Human Mobility and the Global Spread of Infectious Diseases: A Focus on Air Travel

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Greater human mobility, largely driven by air travel, is leading to an increase in the frequency and reach of infectious disease epidemics. Air travel can rapidly connect any two points on the planet, and this has the potential to cause swift and broad dissemination of emerging and re-emerging infectious diseases that may pose a threat to global health security. Investments to strengthen surveillance, build robust early-warning systems, improve predictive models, and coordinate public health responses may help to prevent, detect, and respond to new infectious disease epidemics.

Human Mobility and the Spread of Infectious Diseases

Increases in the global mobility of humans, nonhuman animals, plants, and products are driving the introduction of infectious diseases to new locations. In recent years we have witnessed several infectious diseases spread well beyond their previously understood geographic boundaries, as was demonstrated by the introduction of Zika virus to the Americas. We have also witnessed the emergence and spread of novel pathogens, such as the discovery of a previously unknown Middle Eastern respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia spreading to distant countries such as South Korea [1].

Many factors contribute to the global spread of infectious diseases, including the increasing speed and reach of human mobility, increasing volumes of trade and tourism, and changing geographic distributions of disease vectors. In particular, human travel and migration (especially via air travel) is now a major driving force pushing infections into previously nonendemic settings. Year by year, there are increasing numbers of international tourists [2], more international refugees and migrants [3], greater capacity for shipping by sea [4], and greater international air travel passenger volumes [5]. Air travel poses a growing threat to global health security, as it is now possible for a traveler harboring an infection in one location on earth to travel to virtually any other point on the planet in only 1–2 days. Infections introduced via travel may be sporadic and have little potential for further transmission, such as Lassa fever introduced into European settings [6]. In other situations, infections introduced by air travel may cause self-limited local epidemics such as Chikungunya virus in Italy [7]. More recently, there are a growing number of examples of infections introduced to a new region that ultimately become endemic, such as Chikungunya virus in Latin America and the Caribbean [8].

Vector-borne infections, including arthropod-borne viruses (arboviruses) present unique challenges as disease vectors such as mosquitoes can be carried overland, in boats, or on planes, and may travel between any two points on the globe within their lifespan. Such vectors have the potential to infect nontravelers in their new destination, as is seen in airport malaria [6]. Even if a vector is not infected, that vector may become endemic to a new region if there are suitable environmental conditions, and then potentially enable future epidemics. The most well-known example of this is the now-global distribution of Aedes aegypti and Ae. albopictus mosquitoes.

Highlights

- The volume of global air travel continues to increase annually, and passengers have the capacity to introduce infections to new regions in short time frames.
- Infections transported through air travel may initiate or facilitate epidemics.
- Developing more effective global surveillance tools and mechanisms to better communicate and coordinate between countries can facilitate more rapid and effective responses to epidemics.

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the vectors responsible for a number of arbovirus infections including dengue, Chikungunya, and Zika viruses [9]. Vector introduction is further facilitated by ecological factors, such as climate change and urbanization, that may enable vectors to flourish in new regions.

Clinical and public health care providers must be aware of the fluid boundaries of infectious diseases and be cognizant of the potential for imported infections. Front-line healthcare providers must now have knowledge of an increasingly broad spectrum of emerging illnesses from around the world, and public health teams must be prepared to respond to individual cases that have epidemic potential (e.g., Ebola virus), and coordinate responses at local, national, and international levels. Preparation for planning mass gatherings, such as large sporting events or an annual religious pilgrimage, require special consideration for the potential of these events to contribute to global outbreaks. Here, we outline emerging and re-emerging infectious diseases that are spread via human mobility, with a focus on air travel. We discuss sporadic cases and localized epidemics, international epidemics, and then focus on clinical and public health implications.

Air Travel Contributing to Sporadic Travel-Related Infections of Epidemic Potential, and to Localized Epidemics

Travel-related illnesses are common and mostly mild and self-limited, such as traveler’s diarrhea. However, the list of infections imported by returned travelers is growing [10], and many are capable of causing local epidemics (Table 1).

Malaria

Despite a global push for eradication, malaria continues to cause significant global morbidity and mortality. This protozoal vector-borne infection is transmitted to humans by the bite of infected *Anopheles* mosquitoes that are found in many tropical and temperate countries [11]. Malaria is a common cause of febrile illness in returned travelers [12], and delays in diagnosis may lead to poor patient outcomes, including death [13]. The incubation period varies from weeks to more than a month depending on the species, which frequently contributes to the delayed diagnosis of imported cases.

Airport malaria, where non-travelers near airports are infected by mosquitoes that have been imported by air travel [14], is a challenging diagnosis as local clinicians may not suspect this infection. Although the spraying of arriving planes has reduced the incidence of cases, it continues to be a concern as volumes of travel continue to increase [15] and case reports of malaria in non-travelers continue to grow [16]. Regions that have eradicated malaria but still have *Anopheles* vectors present are at risk of malaria reintroduction, for example in Sri Lanka [17].

The global distribution of drug-resistant malaria is also changing, and strains of multidrug-resistant *Plasmodium falciparum* appear to be spreading [18]. Although multidrug-resistant strains are still generally rare, there is growing concern that such strains may expand beyond their current boundaries through boat and air travel, heightening the need for better surveillance.

Schistosomiasis

Chronic infection with schistosomiasis is associated with gastrointestinal or urogenital pathology [19]. Schistosomiasis is acquired via contact with contaminated fresh water and requires specific snail intermediate hosts for disease transmission [19]. Locally acquired cases of schistosomiasis were discovered recently in France, and these were most certainly introduced
Snails local to Corsica were found to be competent hosts of *Schistosoma haematobium*, *Schistosoma bovis*, and hybrids of the two infections. There is the potential for further disease expansion given ongoing human travel and migration from schistosomiasis-endemic regions to nonendemic areas with the requisite intermediate snail hosts.
Air Travel Contributing to International Epidemics and Pandemics

Air travel has contributed to several epidemics of global health significance in recent years. Typically, an infected individual, either symptomatic or within an incubation period, flies to a distant location and introduces this infection to the local population. Below, we discuss major international epidemics relevant to air travel after 2000.

Severe Acute Respiratory Syndrome (SARS)
The severe acute respiratory syndrome (SARS) outbreak of 2002–2003 is an example of an emerging infection causing several simultaneous epidemics in noncontiguous geographic regions. SARS is a respiratory tract infection caused by a zoonotic coronavirus (SARS-CoV), and is thought to have arisen in horseshoe bats and subsequently transmitted to humans through civets as intermediate hosts [21].

The 2002 SARS epidemic originated in southern China and spread via air travel to 29 countries, causing local epidemics in Hong Kong, Taiwan, Canada, Singapore, Vietnam, and the Philippines [22]. The global epidemic lasted about 8 months, with 8096 probable cases and 774 deaths for a case-fatality rate of 10% [22]. SARS caused widespread panic and cost an estimated US$11 billion worldwide [23]. Although the public health response was swift and ultimately effective, this epidemic highlighted the need for increased international cooperation in the era of rapid global transit. This epidemic spurred revisions to the International Health Regulations (IHR) and introduced the most significant changes since their adoption [24].

Middle East Respiratory Syndrome (MERS)
Another novel zoonotic respiratory coronavirus, MERS-CoV, originated in Saudi Arabia in 2012 [25]. Its reservoir is thought to be the dromedary camel. Similar to SARS-CoV, MERS-CoV causes a respiratory infection, though with a higher case-fatality rate of about 35% [26].

Since 2012, over 2000 cases have been detected in 27 countries. South Korea experienced the largest epidemic outside of Saudi Arabia, which was initiated by a single infected business traveler returning from that country. This one index case at a single hospital resulted in an additional 184 confirmed cases at 17 hospitals, and caused 33 deaths before the epidemic ended 2 months later [27]. Infection risk appeared to be primarily through hospital-based contact and fomites rather than through household contacts [28].

Although the virus is thought to have low epidemic potential, epidemics such as the one in South Korea are not unexpected [29]. There are a number of countries at risk of importing cases via air travel due to close trade and tourism ties to Saudi Arabia [30]. Additionally, the annual Haj pilgrimage brings millions of pilgrims from around the world to Saudi Arabia, raising the potential for future epidemics [31].

Ebola Virus
The 2014 Ebola virus disease (EVD) epidemic in West Africa also highlighted the risks of global infectious disease transmission in an increasingly connected world. This zoonotic virus has a probable bat reservoir [32] and is spread between humans through contact with infected body fluids. EVD can incubate for up to 3 weeks before presenting as a severe febrile illness with multisystem organ failure and hemorrhagic tendencies. Epidemics have largely been confined to Africa, with case fatality rates between 30% to upwards of 80% [33].

The largest EVD epidemic began in Sierra Leone in 2014. Starting in a rural town, the epidemic spread via land travel to bordering Guinea and Liberia. From there, cases began appearing on
several continents via international air travel. In the USA, for instance, one returned traveler infected two healthcare workers before local transmission stopped [34]. Similar imported cases were seen in Italy and the United Kingdom, and a short chain of healthcare-related transmission was documented following the return of an infected Spanish citizen back to Spain [35,36]. An infected individual flew to Nigeria and initiated a larger epidemic, with 19 confirmed cases in two cities resulting in seven deaths [37]. Ultimately, the Nigerian epidemic was halted by the heroic efforts of local public health teams [38]. By the time the West African EVD outbreak ended in 2016, there were 21 868 reported cases and 11 310 deaths, with imported cases in seven countries.

During the 2014 EVD epidemic, many countries hastily instituted policies that limited travel to and from EVD-affected countries. Some countries closed land and air borders with Guinea, Liberia, and Sierra Leone [39,40], and others, including Australia and Canada, temporarily refused to issue visas to travelers from affected countries [41], a policy not aligned with the World Health Organization (WHO)’s IHR. The USA imposed enhanced screening procedures that measured the temperature of returned travelers from affected countries for up to 3 weeks. The 2014 EVD epidemic highlighted how governments may rapidly impose policy related to an emerging infection of epidemic potential, although the effectiveness of many of these policies is still debated.

Influenza
Influenza A virus causes predictable seasonal epidemics in both northern and southern hemispheres. Influenza A virus also circulates in birds and pigs and has the potential to mutate more rapidly compared to influenza B virus, allowing the virus to recombine with different strains and cause epidemics. Many individuals infected with influenza A virus will experience a self-limited febrile illness punctuated with myalgia and malaise, and this infection is also associated with severe illness and is responsible for roughly 300 000–600 000 deaths per year, globally [42].

The 1918 influenza pandemic demonstrated the ability of influenza A virus to cause a global catastrophe in the era of increasing global mobility, as it resulted in an estimated 50 million deaths worldwide [43]. Seasonal influenza strains are now more mobile than ever, and the effect of air travel is a well-established mechanism for facilitating global influenza transmission [44–47]. The 2009 H1N1 influenza pandemic demonstrated the potential for global air travel networks to rapidly disseminate a novel influenza virus that emerged on a pig farm in Mexico and spread to the rest of the world [48,49], resulting in approximately 123 000–203 000 deaths, globally [50].

Air Travel Contributing to Infections with New Areas of Endemicity
Human mobility continues to introduce infections to new geographic locations, and air travel contributes to this process. Occasionally, infections introduced to new regions may become endemic.

*Aedes* spp. Mosquitoes
The global emergence of arboviruses, such as dengue, Zika, and Chikungunya viruses, demonstrates how certain infections may become endemic in new regions if they are imported to areas with suitable ecological conditions. These arboviruses require *Ae. aegypti* or *Ae. albopictus* mosquito vectors for transmission, and at least one of these species of mosquito is now present on every continent except Antarctica [9]. *Ae. albopictus*, the Asian tiger mosquito, is well adapted to urban environments [51] and has contributed to recent arboviral epidemics.
These mosquito vectors have spread along human trade and travel routes [51,52], and diseases carried by such vectors are quickly following the same path.

**Dengue Virus**

Dengue virus, transmitted primarily by *Ae. aegypti*, is one of the most important re-emerging infectious diseases, with an estimated 2.5 billion people living in regions suitable for infection [53]. Dengue virus has four serotypes, each of which circulates independently, causing outbreaks in populations that are naïve to that serotype [54]. Though once well controlled, dengue virus re-emerged in Asia in the 1950s, and is now endemic or epidemic in many tropical and subtropical regions around the world. Its re-emergence over the past half-century has been driven by urbanization, globalization, inadequate vector control [55], and, notably, increasing human travel [56,57]. Autochthonous transmission has now been described in the USA, France, Croatia, and Madeira [58–60], all imported by infected travelers. Air travel is contributing to the increasing frequency of epidemics as new serotypes are introduced into susceptible populations by travelers [61,62]. Interestingly, there is emerging evidence that individuals infected with dengue virus who are asymptomatic or presymptomatic (and presumably have lower levels of viremia) are still able to infect competent mosquito vectors. Such individuals may be more prone to traveling given their lack of symptoms, and are likely contributing to global dengue virus transmission [63,64].

**Chikungunya Virus**

Chikungunya virus is another arbovirus that is transmitted by *Ae. aegypti* and *Ae. albopictus* mosquito vectors. It causes a self-limited febrile illness with a syndrome of arthralgia or arthritis that may last for weeks to months after infection. Chikungunya virus was originally endemic in African and Asian settings, but has caused localized epidemics in Italy in 2007, and in Italy and France in 2017 [7,60,65,66]. The 2007 epidemic in Italy was initiated by a single viremic traveler returning from India [7], highlighting the role of air travel in its spread. In December of 2013, autochthonous cases of Chikungunya infection appeared in Saint Martin, also likely introduced by a viremic traveler. Given the appropriate ecological suitability and competent vectors for transmission, Chikungunya virus rapidly spread throughout Latin America and the Caribbean, affecting 46 countries and over 3 million people, and is now endemic in the Americas [67]. An evaluation of global travel patterns from endemic locations predicted that imported cases of Chikungunya would be common in New York, Miami, and Puerto Rico, with autochthonous transmission in the latter two regions [8], which was ultimately realized 1 year later [68].

**Zika Virus**

Zika virus is also transmitted by *Ae. aegypti* and *Ae. albopictus* vectors and typically causes a self-limited febrile illness in approximately 20% of those affected [69]. The virus has a predilection for developing nervous systems, and microcephaly is well documented in children born to infected pregnant mothers [70]. Zika virus originated in Africa and spread slowly eastward to Asia during the second half of the 20th century, culminating in a large outbreak on the Yap island in 2007 [69]. This was followed by a number of smaller outbreaks in Pacific islands, eventually resulting in an unprecedented epidemic in Brazil in 2015 that spread through much of Latin America and the Caribbean [71]. Although the index case was not identified, molecular clock analyses suggest that the virus was introduced multiple times in 2013 or 2014 from viremic travelers [71]. The virus was accurately predicted to spread throughout Latin America and the Caribbean based on human air travel patterns from Brazil, to regions with suitable ecological conditions and competent mosquito vectors for disease transmission [72]. Similarly, Zika virus is predicted to be reintroduced to African and Asia-Pacific nations based on current air travel patterns [73,74]. It is currently unclear if Zika virus will be established as an endemic
infection in Latin American and Caribbean nations, though there are several parallels with Chikungunya virus in this region, suggesting that this is a likely scenario [75].

Antimicrobial Resistance

The discovery of antibiotics heralded a new era in medicine, but was almost immediately followed by the emergence of drug resistance, such as the early descriptions of penicillin resistance in Staphylococcus aureus species [76]. Treatment of organisms harboring antimicrobial resistance (AMR) genes is associated with treatment failures, worse clinical outcomes, and greater expense [77]. The devastating economic and health impacts of AMR are expected to be amplified in low-income countries [78]. The rapid rise of broad-spectrum AMR among Gram-negative bacteria, especially the Enterobacteriaceae, is a growing public health threat. Soon after the development of extended-spectrum cephalosporins in the 1980s there emerged Enterobacteriaceae with extended-spectrum beta-lactamases (ESBLs) and AmpC cephalosporinases [79]. These resistance genes were soon found worldwide in a variety of Gram-negative organisms, including Klebsiella, Escherichia coli, Salmonella, and others [80]. Carbapenemases are now increasingly commonplace, conferring resistance to some of the broadest-spectrum antibiotics [81].

International air travel is contributing to this global spread of resistant organisms. Travelers returning from areas with a high prevalence of AMR often return colonized with resistant organisms, and these individuals can transmit AMR organisms to others [82]. The New Delhi metallo-beta-lactamase-1 (NDM-1) gene is a recent example of the potential for AMR to spread rapidly. Organisms with NDM-1 are resistant to essentially all cephalosporins and carbapenem antibiotic classes [83]. The first case report of NDM-1 was in a traveler who acquired a urinary infection while in India in 2008 [84]. By 2010, NDM-1 was detected in the USA, Canada, Japan, Kenya, Oman, Australia, the United Kingdom, and multiple other European countries [85]. Similarly, colistin resistance with the mobilized colistin resistance-1 (mcr-1) gene is a very concerning development. From its likely origin in China, mcr-1 has been detected in returned travelers around the world [86,87]. Like NDM-1, it can colonize travelers returning from endemic areas [88], and local transmission is now being seen outside of China [89]. These bacteria are emerging far from their site of origin largely due to human travel and agricultural trade. The WHO has recognized AMR as a major global health threat and has enacted a Global Action Plan to help combat its spread [90]. However, large-scale antimicrobial stewardship programs are currently not realized in much of the world.

Clinical Implications of Infections Transmitted via Air Travel

Given the increases in global tourism and human migration, physicians and other healthcare workers are seeing more travel-related infections. Since infections from distant locales can present to virtually any clinic or hospital in the world in a matter of days, healthcare workers must be aware of both local and international epidemics. For example, the index case of MERS in Korea had visited four healthcare facilities over 8 days before a diagnosis was established [91], and this delayed diagnosis contributed to the epidemic. The ability of a clinician to obtain a quality travel history is increasingly important, even for routine infectious syndromes like an upper respiratory tract infection. Several tools now exist for clinicians to help keep abreast of distant epidemics that may be relevant to their clinical practice, such as ProMED-Mail [92] and HealthMap [93]. However, questions still remain about the best way to consume and process a large volume of data for which there may only be limited pertinent information.

It is also important for clinicians to ask about a more remote travel history. For example, tuberculosis testing is usually considered before starting immunosuppressive medications.
However, asking about potential exposures to parasitic infections, such as *Strongyloides stercoralis*, is frequently forgotten. *Strongyloides* infections can disseminate following immunosuppression and cause a severe and frequently fatal disease [94]. Screening for *Strongyloides* is now recommended prior to initiating immunosuppressive medications in patients who have spent significant time in endemic countries [95]. Similarly, neurocysticercosis should be considered in those with seizure disorders from endemic countries, even if they have not visited an endemic region in many years. The differential diagnosis for common syndromes often expands when a lifetime travel history is considered, and this information has potential to significantly impact clinical decision-making.

**Public Health Implications of Infections Transmitted via Air Travel**

Epidemics such as those caused by SARS, MERS, and Ebola viruses highlight the importance of rapid public health responses to emerging epidemics in the era of expanding global air travel. Public health agencies at local and international levels must be aware of global outbreaks and emerging threats, and have the tools to initiate a rapid and coordinated response. Several systems need to be in place to facilitate such coordinated responses, including surveillance tools and methods of communication and management in various jurisdictions.

The revised IHR adopted after the 2002 SARS outbreak was designed to improve global reporting of outbreaks [24] and this document continues to function as an effective data-sharing agreement. While SARS and the revised IHR have resulted in an increased investment in surveillance among higher-income countries, countries with fewer resources but a higher burden of infectious disease epidemics have ongoing challenges operating surveillance programs. Improving global surveillance capacity is a priority, and countries with limited public health capacity may require logistic and infrastructure support for these global systems to function effectively [96,97]. In addition to disease surveillance networks, early-warning systems are increasingly helpful for monitoring the global spread of infectious diseases. Such systems utilize multiple data sources, including voluntary reports, international news, and social media [92,93,98,99]. Other systems, such as GeoSentinel and TropNet, coordinate tropical and travel medicine clinics that collect data on illnesses in returned travelers. These travelers essentially act as sentinels of emerging epidemics when a source country does not have the capacity to detect these infections in a timely manner. Such networks have detected a sarcocystis outbreak in Malaysia [100], dengue virus outbreaks in Angola [101], and tracked the spread of Zika virus globally [102]. With improved surveillance and early warning systems, and by harnessing travelers as sentinels, it is possible to piece together a global picture of emerging and re-emerging infectious diseases. Responding to these epidemics, though, still poses several challenges.

Travel-related policy and public health responses to epidemics take several approaches, and include travel restrictions to and from affected areas, and passenger screening. Travel bans and restrictions are generally not helpful in halting the spread of infectious diseases [45,103–106]. Such policies also may hinder affected countries coping with the epidemic and can impose significant economic burden above the direct costs of the infectious outbreak [107]. Travel restrictions also violate the revised IHR, effectively punishing countries for participating in global disease surveillance and discouraging open communication [108]. Screening of travelers from affected counties also poses logistical problems. Screening commonly relies on either self-reported symptoms (such as an influenza-like illness), which may be inaccurate, or on periodic body temperature screening such as using thermometers or thermal imaging technology. Travelers may be completely asymptomatic if they are in an incubation period during the time of travel, and this may be especially pertinent for infections with longer incubation periods.
such as Ebola virus [109]. Ultimately, resources may be better channeled to controlling the epidemic at the source.

**Travel-Related Infectious Diseases in Low-Income and Lower-Middle-Income Countries**

The burden of infectious diseases is disproportionately high in low-income and lower-middle-income countries (LICs and LMICs, respectively) [110]. Improving disease surveillance capacities, vector control initiatives, developing laboratory capacity [111–113], and supporting public health interventions such as vaccination, is essential to mitigate local impact and future dissemination of epidemics [114]. If an epidemic of global health significance is detected in an LIC or LMIC, communication and coordination with local public health teams is essential, as is supporting the capacity of local laboratories and personnel. This was recently helpful in halting the 2018 Madagascar plague epidemic [115,116].

**Concluding Remarks**

The capacity for an infected human to rapidly travel between any two points on earth has heralded a new era in global health security as infectious diseases are able to spread more effectively than at any other time in history. The global public health response must be proportional.

Quality surveillance, open communication, and global coordination are key elements to prevent, detect, and extinguish epidemics early. Similarly, vaccine development and vector-control efforts may proactively prevent the emergence of epidemics. New tools are needed to enable front-line healthcare workers to diagnose non-local infections, as well as to facilitate rapid data sharing during outbreaks (see Outstanding Questions). Investing in capacity building targeted at detecting and responding to epidemics in LICs and LMICs is likely to be a very effective and cost-effective mode of preventing disease transmission worldwide.

**Outstanding Questions**

How do we most effectively harness the current global infectious disease surveillance capacity given the existing gaps?

Can stronger modeling more accurately predict where infections will spread through air travel, and can this determine what the next epidemic of global health significance will be?

How can we enable local healthcare workers to more effectively utilize global infectious diseases surveillance data?

How do we develop better methods to screen for passengers harboring infectious diseases prior to traveling, or after arrival?

How can international and local travel-related policies be strengthened to more effectively respond to infectious diseases of epidemic potential?

What is the best way to support low-income and lower-middle-income countries responding to infections with epidemic potential?

**References**

1. Tatem, A.J. et al. (2006) Global transport networks and infectious disease spread. Adv. Parasitol. 62, 293–343
2. UN World Tourism Organization (2017) UNWTO Tourism Highlights. (2017 edition), United Nations
3. United Nations, Department of Economic and Social Affairs, Population Division (2017) International Migration Report 2017: Highlights, United Nations
4. Institute of Shipping Economics and Logistics (2017) World Seaborne Trade and World Port Traffic. Shipping Statistics and Market Review 61
5. International Air Transport Association (2017) IATA Annual Review 2017, IATA
6. Haas, W.H. et al. (2003) Imported Lassa fever in Germany: surveillance and management of contact persons. Clin. Infect. Dis. 36, 1254–1258
7. Angeleri, P. et al. (2007) An outbreak of chikungunya fever in the province of Ravenna, Italy. Euro Surveill. 12, 12–14
8. Khan, K. et al. (2014) Assessing the origin of and potential for international spread of chikungunya virus from the Caribbean. PLoS Curr. 6, 1–11
9. Kraemer, M.U.G. et al. (2015) The global distribution of the arbovirus vectors Aedes aegypti and Aedes albopictus. eLife 4, e08347
10. Leder, K. et al. (2013) GeoSentinel surveillance of illness in returned travelers, 2007–2011. Ann. Intern. Med. 158, 456–469
11. Sinka, M.E. et al. (2012) A global map of dominant malaria vectors. Parasit. Vectors 5, 69
12. Blagiegi, A.K. et al. (2014) Travel-acquired infections and illnesses in Canadians: surveillance report from CanTravNet surveillance data, 2009–2011. Open Med. 8, e20–e32
13. McCarthy, A.E. et al. (2015) Severe malaria in Canada, 2001–2013. Malar. J. 14, 151
14. Isaacson, M. (1989) Airport malaria: a review. Bull. World Health Organ. 67, 737–743
15. Tatem, A.J. et al. (2006) Estimating the malaria risk of African mosquito movement by air travel. Malar. J. 5, 57
16. Pomas-train, C. et al. (2009) Atypical aetiology of a conjugal fever: autochthonous airport malaria between Paris and French Riviera: a case report. Malar. J. 8, 202
17. Wickremasinghe, A.R. et al. (2017) Should chemoprophylaxis be a main strategy for preventing re-introduction of malaria in highly receptive areas? Sri Lanka a case in point. Malar. J. 16, 102
18. Imwong, M. et al. (2017) Spread of a single multidrug resistant malaria parasite lineage (PfPalo) to Vietnam. Lancet Infect. Dis. 17, 1022–1023
19. Ouma, J.H. et al. (2001) Mortality in schistosomiasis: an update. Trends Parasitol. 17, 117–118
20. Ramali, L. et al. (2016) Persistence of schistosomal transmission linked to the Catu river in southern Corumba since 2013. Euro Surveill. Published online 25 January 2018, http://dx.doi.org/10.2807/1560-7917.ES.2018.23.4.18-00017
21. Hu, G. et al. (2017) Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS Pathog. 13, e1006698
22. Christian, M.D. et al. (2004) Severe acute respiratory syndrome. Clin. Infect. Dis. 38, 1420–1427
23. Saywell, T. et al. (2003) The cost of SARS: $11 billion and rising. Nat. Jones Far East Econ. Rev. 166, 12–17
24. Fidler, D.P. and Gostin, L.O. (2006) The new International Health Regulations: an historic development for international law and public health. J. Law Med. Ethics 34, 85–94 4
25. de Groote, R.J. et al. (2013) Middle East respiratory syndrome coronavirus (ME RS-CoV): announcement of the Coronavirus Study Group. J. Virol. 87, 7790–7792
26. Yang, Y.-M. et al. (2017) Impact of comorbidity on fatality rate of patients with Middle East Respiratory Syndrome. Sci. Rep. 7, 11307
27. Kj, M. (2015) 2015 MERS outbreak in Korea: hospital-to-hospital transmission. Epidemiol. Health 37, e2015033
28. Lee, S.S. and Wong, N.S. (2015) Probable transmission chains of Middle East respiratory syndrome coronavirus and the multiple generations of secondary infection in South Korea. Int. J. Infect. Dis. 35, 65–67
29. Kucharski, A.J. and Althaus, C.L. (2015) The role of super-spreading in Middle East respiratory syndrome coronavirus (MERS-CoV) transmission. Euro Surveill. 20, 14–18
30. Gardner, L.M. et al. (2016) Risk of global spread of Middle East respiratory syndrome coronavirus (MERS-CoV) via air transport network. J. Travel Med. 23, 1–8
31. Zuma, A. et al. (2016) Infectious diseases epidemic threats and mass gatherings: Refocusing global attention on the continuing spread of the Middle East Respiratory Syndrome coronavirus (MERS-CoV). BMC Med. 14, 2012–2015
32. Leendertz, S.A.J. et al. (2016) Assessing the evidence supporting fruit bats as the primary reservoirs for Ebola viruses. EcoHealth 13, 18–25
33. Lelefoure, A. et al. (2014) Case fatality rates of Ebola virus diseases: a meta-analysis of World Health Organization data. Med. Mal. Infect. 44, 413–416
34. Regan, J.J. et al. (2015) Public health response to commercial airline travel of a person with Ebola virus infection – United States, 2014. MMWR Morb. Mortal. Wkly. Rep. 64, 63–66
35. Bertoli, G. et al. (2016) Ebola virus disease: Case management in the Institute of Infectious Diseases, University Hospital of Sassari, Sardinia, Italy. J. Infect. Dev. Ctries. 10, 537–543
36. López, M.A. et al. (2015) First secondary case of Ebola outside Africa: epidemiological characteristics and contact monitoring, Spain, September to November 2014. Euro Surveill. 20, 21003
37. Shub, F. et al. (2014) Ebola virus disease outbreak – Nigeria, July-September 2014. MMWR Morb. Mortal. Wkly. Rep. 63, 867–872
38. Hamis, M. et al. (2015) It takes threat of Ebola to see lessons from low income countries. Global Health 11, 16
39. Cohen, N.J. (2016) Travel and border health measures to prevent the international spread of Ebola. MMWR Surveill. Summ. 65, 57–67
40. BBC News (2014) Hawaiian land border shut over Ebola. BBC News 23 August 2014
41. CBC News (2014) Canada won’t issue visas to residents of Ebola outbreak countries. CBC News 21 October 2014
42. Iuliano, A.D. et al. (2018) Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 391, 1285–1300
43. Johnson, N.P.A.S. and Mueller, J. (2002) Updating the accounts: global mortality of the 1918–1920 “Spanish” influenza pandemic. Bull. Hist. Med. 76, 105–115
44. Grau, R.F. et al. (2004) Modeling the spread of annual influenza epidemics in the U.S.: the potential role of air travel. Health Care Manag. Sci. 7, 127–134
45. Brownstein, J.S. et al. (2008) Empirical evidence for the effect of airline travel on inter-regional influenza spread in the United States. Proc. Natl. Acad. Sci. 105, 12366–12371
46. Rvachev, L.A. and Longini, I.M. (1988) A mathematical model for the global spread of influenza. Math. Biosci. 75, 3–22
47. Fishbain, A. et al. (1994) A mathematical model for the European spread of influenza. Eur. J. Epidemiol. 10, 471–474
48. Mena, I. et al. (2016) Origins of the 2009 H1N1 influenza pandemic in swine in Mexico. Science 353, 1167–1167
49. Khan, K. et al. (2009) Spread of a novel influenza A(H1N1) virus via global airline transportation. N. Engl. J. Med. 361, 212–214
50. Simonsen, L. et al. (2013) Global mortality estimates for the 2009 influenza pandemic from the GLAMOR project: a modeling study. PLoS Med. 10, e1001558
51. Bonizzoni, M. et al. (2013) The invasive mosquito species Aedes albopictus: current knowledge and future perspectives. Trends Parasitol. 29, 460–468
52. Brown, J.E. et al. (2014) Human impacts have shaped historical and recent evolution in Aedes aegypti, the dengue and yellow fever mosquito. Evolution 68, 514–525
53. Brady, O.J. et al. (2012) Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoS Negl. Trop. Dis. 6, e1760
54. Thomas, L. et al. (2014) Clinical presentation of dengue by serotype and year of epidemic in Martinique. Am. J. Trop. Med. Hyg. 91, 7–14
55. Guibier, D.J. (2011) Dengue, urbanization and globalization: the unholy trinity of the 21st century. Trop. Med. Health 39, 3–11
56. Wilder-Smith, A. and Guibier, D.J. (2008) Geographical expansion of dengue: the impact of international travel. Med. Clin. North Am. 92, 1377–1390
57. Rizza, G. (2014) Dengue and chikungunya: long-distance spread and outbreaks in naïve areas. Pathog. Glob. Health 108, 348–355
58. Boui, N. et al. (2012) Return of epidemic dengue in the United States: implications for the public health practitioner. Public Health Rep. 127, 259–266
59. Schaffner, F. and Mathis, A. (2014) Dengue and dengue vectors in the WHO European region: past, present, and scenarios for the future. Lancet Infect. Dis. 14, 1271–1280
60. Tomasselli, D. and Schlagenhauf, P. (2013) Chikungunya and dengue autotransmission cases in Europe, 2007–2012. Travel Med. Infect. Dis. 11, 274–284
61. Tian, H. et al. (2017) Increasing airline travel may facilitate circulation of multiple dengue virus serotypes in Asia. PLoS Negl. Trop. Dis. 11, e0005984
62. Nunes, M.R.T. et al. (2014) Air travel is associated with intracontinental spread of dengue virus serotypes 1–3 in Brazil. PLoS Negl. Trop. Dis. 8, e2769
63. Duong, V. et al. (2015) Asymptomatic humans transmit dengue virus to mosquitoes. Proc. Natl. Acad. Sci. U. S. A. 112, 14688–14693
64. Ten Bosch, Q.A. et al. (2018) Contributions from the silent majority dominate dengue virus transmission. PLoS Pathog. 14, e1006965
65. Santé publique France (2017) Chikungunya, dengue et zika – Données de la surveillance renforcée en France métropolitaine en 2017. Santé publique France
66. Venturi, G. et al. (2017) Detection of a chikungunya outbreak in Central Italy, August to September 2017. Euro Surveill. 22, 17–00646
67. Yactayo, S. et al. (2016) Epidemiology of Chikungunya in the Americas. J. Infect. Dis. 214, S441–S445
68. Center for Disease Control and Prevention (2015) Chikungunya: 2014 Final Data for the United States, Center for Disease Control and Prevention
69. Duffy, M.R. et al. (2009) Zika virus outbreak on Yap Island, Federated States of Micronesia. N. Engl. J. Med. 360, 2536–2543
70. Rasmussen, S.A. et al. (2016) Zika virus and birth defects – reviewing the evidence for causality. N. Engl. J. Med. 374, 1981–1987
71. Faria, N.R. et al. (2016) Zika virus in the Americas: Early epidemiological and genetic findings. Science 352, 345–349
72. Bogoch, I.I. et al. (2016) Anticipating the international spread of Zika virus from Brazil. Lancet 387, 335–336
73. Bogoch, I.I. et al. (2016) Potential for Zika virus introduction and transmission in resource-limited countries in Africa and the Asia-Pacific region: a modelling study. Lancet Infect. Dis. 16, 1237–1245
74. Kraemer, M.U.G. et al. (2017) Zika virus transmission in Angola and the potential for further spread to other African settings. Trans. R. Soc. Trop. Med. Hyg. 111, 527–529
75. Sieker, M.U. et al. (2018) Gone or forgotten? The rise and fall of Zika virus. Lancet Public Health 3, e109–e110
76. Plough, H.H. (1945) Penicillin resistance of Staphylococcus aureus and its clinical implications. Am. J. Clin. Pathol. 15, 446–451
77. Cosgrove, S.E. and Carmeli, Y. (2003) The impact of antimicrobial resistance on health and economic outcomes. Clin. Infect. Dis. 36, 1433–1437
78. Adely, O.O. et al. (2017) Drug-Resistant Infections: A Threat to Our Economic Future. vol. 2: Final Report (English). World Bank Group
79. Molton, J.S. et al. (2013) The global spread of healthcare-associated multidrug-resistant bacteria: a perspective from Asia. Clin. Infect. Dis. 56, 1310–1318
80. Bonnet, R. (2004) Growing group of extended-spectrum beta-lactamases: the CTX-M enzymes. Antimicrob. Agents Chemother. 48, 1–14
81. Nordmann, P. et al. (2011) Global spread of carbapenemase-producing Enterobacteriaceae. Emerg. Infect. Dis. 17, 1701–1708
82. Arciola, M.S. et al. (2017) Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. Lancet Infect. Dis. 17, 78–85
83. Kumanasamy, K.K. et al. (2010) Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect. Dis. 10, 597–602
84. Yong, D. et al. (2009) Characterization of a new metallo-beta-lactamase gene, blaNDM-1, and a novel enlothrombinase esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. Antimicrob. Agents Chemother. 53, 5046–5054
85. Bermejo, M. et al. (2014) New Delhi Metallo-beta-lactamase around the world: an overview using Google Maps. Euro Surveill. 19, 20098
86. Payne, M. et al. (2016) mcr-1-Positive colistin-resistant Escherichia coli in traveler returning to Canada from China. Emerg. Infect. Dis. 22, 1673–1675
87. Schwarz, S. and Johnson, A.P. (2016) Transferable resistance to colistin: a new old threat. J. Antimicrob. Chemother. 71, 2066–2070
88. Bernasconi, O.J. et al. (2016) Travelers can import colistin-resistant enterobacteriaceae, including those possessing the plasmid-mediated mcr-1 gene. Antimicrob. Agents Chemother. 60, 5080–5084
89. Ellner, J.A. et al. (2017) Locally acquired mcr-1 in Escherichia coli, Australia and 2013. Emerg. Infect. Dis. 23, 1160–1163
90. World Health Organization (2015) Global Action Plan on Antimicrobial Resistance. World Health Organization
91. Cowling, B.J. et al. (2015) Preliminary epidemiological assessment of MERS-CoV outbreak in South Korea, May to June 2015. Euro Surveill. 20, 7–13
92. Yu, V.L. and Madoff, L.C. (2004) ProMED-mail: An early warning system for emerging diseases. Clin. Infect. Dis. 39, 227–232
93. Freifeld, C.C. et al. (2008) HealthMap: global infectious disease monitoring through automated classification and visualization of internet media reports. J. Am. Med. Inform. Assoc. 15, 150–157
94. Mejia, R. and Nutman, T.B. (2012) Screening, prevention, and treatment for hyperinfection syndrome and disseminated infections caused by Strongyloides stercoralis. Curr. Opin. Infect. Dis. 25, 458–463
95. Boguld, A.K. et al. (2016) CATMAT statement on disseminated strongyloidiasis: prevention, assessment and management guidelines. Can. Commun. Dis. Rep. 42, 12
96. World Health Organization (2017) Global Antimicrobial Resistance Surveillance System (GLASS) Report: Early Implementation 2016–2017, World Health Organization
97. Tambo, E. et al. (2014) Need of surveillance response systems to combat Ebola outbreaks and other emerging infectious diseases in African countries. Infect. Dis. Poverty 3, 29
98. Wang, Y.A. and Barry, M. (2017) Making online outbreak surveillance work for all. Ann. Glob. Health 83, 625–629
99. Dion, M. et al. (2015) Big data and the global public health intelligence network (GPHIN). Can. Commun. Dis. Rep. 41, 209
100. Esposito, D.H. et al. (2014) Acute muscular sarcospongiosis: an international investigation among 8 travelers returning from Timor Island, Malaysia, 2011–2012. Clin. Infect. Dis. 59, 1401–1410
101. Schwartz, E. et al. (2013) Detection on four continents of dengue fever cases related to an ongoing outbreak in Luanda, Angola, March to May 2013. Euro Surveill. 18, 20488
102. Leder, K. et al. (2017) Zika beyond the Americas: Travelers as sentinels of Zika virus transmission. A GeoSentinel analysis, 2012 to 2016. PLoS One 12, e0185689
103. Bajardi, P. et al. (2011) Human mobility networks, travel restrictions, and the global spread of 2009 H1N1 pandemic. PLoS One 6, e16591
104. Aledort, J.E. et al. (2007) Non-pharmaceutical public health interventions for pandemic influenza: an evaluation of the evidence base. BMC Public Health 7, 208
105. Chong, K.C. and Ying Zee, B.C. (2012) Modeling the impact of air, sea, and land travel restrictions supplemented by other interventions on the emergence of a new influenza pandemic virus. BMC Infect. Dis. 12, 309
106. Bogoch, I.I. et al. (2015) Assessment of the potential for international dissemination of Ebola virus via commercial air travel during the 2014 west African outbreak. Lancet 385, 29–35
107. World Bank (2014) The Economic Impact of the 2014 Ebola Epidemic. Short and Medium Term Estimates for West Africa, World Bank
108. Piattoni, R. (2015) Unsanctioned travel restrictions related to Ebola unraveled the global social contract. CMAJ 187, 166–167
109. Gostic, K.M. et al. (2015) Effectiveness of traveller screening for emerging pathogens is shaped by epidemiology and natural history of infection. eLife 4, e05564
110. Hay, S.I. et al. (2017) Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 390, 1260–1344
111. Alemriji, G.A. et al. (2014) Strengthening national health laboratories in sub-Saharan Africa: a decade of remarkable progress. Trop. Med. Int. Health 19, 450–458
112. Wertheim, H.F.L. et al. (2010) Laboratory capacity building in Asia for infectious disease research: experiences from the South East Asia Infectious Disease Clinical Research Network (SEAICRN). PLoS Med. 7, e1000231
113. Zumla, A. et al. (2016) Zika virus outbreak and the case for building effective and sustainable rapid diagnostics laboratory capacity globally. Int. J. Infect. Dis. 45, 92–94
114. Hotez, P.J. et al. (2016) New vaccines for the world’s poorest people. Annu. Rev. Med. 67, 425–417
115. Bogoch, I.I. et al. (2018) Potential plague epidemic from Madagascar via international air travel. Lancet Infect. Dis. 18, 247–248

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116. World Health Organization (2018) Revamp of the Plague Detection in Madagascar Yields Quick and Sustainable Wins, World Health Organization

117. Chin, C.-S. et al. (2011) The origin of the Haitian cholera outbreak strain. N. Engl. J. Med. 364, 33–42

118. Liu, Y.-Y. et al. (2016) Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect. Dis. 16, 161–168

119. Mackay, I.M. and Arden, K.E. (2015) MERS coronavirus: diagnostics, epidemiology and transmission. Virol. J. 12, 222

120. Pan American Health Organization (2017) Number of Reported Cases of Chikungunya Fever in the Americas – EW 51 (December 22, 2017), Pan American Health Organization

121. Leparc-Goffart, I. et al. (2014) Chikungunya in the Americas. Lancet 383, 514