http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/leia-mais-o-ministerio/440-secretaria-svs/viajante/viajante-en/9654-brazilians-abroad">http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/leia-mais-o-ministerio/440-secretaria-svs/viajante/viajante-en/9654-brazilians-abroad</a> (26 October 2016, date last accessed)
South Africa	No travel guidelines <sup>b</sup>	No travel guidelines <sup>b</sup>	

<sup>a</sup>Ministry of health of Saudi Arabia have made influenza vaccination compulsory for Hajj and Umrah related visa applications.<sup>b</sup>South African ministry of health recommend a yearly flu vaccine for everyone 6 months of age and older.

people in Hongkong, 6 of whom died,<sup>91–93</sup> 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.<sup>94</sup> 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 severe pneumonia associated with a combined H5N1 and mycoplasma infection.<sup>95</sup> Although the risk of acquiring avian influenza is relatively low, such rare but frequently fatal infections in travellers must be considered during pre-travel advice. A low pathogenic (for poultry) avian influenza H7N9 virus has recently emerged in China and has infected hundreds of humans with a case fatality rate of about 20%.<sup>6,74</sup> H7N9 cases imported by travellers have been reported from numerous countries outside China where poultry-to-human transmission is continuing.<sup>6</sup> So far, human-to-human transmission of these

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

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<sup>6</sup> 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.<sup>96,97</sup> While currently relying on such generic preventive measures, vaccine development efforts for H5N1 and H7N9 viruses are on-going.<sup>81</sup> 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.<sup>3,4</sup> 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 life 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/](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.<sup>98</sup> 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.<sup>65,74</sup>

### 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.<sup>79,99–101</sup> 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 immunocompromised 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.<sup>74</sup> 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, travellers 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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