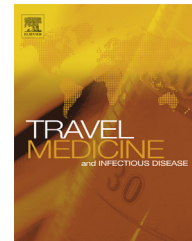




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FIRST LOOK - STUDENT RESEARCH

Chinese travellers visiting friends and relatives – A review of infectious risks



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Summary *Background:* Travellers are potential vectors in the transmission of infectious diseases across international borders. Travellers visiting friends and relatives (VFR) have a particularly high risk of acquiring certain infections during travel. Chinese VFR travellers account for a substantial proportion of all travel in Western countries with high migrant populations.

Methods: A literature review was undertaken regarding major infectious disease risks for VFR travellers visiting China. This included an examination of the previous pandemics arising in China, the likelihood of future outbreaks in China from H5N1 and H7N9 avian influenza viruses, the potential role of travellers in disease transmission, and the special risks for VFR travellers.

Results: China has been the origin of several influenza pandemics in past few decades, and the origin of several emerging infectious diseases with pandemic potential, including SARS. Travel to and from China has the potential for global spread of emergent infectious diseases, as seen in the SARS outbreak in 2003. For VFR travellers, the risk of other infectious diseases may also be greater in China compared to their countries of migration, including hepatitis A and B, dengue fever, typhoid, and other diseases.

Conclusions: VFR travel to China may be associated with increased risk of acquiring a range of infectious diseases, and also poses a potential risk for importation of future pandemics to other countries. Chinese VFR travellers need to be cognisant of these risks and health professionals should consider educational interventions to minimise these risks.

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1. Introduction

In light of the recent outbreak of human H7N9 influenza cases in China [1], concerns of an influenza pandemic have again been heightened. Emerging infections, once they arise, can spread rapidly around the world via international travel, as was the case with Severe Acute Respiratory Syndrome (SARS) [2–4]. Travellers are an important vector in the global spread of infectious diseases, especially during outbreaks. Historically, China has been a major source of emerging infectious diseases of international concern [5]. The easing of government-imposed travel restrictions has resulted in a rapid expansion of international travel to and from China over the last decade. In 2012, outbound Chinese were the largest tourist source nation and China ranked third in the number of inbound tourist arrivals, and is expected to receive the largest number of international arrivals by 2020 [6]. With this high and increasing volume of cross-border movements, the global spread of infectious diseases from China warrants consideration.

Travellers are at risk of acquiring and transmitting infectious diseases, both in the country to which they travel and upon their return. The risk of infectious disease and subsequent importation of disease is greater in travellers visiting friends and relatives (VFR) travellers [7–9]. VFR travellers commonly acquire similar infectious diseases as do other travellers [10], but they may be especially at risk for certain diseases [11]. Whilst there is no standard definition of a VFR traveller, the term most commonly refers to both first and second generation immigrants who are ethnically distinct from the majority population of their country of residence, who return to their country of origin to visit friends and relatives [12,13]. The term generally refers to those travelling from high income to lower income countries [12] where their risk of infectious diseases are greater [7–9]. A range of factors related to higher risk of exposure and lower uptake of preventative health measures contribute to the higher risk in VFR travellers [11]. While there are no data on the travel patterns and travel health practices of Chinese VFR travellers, evidence suggests that the proportion of Asian travellers seeking pre-travel health information is lower than that of Western travellers [14–16].

There is a strong correlation between migration and VFR travel and an increase in global migration, coupled with the affordability of travel for migrants and their children, is contributing to the increase in the proportion of travel for the purpose of visiting friends and relatives [17]. Globally, international travel for the purpose of visiting friends and relatives accounted for a quarter of international tourist arrivals in 2012 [6], particularly originating from Western countries [18,19]. In 2011, 46% of outbound international travel by US residents was to visit friends and relatives [18], whilst the main purpose of travel for 23% of Australian resident departures in 2012 was for the purpose of 'visiting friends and relatives' [19]. Ethnic Chinese are one of the largest cultural groups in many Western countries including Australia [20], Canada [21] and the USA [22] and was the largest source country for migration to Organisation for Economic Co-operation and Development (OECD) countries in 2011 [23]. In Australia, travel to mainland China and

Hong Kong accounts for a significant proportion of all overseas travel. Of resident Australian departures in 2010, 4.7% were to mainland China and 3.0% were to Hong Kong [24], of those 28.9% were for the purpose of visiting friends and relatives [25]. Chinese VFR travellers contribute substantially to the volume of travel to China from Australia and other Western countries.

This review describes recently emerged and travel-associated infectious diseases originating from China and the risk to international travellers, particularly those visiting friends and relatives. Travellers play a pivotal role in the spread of infectious diseases across international borders, and infectious disease risk awareness, preventative practices and behaviour modification are crucial to the comprehensive control of infectious diseases on a global scale. Awareness of emerging infectious disease risks is important for travellers to China and for health professionals providing pre-travel health advice to Chinese VFR travellers.

2. Methods

A literature review was conducted of infectious disease risks in China, and with a focus on [1]: recent outbreaks including the 2003 SARS outbreak and the H5N1 and H7N9 avian influenza outbreaks and [2] diseases identified as highly relevant for Chinese VFR travellers. Only diseases identified as highly relevant for Chinese VFR travellers, either due to a known increased risk for VFR travellers in general [26] or relevance across multiple urban and rural regions of China, were explored. The diseases identified include hepatitis A and B, tuberculosis, malaria and typhoid. Hepatitis A and B and tuberculosis are prevalent across China [27,28], and tuberculosis, malaria and typhoid are all known to disproportionately affect VFR travellers [7].

The Medline database Published literature were retrieved from the Medline database for each included disease using a combination of keywords and MeSH headings, for example, 'SARS' and 'China' or 'Hong Kong'. Articles were assessed using their titles and abstracts and selected for possible inclusion based on their relevance. Articles potentially relevant to travel health, articles discussing the spread of the outbreak, and articles discussing potential future outbreaks in China or Hong Kong were considered for inclusion. All study designs, including review papers, were considered for inclusion. As H7N9 was a new outbreak virus that had only caused outbreaks in China, no restriction of the search to articles on China was applied. Articles published before 31 March 2014 were included. Studies were restricted to English language. References of all relevant articles, including reviews, were checked to identify additional studies.

We also searched the grey literature, including the WHO, CDC and Australian government websites for information on infectious risks of relevance to Chinese VFR travellers. In addition, a general overview of other infectious disease risks present in China, according to the WHO, CDC and Australian government websites, was prepared. To provide a geographical reference for readers unfamiliar with the location of Chinese provinces, maps showing the origins of

the recent SARS and avian influenza outbreaks were prepared. Maps of selected diseases which have a geographically uneven distribution were also prepared from data identified in the literature review indicating affected provinces.

3. Pandemic threats in China

China has been the source of some of the most important pandemics of recent decades, including Severe Acute Respiratory Syndrome (SARS) and numerous influenza pandemics [5]. In addition, H5N1 and H7N9 have recently emerged in China as potential global threats.

3.1. Lessons from SARS

Human cases of SARS originated in Guangdong province, southern China in November 2002. Able to efficiently spread between humans, the SARS virus resulted in a pandemic with significant morbidity and mortality [2]. The SARS coronavirus was of zoonotic origin [29] and Chinese wet markets were likely to have played an important role in the emergence of SARS. A similar virus was isolated in civet cats and racoon dogs in wet markets in Guangdong province during the pandemic [30]. After the initial spread from mainland China to Hong Kong, air travel was central to the global spread of the SARS virus. As with other outbreaks of newly emerged pathogens, infection control measures early in the pandemic were hampered by the lack of knowledge of the virus [31]. As a result, those countries with importations via international travel early in the pandemic, before the virus could be properly identified and proper control measures were in place, observed the highest number of cases outside China, including Canada, Singapore and Vietnam [32,33]. VFR travel also played an important role in the SARS pandemic. The index case of SARS in Canada was a VFR traveller [34]. SARS demonstrated the importance of travellers in national disease control efforts aiming to prevent or delay the introduction of an emerging infectious disease and future pandemic planning. Part of that effort needs to be directed at VFR travellers and their role in spreading emerging infectious diseases across international borders.

3.2. Avian influenza A (H7N9)

The recent human outbreak of avian influenza A subtype H7N9 began in Eastern China in February 2013 (Fig. 1) and as of 27 January 2014, 239 cases including 53 deaths have been reported in multiple provinces throughout China [35]. In January 2014, there was a spike in cases (at least 95 cases in this month compared to 144 cases in the whole of 2013) but associated with a lower death rate [35]. The reason for this is currently unclear. Sustained human-to-human transmission of H7N9 has not been documented [35], but efficient human-to-human transmission through further mutations or reassortment is a possibility [36], with H7 viruses having tendencies towards genetic promiscuity [37]. In addition, H7N9 appears more transmissible to humans than H5N1 [38].

H7N9 has a high case-fatality rate, estimated at 34% based on data up to December 2013 [1]. The majority of known cases and deaths have been in older adults, with a median age of approximately 60 years, with underlying medical conditions [39,40]. However, there have been reports of cases in children, one asymptomatic child in Beijing tested positive for H7N9 [36], and two mildly symptomatic cases in children aged under 5 years [39]. Therefore, it is not yet known if H7N9 is more severe in certain sub-populations, nor the extent of asymptomatic infection in the wider population. Also, whilst most cases have had known animal contact, human to human transmission could not be ruled out in a small number of cases [1]. To date, there have been no known cases involving VFR travellers.

As with all other new zoonotic origin influenza infections associated with a high mortality rate, travellers to China are advised to be particularly vigilant about their personal hygiene, and avoid direct contact with animals in live markets [41]. In October 2013, the Chinese National Influenza Center announced the development of a vaccine for the new virus [42]. However the vaccine is not currently available for travellers.

3.3. Other avian influenza A subtypes

The recent emergence of the H5N1, H7N2, H7N3, H7N7, H7N9, H10N7, H10N8, H6N1 and H9N2 subtypes of avian-origin influenza viruses as human pathogens are of international concern [30,43]. Importantly, two of the four influenza pandemics of the past century originated in China, and three of the four newly emerged subtypes also originated in China.

Of the avian influenza viruses that have recently infected humans, the highly pathogenic avian influenza virus H5N1 subtype (HPAI H5N1) has caused the most concern, due to multiple outbreaks in humans around the world, and a high mortality rate. In 2003–2013, globally there have been 648 cases, including 45 from China, and 384 deaths, including 30 from China [44]. HPAI H5N1 has caused outbreaks in multiple provinces of China [45,46]. However, there have been no known cases involving Chinese VFR travellers. The crude mortality rate is around 60%, with the highest mortality rate, of greater than 70% in cases aged 10–39 years [47]. The HPAI H5N1 virus appears to have originated from Southern China (Fig. 1) [45]. Since 1999, HPAI H5N1 has been consistently isolated from animals in southern China, and is now considered endemic in poultry [48]. This virus is not capable of human-to-human spread presently except in limited cases [30]. Concerns remain that further genetic reassortment with human viruses, for example occurring in a pig, could lead to direct human to human transmission capabilities and global spread with significant global morbidity and mortality, as well as substantial economic impact [30,49].

There are a few important differences between H5N1 and H7N9 epidemiology. Whilst H7N9 has caused a much higher incidence of infections compared with H5N1 using the same timeframe, H7N9 cases tend to be in geographically contiguous areas, whilst H5N1 cases have spread globally in a way consistent with wild bird migration and poultry trade patterns [50]. Whilst H5N1 is more often



Fig. 1 Likely origins of the H5N1, SARS and H7N9 viruses [2,35,45].

acquired via close and high-risk contact with birds, H7N9 appears to be often acquired via only incidental contact [50]. For unknown reasons, whilst H7N9 avian influenza has mainly affected older individuals, especially those over 60 years of age [39,40,43], H5N1 avian influenza has more often affected younger individuals [43,51], especially those under 18 years of age [52]. Therefore, VFR travellers at the extremes of age should be especially cautious in the event of avian influenza outbreaks.

There have also been reported cases of human infection with avian influenza type H9N2 in Hong Kong, and H9-like illness in Guangdong province, but none have been fatal [53]. In addition, there have been reports of H10N8 infections in China recently [54]. Since so many different avian influenza subtypes have been able to infect humans directly, it must now be assumed that all subtypes of influenza viruses, including H1-15 and N1-9, have the potential to become the new pandemic strain [49]. This new view of pandemic influenza means that there is now a much larger pool of precursor influenza viruses that may trigger a pandemic and the threat of avian influenza outbreaks in humans is ever-present. Awareness of the risk of highly pathogenic influenza should be raised amongst VFR travellers to China and agencies and professionals dealing with such travellers. Health professionals who may treat returned Chinese VFR travellers should also be well informed regarding the latest outbreaks, so that prompt diagnosis may be made in returning travellers.

3.4. Why is China the origin of so many pandemics?

The SARS, H5N1 and H7N9 pandemics have all originated in South-eastern China (see Fig. 1). It has been hypothesized that Southern China is an epicentre for the emergence of

new, pandemic causing viruses [5,55,56]. There are various reasons for this, including farming practices, close proximity of humans and livestock, and food preferences in Chinese culture [5]. Practices potentially encouraging the development and spread of new strains of influenza and other viruses include duck farming on flooded rice fields close to human housing, live poultry markets and wet markets, and the sale and consumption of exotic meats including snakes and civet cats, all potential sources of a range of zoonotic pathogens [5]. These are all long-held cultural practices, deeply embedded in Chinese history and culture [5]. Various provincial and local governments in China have attempted to make changes to these practices, such as requiring enhanced disinfection and regular closure of wet markets to mitigate risks [57,58]. Whilst these measures may be somewhat effective [57], they may not significantly reduce the risks. For example, the Hong Kong government has ordered that certain animals including ducks, quail and geese be excluded from wet markets, and that all markets be simultaneously emptied and cleaned twice a month. However, even this has not been effective in keeping H5N1 out of wet markets [58]. Radical changes like permanently closing all wet markets are not generally considered a practical option. Banning the sale of live poultry, as practiced in Beijing, may not be effective, as illegal live poultry trade has continued [59]. As these measures have been implemented regionally rather than nationally, their effectiveness may also be further limited. With the continued potential source of zoonotic pathogens remaining, Southern China will continue to be a source for the emergence of epidemics in humans. Outbreak awareness, and awareness of respiratory infection control procedures in the event of a new outbreak arising during

travel, should therefore be important components of pre-travel advice and education for Chinese VFR travellers.

3.5. Wet markets - a special risk for VFR travellers

Chinese wet markets have received particular attention regarding their potential role in the emergence of infectious diseases of pandemic potential [49]. Wet markets, where live poultry and other animals are slaughtered and sold to the public, are visited daily by large numbers of people and are common across China. Wet markets provide an ideal environment for the emergence of new pathogens. Numerous species of live and slaughtered animals are kept in close proximity to each other and to humans, promoting genetic reassortment and recombination between pathogens originating from different species and are easily transmitted to humans, who are also present in great numbers at the markets [60]. Frequenting live poultry markets is not likely a common activity for travellers to China for the purpose of holiday or business. However, VFR travellers are more likely to have close contact with the local population, use local facilities and eat local food [17], compared to other travellers. It can be expected that many Chinese VFR travellers will visit wet markets during their return visit.

Live poultry markets were the likely source of the 1997 Hong Kong H5N1 outbreak [49]. More recently, H5N1 viruses were isolated from live poultry markets associated with cases of human infection in Beijing and in the provinces of Guizhou, Hunan, and Xinjiang, suggesting a continuing link between live poultry markets and cases of human infection [61]. Also, during the SARS epidemic, the SARS coronavirus was isolated from caged animals in wet markets in Guangdong province, southern China [60]. Chinese wet markets are important not only for the transmission of newly emerged pathogens, many other important infectious diseases, including bacterial and parasitic infections, can be acquired either when visiting the market, or during food preparation or consumption [60]. Whilst there have been no reported cases of infection via wet markets associated with VFR travel, the visiting of wet markets should be considered a potential risk factor for various infections in Chinese VFR travellers.

4. Other important infectious risks in China

China is a middle income country with many infectious disease risks that are uncommon in high income countries. While the risk to travellers of acquiring vaccine preventable diseases in China's major cities is relatively low [28], the incidence of common vaccine preventable diseases, for example measles [62], are substantially higher than in most high income countries. Therefore ensuring routine vaccinations are up to date is an important consideration for travellers to China. Importantly, VFR travellers may have different travel patterns to other tourists, placing them at higher risk of acquiring certain infectious diseases than those travelling for other purposes [11,17]. China is a vast country, with a diversity of infectious diseases risks across different regions [28]. VFR travellers are more likely to travel to rural or remote regions [11], and may require a

pre-travel preparation program (including vaccinations) designed specifically with their destination in mind.

4.1. Viral hepatitis

Both hepatitis A and B are considered highly endemic in China [28]. In China, 9.8% of the population are carriers of the hepatitis B virus, and 3.2% of the population are carriers of the hepatitis C virus [63]. This high prevalence has particular implications for travellers who may seek healthcare in China, either due to medical emergencies or planned medical tourism, including dentistry. There is a higher risk of exposure to unsafe blood and blood products in regional areas, which may pose a risk of hepatitis B, C and E as well as other blood-borne viruses [64]. As hepatitis A is transmitted via the faecal-oral route, VFR travellers who are more likely than tourist travellers to consume the local food are at increased risk of hepatitis A, as seen with VFR travellers originating from other intermediate and high risk countries [65]. The incidence of hepatitis E is highest in East and South East Asia, with the estimated seroprevalence of 23% in China [66]. A hepatitis E vaccine is manufactured in China but not currently available outside China [67].

4.2. Tuberculosis

China is considered a moderate incidence country for tuberculosis, with a high burden of multidrug resistant cases [27]. Whilst the risk to tourist and business travellers is generally low [27], the risk of acquiring tuberculosis has been shown to be greater for VFR travellers in general [7]. Tuberculosis requires prolonged contact for transmission [68], it is especially relevant to VFR travellers, who often have prolonged contact with the local population and longer lengths of stay than tourist travellers [69]. Whilst VFR travellers may acquire tuberculosis during their travels, if such travellers present with tuberculosis it may also be due to disease already acquired at the time of immigration, and reactivated after immigration [10,69].

4.3. Malaria

Malaria is considered endemic in the rural parts of Hainan, Henan, Yunnan, Fujian, Guangdong, Guangxi, Guizhou, Sichuan, Tibet (Zanbo Valley), Anhui, Hubei, Hunan, Jiangsu and Jiangxi provinces (see Fig. 2), but is not present in urban areas of China [70]. A 2012 study in five provinces affected by malaria in central China found that the incidence rate for each province was 0.05 per 100,000 or less [71]. The malaria species found in China is primarily *Plasmodium vivax*, with *P. falciparum* common in select locations [72] with evidence of resistance to chloroquine and mefloquine [72]. There are no known reports of malaria in VFR travellers returning from China, and GeoSentinel Surveillance data between 1998 to November 2007 report no cases of malaria amongst travellers to China [73]. Despite this, the risk remains and chemoprophylaxis should be used by travellers to malarious areas in Hainan, Yunnan, Anhui, Guizhou, Henan, and Hubei provinces, with recommended regimens reflecting known drug resistance. Mosquito



Fig. 2 Provinces where malaria has been reported [70]. Note that only certain rural areas are affected in each province.

avoidance measures alone are recommended for travellers to all other malarious areas [72].

4.4. Dengue fever

Dengue fever is found in Guangdong, Hainan, Guangxi, Fujian, Zhejiang, and Yunnan provinces in China (see Fig. 3)

[74]. As the vector is also present in other provinces, there is the potential for further spread [75]. In the past three decades, there have been more than 650,000 reported cases nationwide, with at least 610 deaths [74]. Dengue outbreaks now occur frequently in southern China, often as a result of the virus being introduced by travellers returning from Southeast Asia where dengue is endemic [75]. As there



Fig. 3 The provinces where dengue fever has been reported [74].



Fig. 4 The four provinces where most typhoid cases occur [76].

is no vaccine, prevention is by mosquito avoidance and vector management [75].

4.5. Enteric fever (typhoid and paratyphoid)

Enteric fever is endemic in China, but improvement in sanitation has been associated with a sharp decline in incidence [76]. In 2004, there were 3.9 cases of enteric fever (typhoid and paratyphoid) per 100,000 people nationally, with more than half of total reported cases in Guangxi, Guizhou, Yunnan and Zhejiang provinces (See Fig. 4) [76]. China is considered a medium incidence country for typhoid [77,78]. Typhoid fever is a risk in areas where hygiene is poor in China [28] and the typhoid vaccination is recommended for most travellers to China, and is especially recommended for VFR travellers [27].

4.6. Other infections

Several other infectious diseases may also pose an increased risk to certain VFR travellers. Japanese Encephalitis is a risk for those travelling to certain rural areas [28]. Rabies is a risk for those involved in outdoor activities in rural areas [28]. Rabies most commonly occurs in southern China, with an increase in the incidence of rabies in China in recent years [79]. Hand, foot and mouth disease is common in parts of China and sporadic outbreaks occur [64]. Poliomyelitis is considered eradicated in most of China [28]. However, an outbreak in Xinjiang province in 2011 [64] highlights the remaining risk of re-introduction to remote and rural parts of China.

In addition, some diseases are found only in certain regions of China (Table 1). Tick-borne encephalitis is found in

the north-eastern forests of China. Schistosomiasis is found in focal areas especially in the Yangtze River basin, and Leptospirosis is found mainly in tropical areas. Chikungunya, leishmaniasis, filariasis and plague are found in certain regions of China [70]. While these regions are not common destinations for tourist travellers, VFR travellers are more likely than other travellers to visit rural and remote areas where disease risk is higher. Strongyloidiasis, an intestinal

Table 1 Potential infectious disease risks for travellers to China [28,64,70].

Relevant for all travellers

Influenza (including Avian influenza)
Measles
Hepatitis A and B
Tuberculosis

Relevant for travellers visiting certain regions only

Japanese encephalitis
Hand, foot and mouth disease
Typhoid
Rabies
Malaria
Tick-borne encephalitis
Schistosomiasis
Leptospirosis
Dengue Fever
Chikungunya
Leishmaniasis
Filariasis
Plague

parasitic infection spread mainly by larvae penetrating the skin and mucous membranes, is also an emerging problem in China, with rising incidence rates [80]. Immunocompromised patients are most often affected [81]. Infection can be prevented by not walking barefoot and washing fruit and vegetables thoroughly [80].

4.7. Vaccination recommendations

In addition to the routine vaccines recommended in developed countries, including MMR and DTP, travellers to China should also consider hepatitis A vaccination, as it is highly endemic in China. In addition, typhoid vaccination should be considered for those travelling outside major cities, inactivated poliovirus vaccine is recommended for those who will visit Xinjiang province, and Japanese encephalitis vaccination should be considered for those staying in rural areas for extended periods during June to September [28]. The CDC also recommends hepatitis B vaccination for all travellers, and rabies vaccination for those who are planning outdoor activities especially in rural areas [70] and for those who will have contact with bats in Hong Kong [82].

5. Conclusion

Travel to and from China including VFR travel amongst migrant ethnic Chinese populations in countries outside of China, is of considerable volume [18,19]. Moreover, China has been the source of many global epidemics, as the world was reminded recently with the H7N9 outbreak. Research on Chinese VFR travellers and their travel behaviours and infectious disease risk perceptions is lacking. There have been no studies on travel patterns and traveller behaviour in this population. A greater understanding of Chinese VFR traveller risk perceptions and behaviours are required to inform the control of travel-associated infectious diseases. Travellers play a significant role in the spread of infectious diseases across international borders and responsible travel through preventative practices and behaviour modification is crucial to the comprehensive control of infectious diseases on a global scale. Research can inform preventive strategies to effectively target Chinese VFR travellers to address their infectious disease risks, reduce the risk of pandemics and the spread of diseases, and improve their travel health outcomes.

Conflicts of interest

TEM has no conflict of interest to declare. AEH has received funding to conduct investigator-driven research from GSK and Sanofi Pasteur. CRM receives funding from vaccine manufacturers GSK and CSL Biotherapies for investigator-driven research.

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