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Chapter 37

The Spread of Disease in the 20th Century and Lessons for the 21st Century

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Movement and the emergence of infectious diseases have always gone hand-in-hand. One needs only to think back to the spread of plague from Asia to Europe in the 14th century (ushering in the concept of quarantine), the introduction of smallpox to the Americas with the voyages of discovery in the late 1400s, the transfer of syphilis back to the old world on those same voyages, and theories regarding emergence of tuberculosis in sub-Saharan Africa via European colonization. Movement is probably a better term for this phenomenon than travel. The latter usually refers only to people, whereas the former includes goods, animals, and insects in addition to people. All have played a role in the spread of infectious diseases.

The tendency for diseases to move took off in the 20th century as movement itself accelerated. Not only did the variety of conveyances increase (e.g., automobiles, trucks, buses, aircraft, and spacecraft) but also everything got bigger and faster, even trains and ships. These modes of transportation allowed us to probe places we had never been to before: remote terrestrial locations, the oceans, and aerospace. In some instances, microbes came along for the ride.

Examples of movement-associated emerging disease from the early 20th century include the introduction of plague into the Americas and the Spanish flu. *Yersinia pestis* came ashore with rodents from a ship, which had traveled from Hong Kong to San Francisco at the dawn of the 20th century, sparking a plague outbreak in the city in 1900 (Kinyoun & Wyman, 2006). From that single introduction, the organism has gradually but relentlessly extended its range in animals and conveyances until today it is found throughout large portions of the western half of North America. Fortunately the human disease impact of plague in North America remains small (Centers for Disease Control and Prevention, 2006).

The 1918 Spanish flu is entirely another matter, proving to be the single most devastating epidemic the world has ever seen. This event is estimated to have killed 50 million people globally over a period of only a few short months, devastating whole communities virtually overnight (Taubenberger & Morens, 2006). With the current growing interest in avian

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influenza, images of the 1918 pandemic have resurfaced, including makeshift hospitals in gymnasiums and armories, masked security personnel, and corpses littering the streets. As a result of this epidemic, life expectancy temporarily plummeted all over the world; in the United States life expectancy decreased from 51 to 39 years. Although no one knows for sure how the Spanish flu spread, travel surely contributed. We were in the midst of World War I. Mass displacements and malnutrition among civilian populations affected by the war were common. Ships carried thousands of soldiers back and forth from the Americas to Europe, and troops were moving all around the continent. This was the perfect recipe for a disease explosion. Many accounts suggest that the 1918 virus first appeared in the United States Midwest, moved to the east coast, then from America to Europe along with the troops, alit in Spain, and spread exponentially from there. All this was at a time when travel was still relatively slow. In 1918, that journey took months; today it would take hours.

Like its filovirus cousin Ebola, Marburg virus is an African pathogen that causes severe hemorrhagic fever. Yet in 1967 it was first identified not in Africa, but in a small university town in Germany (which is how the virus got its name) (Slenczka, 1999). How did it get there? The virus hopscotched from Africa to England to Germany, in a group of African monkeys whose kidneys were to be used for tissue culture purposes. A strange disease then occurred among workers who handled the monkeys or their tissues in both Germany and Yugoslavia, killing almost a fourth of those infected. A similar episode in the late 1980s in Washington DC (involving an Ebola virus variant of no obvious pathogenicity to humans) occurred in cynomolgus monkeys and their handlers originating from the Philippines (Jahrling et al., 1990). It prompted the international best seller *The Hot Zone* by Richard Preston, vaulting emerging infectious diseases to the forefront of public consciousness (Preston, 1994).

In 1976, a new cause of pneumonia was recognized among those who traveled to an American Legion convention in Philadelphia, Pennsylvania (Fraser et al., 1977). This illness, known ever since as Legionnaires disease, had as its source the cooling system of an upscale, downtown hotel named the Bellevue Stratford. Apropos for a disease that got its start at a convention, many subsequent Legionnaires disease outbreaks have been associated with travel settings. Among the more common are hotels; others include spas, cruise ships, and flower shows (Fields, Benson, & Besser, 2002).

Travel has played a prominent role in the second devastating epidemic of the 20th century. This, of course, is acquired immune deficiency syndrome (AIDS) caused by the human immunodeficiency virus. This disease was first identified in 1981 (Gottlieb et al., 1981). While the origin of AIDS is considered to involve a virus that jumped the species barrier from great apes to humans, its subsequent spread was greatly assisted by human movement. Although details remain murky, the disease clearly spread from its origins in central Africa by road, hitch hiking with long-haul truckers. Movement to the western hemisphere may have been facilitated through persons who went to Africa like workers from Haiti and soldiers from Cuba. North American visitors to Haiti, which was then a popular tourist destination, carried the disease from the Caribbean back home with them. Once HIV emerged in places like Thailand, its global spread was furthered by the large-scale sex tourism industry of the 1980s and 1990s in that country. The international spread of HIV could be documented because of clades (or subtypes) of the virus, which appeared in different locations (McCutchan, 2000). In a number of small, isolated locations like Pacific island countries, the first appearance of HIV was often linked to locals who had traveled abroad for school

or work. The long latency of HIV before the appearance of symptoms gave ample opportunity for this virus to spread undetected via population movements and tourism. Unfortunately, the disease burden of HIV continues to mount. At last count, more than 65 million persons have been cumulatively infected and more than 25 million have died (UN AIDS, 2006).

South America was cholera-free for almost the entire 20th century. But in 1991, the disease suddenly appeared in several areas of coastal Peru almost simultaneously (Swerdlow et al., 1992). From there, cholera quickly spread throughout the entire continent of South America, into Central America, and as far north as Mexico, over a brief period of less than two years. Almost 1.3 million cases were recorded over the next decade, with close to 13,000 fatalities (Pan American Health Organization, 1991–2002). It took many years and billions of dollars in sanitation improvements to bring the disease under control in affected areas. Although some have suggested that this outbreak was a natural event related to movement of the organism on sea-currents, a more likely explanation is that it was introduced in ballast released from a ship traveling from a cholera-endemic area. Its subsequent spread was aided by the absence of population immunity, but it was travelers and movement of goods that rapidly spread the organism. Infections linked to air travel and to foods were well documented.

The last major infectious disease event of the 20th century, and the first naturally occurring ones of the 21st century, illustrate the powerful role movement and travel now play in the emergence of infectious diseases. In August of 1999, a cluster of encephalitis cases was identified in New York City. This human cluster occurred at the same time bird die-offs were reported in the region. Investigations found that the human and avian outbreaks were linked and the causative agent was identified as West Nile virus, an arbovirus never previously seen in the western hemisphere (Asnis, Conetta, Texeira, Waldman, & Sampson, 2000). Over the next five years, the virus methodically marched across North America, reaching the Pacific coast in 2004. In its wake, it has caused hundreds of thousands of infections, almost 25,000 illnesses, and close to 1,000 deaths in the United States and Canada. It has reappeared annually in all areas that it has invaded, suggesting it is a permanently entrenched part of the microbial flora in North America. It has also progressively moved south and has been identified in Central America, the Caribbean, and as far south as Argentina.

How West Nile virus moved from its natural range (Africa, the Middle East, Europe, and Western Asia) to North America remains a mystery. Studies showed that the virus found in New York City was closely related to one identified a year earlier in the Middle East, suggesting this as the source of introduction (Lanciotti et al., 1999). All subsequent West Nile viruses in North America have been clonal descendants of the 1999 New York strain, suggesting a single discreet introduction. Possible explanations include movement of infected mosquito vectors on a plane or in cargo or movement of an infected bird (intentionally or naturally), animal, or human. The latter two explanations are less likely, as mammalian West Nile viremias tend not to be high enough to allow back-transmission to biting mosquitoes. Regardless, movement of something from the Old World to the New World was surely involved. Bird movement is thought to explain the steady westward migration of the virus. Travel-associated disease has been a feature of West Nile since 1999, being reported in persons traveling to North America and in North Americans traveling from uninfected to infected areas. This episode serves as a stark reminder of how easy it now is for vector-borne pathogens considered to be geographically specific to move to new locations.

In the spring of 2000, the annual pilgrimage (Hajj) to Mecca took place. This event is the single largest annual gathering in the world; millions of travelers from throughout the Muslim world participate. Pathogens have been known to also make the pilgrimage, causing outbreaks during the event and disseminating from the event. The 2000 and 2001 Hajjs were no exception. The pathogen was *Neisseria meningitidis* W135. As a result of previous episodes of meningococcal disease at the Hajj, the Saudi government required all pilgrims to be vaccinated. However, while the U.S. vaccine produced immunity against four types (A,C,W135, and Y), the European vaccine only protected against types A and C. After the event, pilgrims returned home carrying the Hajj-specific W135 strain and sparked outbreaks (in themselves or in contacts) in at least 11 countries, mostly locations where the pilgrims had not been protected against W135. These outbreaks resulted in more than 300 cases of disease in both 2000 and 2001, with a mortality rate of approximately 25% (World Health Organization, 2002). There is strong evidence that the dissemination of W135 from the Hajj into a number of locations, especially the African meningitis belt, altered the usual distribution of circulating meningococcal types over the next several years (Traore et al., 2006).

Severe acute respiratory syndrome (SARS), which was recognized in early 2003, was through-and-through a travel-related disease. The pivotal event occurred on the weekend of February 21st, when a medical professor from Guangdong China, and his wife, traveled to Hong Kong to attend a family wedding. This professor had been caring for persons with a mysterious new disease, and despite not feeling well, elected to attend the wedding. The couple stayed on the 9th floor of the Metropole Hotel in Hong Kong. Although the professor attended the wedding, he was otherwise too sick to do much else while in the hotel. He died in a Hong Kong hospital shortly after the wedding (Centers for Disease Control and Prevention, 2003).The majority of subsequent SARS outbreaks can be directly linked back to ten other guests who stayed at the hotel (all but one on the 9th floor) that same weekend. After they were exposed in unknown fashion, these guests flew to Canada, the United States, Ireland, Singapore, and Vietnam, while some remained in Hong Kong. In several instances, prolonged chains of transmission involving hundreds of cases were the result. Movement of infected persons resulted in a small outbreak in Thailand and of diagnosed illness in Germany. Air travel from Hong Kong caused the spread of disease to locations in Mainland China and Taiwan. Beijing was hit especially hard. Ultimately 8,096 cases and 774 fatalities were diagnosed in 30 different countries (World Health Organization, 2003a). Transmission was documented on several transportation modes, including commercial planes, taxis, and trains. Absent specific medical interventions, the disease was eventually brought under control through a concerted global public health effort that included intensive surveillance and screening procedures, isolation and quarantine, travel restrictions, and barrier precautions. The outbreak resulted in severe disruptions to the global economy, to travel, and to commerce (World Health Organization, 2003b). Every part of the world was affected, either directly or indirectly. The last documented SARS case was in 2004; the potential for reintroduction and subsequent spread through travel is unknown.

Among today's infectious disease threats, none has engendered more concern than the potential for a pandemic due to the emergence of human disease related to avian influenza subtype A (H5N1). Human infection was first recognized in 1997 in Hong Kong, when 18 cases and six fatalities occurred (Yuen et al., 1998). At that time, the poultry and human

outbreaks were aborted through the destruction of all poultry in the territory. In 2003, H5N1 reemerged in Vietnam and China. Since then, the virus has spread widely, mostly through poultry movement and in migratory birds. Movement of the virus in smuggled birds has been documented (Van Born et al., 2005). Avian disease due to H5N1 has now appeared in more than 50 countries in Asia, Europe, and Africa (World Health Organization, 2006a), either killing or requiring the destruction of hundreds of millions of birds.

In humans, H5N1 has caused a severe disease marked by fulminate respiratory failure and pneumonia (WHO, 2005). More than 250 human cases have been confirmed by the World Health Organization in 10 countries, with the largest numbers in Vietnam, Indonesia, Thailand, China, and Egypt (World Health Organization). The median age of affected persons has been 20 years (range 3 months to 75 years), and overall mortality has been close to 60% (World Health Organization, 2006b).These factors qualify this virus as one with high pandemic potential. It has already met two of the three criteria generally associated with a pandemic strain. First, it is an unusual influenza subtype, never having been associated with human disease prior to 1997. Second, it causes unusually severe disease. To date, the third criterion, that the virus easily spreads from person-to-person, has not been met. Virtually all human cases have had direct or close contact with sick and dying poultry. Although several clusters either confirmed as, or strongly suggesting, person-to-person transmission have been identified, none have shown sustained human-to-human spread (Wong & Yuen, 2006). If this occurs through virus mutation or recombination, a pandemic would be virtually assured, since there is virtually no population immunity in humans against the H5 subtype. Although no one knows how severe the pandemic would be, H5N1 human disease presently exhibits some of the characteristics seen with the 1918 Spanish flu, especially its predilection to affect healthy young adults.

Health authorities around the world have voiced concern that H5N1 could trigger a 1918-type pandemic, even though we have tools at our disposal like antiviral drugs and vaccines that were unavailable a century ago. However, the ability for rapid global dissemination of an easily transmissible strain (a la SARS) through travelers also did not exist a century ago. While to date travelers have not figured in the epidemiology of H5N1 human disease, this situation is unlikely to continue, even given the present limited person-to-person spread. Should the virus acquire the capacity for such spread, travel will without question be a critical factor in its dissemination.

In spite of the medical and technologic advances of the last century, there is every reason to think that the patterns of infectious disease emergence seen in the 20th century will continue to be replicated in the 21st century. If anything, movement will play an even more prominent contributing role to this phenomenon, resulting in widespread, multinational outbreaks *a la* meningococcal disease from the Hajj and SARS. This is because the number of people traveling, the volume of international commerce, the size of conveyances, and their speed, will continue to rise. Microbes will continue to be unwitting hitch-hikers on this global (and may be even extra-terrestrial) merry-go-round. How we deal with these trends, whether through improved global monitoring of travelers, improved detection methods, and better prevention and control measures, will in large part determine whether we humans are able to maintain our equilibrium with the ever-changing microbes that cohabit our world.

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