
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

# CHAPTER 3

# Emerging Infectious Diseases and the International Traveler

Camilla Rothe and Elaine C. Jong

In 1992 a landmark report by the Institute of Medicine titled "Emerging Infections: Microbial Threats to Health in the United States" highlighted the importance of the often underappreciated concept of emerging infectious diseases (EIDs). This report brought EIDs back into scientific discourse; however, the awareness that diseases emerge and periodically reemerge goes back millenia, as Morens and colleagues (2008) highlight in their historical review.

The term "emerging infectious diseases" is broad. It covers newly recognized human diseases caused by pathogens that have recently jumped species as well as older pathogens that have emerged in new populations due to changes in human behavior or modifications to natural habitats. It also encompasses older pathogens that are reemerging in areas once brought under control, often due to microbiological adaptation or breakdown of public health measures. An overview of recent travel-related EIDs in the 21st century is given in **Table 3.1**.

According to a recent comprehensive literature review by Taylor et al. (2001), more than 1400 species of infectious organisms known to be pathogenic to humans were identified. Around 175 pathogenic species were associated with diseases considered to be emerging, and of these, 75% were zoonotic. Causal factors contributing to the emergence of new pathogens include human population growth resulting in human encroachment on wildlife habitats, increased human contact with domestic and wild animals, changes in agricultural practices, and globalization of food markets.

Travelers are an important factor in the global dissemination of EIDs due to the increased frequency and speed of both local and international travel. International travelers may have been in direct or indirect contact with previously isolated, remote populations and ecosystems. The challenge is that travelers returning home may harbor exotic infections that are still in the incubation stage. During the acute stage of illness, nonspecific flu-like clinical signs and symptoms may not suggest the correct diagnosis to local healthcare providers. Thus, infections acquired during travel may be transmitted to others in the community by returned travelers before the diagnosis can be made. In addition to international travelers, imported animals, birds, foods, and insects from abroad, especially from tropical developing countries, can also pose a significant threat to the public health of receiving countries by serving as means of transportation for pathogens into new geographic areas.

## APPROACH TO INTERNATIONAL TRAVELERS

The burden of detection of imported infectious diseases among returning travelers is most likely to fall on primary healthcare providers who initially see the ill traveler, and the public health officials to whom they report. In the 21st century, all persons presenting for diagnosis and treatment of an acute illness should be asked, "Where have you traveled?" as part of

**TABLE 3.1 Examples of Travel-Associated Emerging and Reemerging Infections in the 21st Century**

| Year | Travel-Related Emerging Diseases in the 21st Century |
|---|---|
| 2003 | Global outbreak of severe acute respiratory syndrome (SARS) caused by a novel coronavirus. SARS was spread by travelers to 30 countries on five continents. |
| 2005-2007 | Reemergence of chikungunya fever leads to a large outbreak, affecting the islands in the Indian Ocean and large parts of South and Southeast Asia (1). The spread is facilitated by adaptation of the chikungunya virus (CHIKV) to a new vector, *Aedes albopictus*. Imported cases in Italy and France prompt autochthonous infections in both countries (2). CHIKV infections are confirmed in travelers returning to Europe, Australia, the United Kingdom, and the United States. |
| 2008 | First outbreak of Lujo hemorrhagic fever. The novel arenavirus is named after the origin of the index patient, a travel agent from Lusaka who was airlifted to Johannesburg for treatment, causing several further cases through nosocomial spread. |
| 2009-2010 | "Swine flu pandemic" caused by influenza A (H1N1). A virulent variant of H1N1 had also caused the Spanish flu in 1918-1919, killing tens of millions of people worldwide. |
| 2011-2012 | Outbreak of acute muscular sarcocystosis among international travelers returning from Tioman Island, Malaysia (3). |
| 2012-2013 | First recorded outbreak of Middle Eastern respiratory syndrome caused by a novel coronavirus (MERS-CoV). |
| 2012-2014 | Outbreak of schistosomiasis in German and Canadian travelers returning from Corsica (France). |
| 2013-2015 | First recorded chikungunya outbreak in the Western hemisphere starts from the Caribbean Islands, spreading to the United States, Latin America, and French Polynesia. |
| 2013-2014 | Zika virus outbreaks in the Western Pacific and Southeast Asia lead to a number of imported infections in international travelers. |
| 2014 | Fatal case of influenza (H5N1) in a Canadian traveler returning from China. |
| 2014 | Chikungunya virus imported by a traveler from Cameroon into France leads to 14 autochthonous cases (4). |
| 2014-2015 | Large Ebola Zaire outbreak in Guinea, Liberia, and Sierra Leone. A Liberian traveler visiting friends and relatives imports Ebola into the United States, causing two consecutive cases among healthcare workers. |
| 2015 | First case of influenza A (H7N9) outside China found in a Chinese traveler to Malaysia. |
| 2015 | Zika virus cases documented in South America for the first time. |

Sources

1. Burt, F.J., Rolph, M.S., Rulli, N.E., Mahalingam, S., Heise, M.T., 2012. Chikungunya: a re-emerging virus. Lancet 379 (9816), 662–671.
2. Tomasello, D., Schlagenhauf, P., 2013. Chikungunya and dengue autochthonous cases in Europe, 2007-2012. Travel Med. Infect. Dis. 11 (5), 274–284.
3. Esposito, D.H., Stich, A., Epelboin, L., Malvy, D., Han, P.V., Bottieau, E., et al., 2014. Acute muscular sarcocystosis: an international investigation among ill travelers returning from Tioman Island, Malaysia, 2011–2012. Clin. Infect. Dis. 59 (10), 1401–1410.
4. Delisle, E., Rousseau, C., Broche, B., Leparc-Goffart, I., L'Ambert, G., Cochet, A., et al. 2015. Chikungunya outbreak in Montpellier, France, September to October 2014. Euro. Surveill. 20 (17), pii:21108.

the routine medical history, since so many individuals in our global society have traveled to or may have originated in tropical developing areas.

The travel history should be as specific as possible in terms of the cities and areas of each country visited. Activities and exposures, such as swimming in freshwater lakes or rivers, walking barefoot on beaches or muddy trails, receiving many insect bites, eating raw or exotic foods, drinking unsafe water or beverages with ice cubes in countries with low sanitation, and close/intimate contact with new partners should also be subject to inquiry. Since most of the EIDs are specifically discussed in other chapters of this book, the purpose of this chapter is to provide a conceptual framework for their consideration and recognition.

## EMERGING AND REEMERGING ZOONOSES

Many factors are responsible for emergence of infectious pathogens that originate in wild animals. These include travel into previously uninhabited areas, changes in land use and demographic patterns with disruption of stable ecosystems, greater contact with previously isolated animal populations, changing agricultural practices that allow transfer of pathogens between wild and domestic animals, and food customs that involve hunting, butchering, and ingesting wild game including nonhuman primates (bush meat).

Two transmission patterns have been described for transmission of pathogens from wild animals to humans. One pattern consists of rare events when direct animal-to-human transmission of an animal pathogen occurs, but then direct human-to-human transmission maintains the infection in the human population for a limited time or permanently. Examples of diseases with this transmission pattern are human immunodeficiency virus (HIV), influenza A, Ebola virus, and severe acute respiratory syndrome (SARS).

The second pattern of transmission is where human infections with animal pathogens result from repeated episodes of direct animal-to-human transmission or repeated vector-mediated animal-to-human transmission, and the infections are not usually propagated by human-to-human transmission. Examples of diseases with this transmission pattern are rabies and other lyssa viruses, Nipah virus, West Nile virus, Hantavirus, Lyme borreliosis, tularemia, leptospirosis, and ehrlichiosis.

## VECTOR-BORNE DISEASES

Many emerging infections are vector-borne diseases. When competent vectors such as mosquitoes, ticks, and fleas preexist in a geographic environment, movement of infected human or animal hosts into that area can lead to rapid expansion of transmission.

### West Nile Virus

A prime example of an emerging vector-borne disease was the spread of West Nile virus in North America, transmitted from birds to humans and horses by *Culex* mosquito vectors. Following the initial 1999 detection of the agent in Queens, New York, the new pathogen (thought to have been introduced by an infected human traveler or migrant bird) spread rapidly across the continental United States from coast-to-coast within 5 years—affecting human activities, veterinary practices, and blood-banking guidelines in the wake of its spread (**Fig. 3.1**).

### Chikungunya Virus

One of the most important emerging vector-borne viruses in the recent years has been chikungunya virus (CHIKV). The alphavirus is transmitted to humans by the bite of infected daytime-biting *Aedes* mosquitos, mainly *Aedes aegypti* and, since more recently, *Ae. albopictus*. The disease has been reported among travelers returning from endemic areas as a cause of acute illness characterized by sudden onset of fever, chills, severe joint pain with or without swelling, lower back pain, and a maculopapular rash, similar to the symptoms of dengue fever. In some CHIKV patients, residual joint pain and impairment persists for months and even years after the acute illness, leading to considerable morbidity.

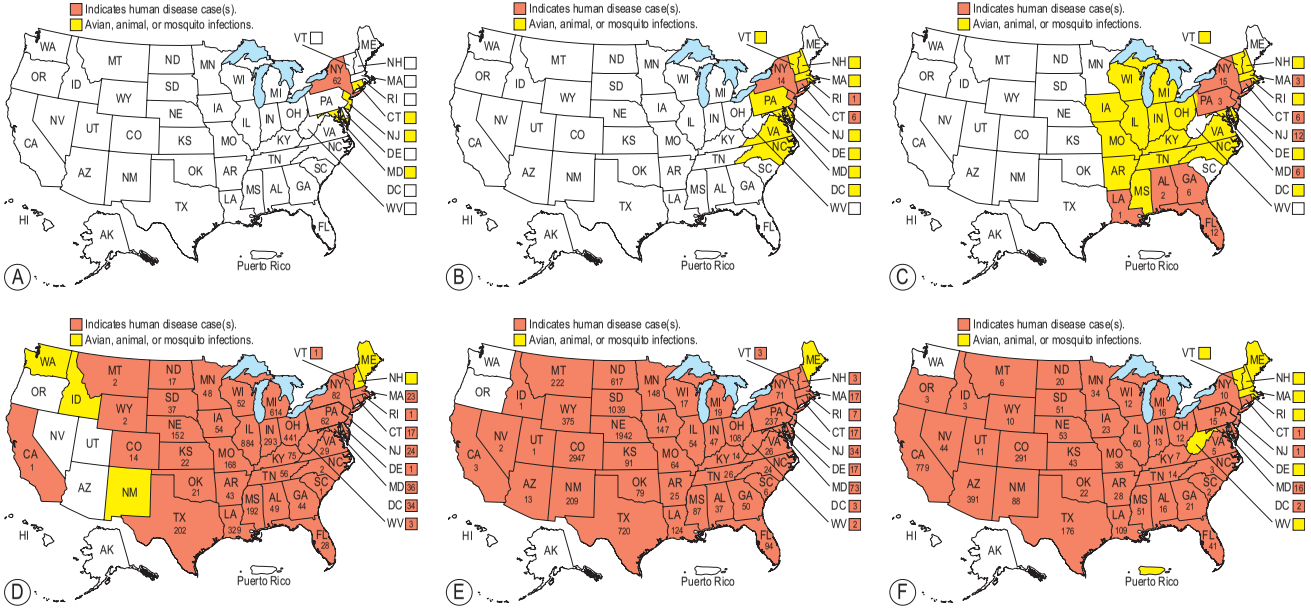


**Fig. 3.1** **Spread of West Nile Virus transmission in the United States, 1999-2005. (A) 1999, (B) 2000, (C) 2001, (D) 2002, (E) 2003, (F) 2004.** (Source: CDC Division of Vector-Borne Infectious Diseases. Online. Available at http://www.cdc.gov/ncidod/dvbid/westnile/mapactivity/surv&control.htm#maps. Accessed 03/24/2008.)

As reviewed by Weaver et al. (2015) a large outbreak of chikungunya emerged in 2004 in coastal Kenya; in 2005 it spread to the Indian Ocean islands and subsequently to India and many countries in Southeast Asia, causing several million cases. In 2007 cases of chikungunya were first reported from Europe: infected air travelers imported the disease into France and Italy, which led to local autochthonous transmission. It turned out that the virus had adapted to a new vector, *Aedes albopictus*, facilitating viral spread to an even wider geographic region. Further factors contributing to the magnitude of the outbreak were an increase in air travel to and from affected areas, previous lack of exposure to the virus of the newly involved populations, and spread of *Ae. albopictus* from its native Asia to islands of the Indian Ocean basin and to Southern Europe. In 2013 a further large outbreak originated on the Caribbean island of St. Martin. It rapidly spread through the Caribbean, to the United States, to Latin America, and to French Polynesia, causing several million cases. This was the first time a chikungunya outbreak had officially been recorded in the Western hemisphere.

### Zika Virus

Another emerging virus transmitted by *Aedes* spp. is Zika virus (ZIKV). Zika is a flavivirus that causes a clinical picture indistinguishable from chikungunya or dengue. Even though it usually causes a mild illness, the development of subsequent Guillain Barré syndrome has been reported in a number of cases. Zika was known to be endemic in Africa and Southeast Asia. In 2007, an outbreak of Zika virus infection occured on Yap island (Micronesia). These were the first recognized cases outside Africa and Asia. The emergence of ZIKV on the isolated island community showed the potential of the virus to spread through commerce and travel across long distances. An even larger outbreak occurred in 2013-2014 in French Polynesia, causing an estimated 32,000 cases and spreading within the region. In the context of this outbreak, cases related to international travel were reported by Zammarchi et al. (2015) in two Japanese, one Norwegian, and two Italian travelers. A number of further travel-related cases of Zika virus were reported. Interestingly, one scientist returning to the United States from Cameroon with ZIKV later infected his wife, probably by sexual transmission, as discussed by Foy et al. (2011). In 2015, Zika was first detected in Brazil, leading to autochthonous transmission of the virus.

### Dengue Virus

Dengue fever virus is the most common arbovirus infection among international travelers to endemic regions (Chapter 21). Its incidence has increased 30-fold in the past 50 years due to international trade and travel as well as failing public health measures. Dengue is also on the rise in formerly non-endemic areas such as Europe and East Asia as a consequence of increasing migration, the tourist industry, international trade, and demographic changes. Quam et al. (2015) show an increasing trend of imported dengue into Italy and project a further fourfold increase by 2020. Recent dengue fever virus outbreaks as reported by Knope et al. (2013) in Australia, China, Japan, France, and Italy were linked to importation of the virus in infected travelers and the presence of *Aedes* mosquitoes in the local environment, which promoted subsequent human-to-human spread in the local populations.

### *P. knowlesi* Malaria

A growing number of travelers from industrialized countries are visiting malaria-endemic areas annually. Nevertheless, the number of malaria cases recorded in international travelers is decreasing. Emerging, however, is the number of cases of *Plasmodium knowlesi* malaria seen in travelers. *P. knowlesi* was first described in the 1920s as a simian malaria parasite, and it was not known to infect humans until the 1960s when it was found in malaria patients in Malaysia. This led to its recognition as the fifth human malaria parasite. In 2006 it first appeared in the context of travel medicine when a Swedish traveler returning from Malaysia was diagnosed with *P. knowlesi* infection. Muller et al. (2014) in their review highlight several reports of imported *P. knowlesi* cases in travelers from all over the world. *P. knowlesi* is not geographically restricted to Malaysia but was also found in Vietnam,

Singapore, Thailand, Cambodia, and the Philippines and may well occur in jungle or forest areas in other countries of the region. On microscopy *P. knowlesi* closely resembles *Plasmodium malariae*. It is therefore not completely clear if the parasite is truly emerging or has rather been misclassified in the past. Travel in or near forested areas is considered a risk factor. Cases are mostly mild, but severe and fatal cases have been reported (Chapter 20).

### Artemisinin-Resistant *P. falciparum* Malaria

Emergence of artemisinin resistance among *Plasmodium falciparum* strains has been reported from the Thai-Cambodian border. Few published cases so far document artemisinin-resistant *P. falciparum* malaria in returning travelers, although, interestingly, some are found in travelers returning from Sub-Saharan Africa and not from the known high-risk areas in Southeast Asia, as Van Hong et al. (2014) report.

### Lyme Borreliosis

Increased case numbers of Lyme borreliosis (*Borreliaburgdorferi*) in North America have been reported over the past decade. Causal factors include increasing populations of humans as well as animal reservoirs (white-footed mice, white-tailed deer, *Ixodes* ticks) and mutual encroachment on traditional habitats. These have resulted in expanded opportunities for tick-borne transmission of Lyme borreliosis in suburban areas close to human dwellings as well as in the recognized transmission risk areas of grasslands and shrubs at the edge of forests (Chapter 24).

## AIR-BORNE DISEASES

Pathogens that are transmitted directly or indirectly through aerosolized droplets have huge potential for rapid global spread. Disease transmission of air-borne pathogens may occur whenever a susceptible person is in close proximity to an infectious person, and wherever large groups of people are crowded together. Additionally, direct inoculation from contaminated fingers to mucosal surfaces of the mouth, nose, and eyes is probably as significant as droplet inhalation in transmission of respiratory viruses. Personal hygiene measures including frequent hand cleansing and respiratory etiquette can help prevent the spread of infections. Continued public health guidance and a legislative framework for implementation of mandatory screening, isolation, and quarantine of travelers meeting infectious case definitions are necessary to prevent transmission and prevent outbreaks.

### SARS-CoV

Severe acute respiratory syndrome coronavirus (SARS-CoV), spread by travelers to 30 countries on five continents in 2003, was termed by Heymann et al. (2013) the "first pandemic of the 21st century." The SARS pandemic illustrated the pivotal role of international travelers in the rapid global spread of an air-borne EID and showed the challenges of detecting and detaining infectious individuals. Al-Tawfiq et al. (2014) point out that in addition to significant morbidity and mortality, the SARS pandemic resulted in economic costs of an estimated 100 billion USD.

### MERS-CoV

In 2012 another novel virus closely related to SARS was discovered in the Kingdom of Saudi Arabia (KSA) named Middle Eastern respiratory syndrome coronavirus (MERS-CoV).

Great concern arose since the KSA hosts two of the largest mass gatherings worldwide every year, namely the Hajj and Umrah pilgrimages. So far no case of MERS-CoV could be linked to one of these events. However, MERS-CoV was detected in travelers from the Saudi Arabian peninsula to more than a dozen countries in Northern Africa, Europe, Asia, and North America. MERS-CoV is a zoonotic virus and infection primarily occurs through contact with camel or camel products. Embarek et al. (2015) point out that the risk of human-to-human spread is considered low outside healthcare settings, and so far no sustained onward transmission to persons in contact with infected travelers on aircraft has been reported.

Other examples of pathogens in this group are influenza A, including avian influenza (H5N1 and H7N9), measles, and tuberculosis.

## FOOD- AND WATER-BORNE DISEASES

Changes in animal production systems and in the food production chain are thought to be among the main factors causing emergence of food-borne zoonoses. The most important food-borne zoonotic pathogens include *Salmonella* spp., *Campylobacter* spp., enterohemorrhagic *Escherichia coli*, *Giardia lamblia*, and *Cryptosporidium parvum*. Whether these pathogens are just common or truly "emerging" in travelers is difficult to assess, since most data from travel-related surveillance networks lack a clear denominator.

New pathogens of fecal origin can lead to water-borne outbreaks when water supplies are contaminated through wildlife or domestic animal feces. If contaminated water supplies are used for agricultural production, transmission of pathogens of zoonotic origin can occur through human ingestion of contaminated fruits and vegetables.

### Sarcocystosis

One recent example of an emerging zoonotic food- or water-borne disease is sarcocystosis, caused by an intracellular coccidian parasite of the genus *Sarcocystis*. A large outbreak of acute muscular sarcocystosis occurred in 2011-2012 among tourists on Tioman Island (Malaysia). The travelers who presented with fever and severe myalgias were found to have marked eosinophilia and raised creatine kinase levels. The muscle biopsy from six of the patients was histologically diagnostic for acute muscular sarcocystosis, and DNA of the snake-associated parasite *Sarcocystis nesbitii* could be isolated in one case. Two international travel surveillance programs, GeoSentinel and TropNet, contributed greatly to the investigation of the outbreak, alerting their network members and thereby facilitating the identification of further cases of this otherwise rarely reported zoonotic disease.

Acute muscular sarcocystosis is usually caused by ingestion of sporocyst-containing food or water contaminated with feces from infected carnivorous final hosts (e.g., cats, snakes, humans). The source of infection in the case of the Tioman Island outbreak remained unclear; however, almost all travelers reported potential exposure to untreated water. Another series of cases was suspected in travelers returning to Germany from the same island, as Tappe et al. (2014) report.

Prevention of food-borne and water-borne diseases involves personal precautions and further development and implementation of food safety programs. Individual travelers can reduce their personal risk of exposure by selection of safe foods and beverages (see Chapter 8). Nations can improve the safety of their food and water supplies by adopting integrated approaches to food safety and designating a responsible authority to assure compliance. The Food and Agriculture Organization (FAO)/World Health Organization (WHO) have recently established a new framework of microbiologic risk assessment to guide efforts of member countries in reducing pathogen contamination at relevant points in food production chains.

## OTHER

### *S. haematobium* Urinary Schistosomiasis

An outbreak of urinary schistosomiasis was reported in 2013-2014 from a non-endemic area in Corsica (France) affecting several German, French, and Canadian travelers. The parasite, *Schistosoma haematobium*, had presumably been introduced from the African continent by a traveler or migrant (Chapter 48). The species of water snail required to maintain the infection cycle was later found in the Cavu river, where the affected travelers had bathed, as highlighted in a case series from Gautret et al. (2015).

### Ebola Virus

See Chapter 28, "Viral Hemorrhagic Fever."

**TABLE 3.2 Important Sources in Emerging Travel-Related Diseases: Emerging Diseases, Outbreaks, and Surveillance News**

| Source | URL |
|---|---|
| CDC Health Alert Network | http://www2a.cdc.gov/HAN/ArchiveSys/ |
| CDC MMWR Weekly Surveillance and Summaries | http://www.cdc.gov/mmwr |
| European Centre for Disease Prevention and Control (ECDC) | http://www.ecdc.europa.eu/en/Pages/home.aspx |
| Eurosurveillance | http://www.eurosurveillance.org/ |
| GeoSentinel Surveillance Network | http://www.geosentinel.org |
| HealthMap | http://www.healthmap.org |
| ProMed Mail | http://www.promed.org |
| UK Health Protection Report | http://www.hpa.org.uk/hpr/ |
| WHO Global Response and Alert | http://www.who.int/csr/en |
| WHO Global Response and Alert Outbreak News | http://www.who.int/csr/don/en/ |
| WHO Weekly Epidemiological Record | http://www.who.int/wer/ |

## INFORMATION RESOURCES FOR EMERGING INFECTIOUS DISEASES

Numerous EIDs, some of which constitute potential risks to international travelers, are discussed in the journal *Emerging Infectious Diseases*, published by the Centers for Disease Control and Prevention (CDC) in the United States. Several hundred emerging infections have been mentioned in the Federation of American Scientists' Program for Monitoring Emerging Diseases (ProMED), which is a simple bulletin board system that contains the most up-to-date reports of disease outbreaks. Bulletins are sent out via electronic mail, and free subscriptions are available by registering your e-mail address at the website (see **Table 3.2** for these and further sources).

The world is dynamic, and what happens in one area can rapidly affect other areas at great distances. This has enormous implications for travel medicine, since a disease that is endemic in one area can rapidly become epidemic in another area through the movements of global travelers. Those providing pre-travel counseling and post-travel treatment need to be aware of potential hazards and outbreaks in regions in which the traveler will be visiting, or from which the traveler is returning.

## REFERENCES AND FURTHER READING

Al-Tawfiq, J.A., Zumla, A., Memish, Z.A., 2014. Travel implications of emerging coronaviruses: SARS and MERS-CoV. Travel Med. Infect. Dis. 12 (5), 422–428.

Embarek, P.K.B., Van Kerhove, M.D., 2015. Middle East Respiratory Syndrome Coronavirus (MERS-CoV): Current Situation 3 Years after the Virus Was First Identified. World Health Organization (WHO), Geneva. May 15, 2015.

Foy, B.D., Kobylinski, K.C., Chilson Foy, J.L., et al., 2011. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg. Infect. Dis. 17 (5), 880–882.

Gautret, P., Mockenhaupt, F.P., von Sonnenburg, F., et al., 2015. Schistosomiasis ex Corsica: local and global implications. Emerg. Infect. Dis. 21 (10), 1865–1868.

Heymann, D.L., Mackenzie, J.S., Peiris, M., 2013. SARS legacy: outbreak reporting is expected and respected. Lancet 381 (9869), 779–781.

Institute of Medicine Committee on Microbial Threats to Health, 1992. Emerging Infections: Microbial Threats to Health in the United States. Washington, DC, National Academy Press, 1–294.

Knope, K., National, A., Malaria Advisory, C., et al., 2013. Increasing notifications of dengue in Australia related to overseas travel, 1991 to 2012. Commun. Dis. Intell. Q. Rep. 37 (1), E55–E59.

Morens, D.M., Folkers, G.K., Fauci, A.S., 2008. Emerging infections: a perpetual challenge. Lancet Infect. Dis. 8 (11), 710–719.

Muller, M., Schlagenhauf, P., 2014. *Plasmodium knowlesi* in travellers, update 2014. Int. J. Infect. Dis. 22, 55–64.

Quam, M.B., Khan, K., Sears, J., et al., 2015. Estimating air travel-associated importations of dengue virus into Italy. J. Travel Med. 22 (3), 186–193.

Tappe, D., Stich, A., Langeheinecke, A., et al., 2014. Suspected new wave of muscular sarcocystosis in travellers returning from Tioman Island, Malaysia, May 2014. Euro. Surveill. 19 (21), article 2.

Taylor, L.H., Latham, S.M., Woolhouse, M.E., 2001. Risk factors for human disease emergence. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 356 (1411), 983–989.

Van Hong, N., Amambua-Ngwa, A., Tuan, N.Q., et al., 2014. Severe malaria not responsive to artemisinin derivatives in man returning from Angola to Vietnam. Emerg. Infect. Dis. 20 (7), 1199–1202.

Weaver, S.C., Lecuit, M., 2015. Chikungunya virus and the global spread of a mosquito-borne disease. N. Engl. J. Med. 372 (13), 1231–1239.

Zammarchi, L., Stella, G., Mantella, A., et al., 2015. Zika virus infections imported to Italy: clinical, immunological and virological findings, and public health implications. Journal of Clinical Virology: The Official Publication of the Pan American Society for Clinical Virology 63, 32–35.