

# SCOR Papers

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## The Globalization of Infectious Diseases

### Abstract

*In a globalized world with rapidly evolving ways of life, the monitoring of emerging infectious diseases is becoming even more important. Recent epidemics, such as HIV/AIDS, SARS and H1N1, highlight patterns of emergence and propagation that will likely be repeated. Only strict monitoring and strong action can help to prevent the occurrence of an event such as the 1918 flu.*

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Infectious diseases have played an important role throughout history. Perhaps the earliest mention is the Black Death in the 14th century. In actuality, the Black Death's origins are much earlier, dating back to the reign of the Byzantine Emperor Justinian, 800 years earlier.

Diseases have emerged and mostly waned throughout history: Yellow Fever and dengue – two viral fevers – and their mosquito vector, *Aedes aegypti*, have spread throughout the world since the 1600s and continue today predominantly in areas of Africa and South America. Waves of cholera spread from the Old World to the New in the 19th and early 20th Centuries by steamships, a process that again continues today in a slightly different way, through the ballast water of ships.

So the phenomenon of infectious disease contagion is not new, but the magnitude and speed at which these infections spread arguably are, enabled by increasing globalization. This is often one of the unintended consequences of technological and societal advances.

Despite the material mortality and morbidity consequences, society has more or less addressed infectious diseases casually. Some of this complacency is driven by prominent interventions – the antibiotic era, immunizations, improved public health measures – all of which have led to people in developed economies living longer and dying of chronic, not infectious, diseases. Unfortunately, this has not been true in many developing countries. In much of the world, infectious diseases remain the major causes of illness and death.

## 1. The Impact of HIV/AIDS

HIV/AIDS was, of course, the infection that drew significant attention in the West initially and increased awareness about the potential lethality of contagious diseases. The HIV infection and AIDS started from obscurity, but became the leading cause of death in the United States by 1994.

Molecular examples of HIV were actually available in Zaire as early as 1969, but that was a virtually unique finding. In the 1970s, there were reports of a few cases in Africa, but these rarely made news. Its discovery in the US in the early 1980s grabbed everyone's attention and, in fact, surpassed all other causes of death in healthy young people.

HIV, of course, was quite a surprise: it spread quickly, was lethal, and its source – at least at the beginning – was unknown. In a sense it seems like the real-world intersected with the science-fiction classic *The Andromeda Strain*. We had thousands of years of experience with infections, some of them historically recorded in some detail. Some of them are still unidentified, and we still argue about what they were. But a disease that actually kills by undermining the immune system directly was a novel mechanism of pathogenesis. How often does one find a new mechanism of pathogenesis in a disease that, clinically, appears in contrast to the thousands of years of experience that we have had? Its discovery was quite remarkable.

Since then, the contrast has been dramatic. Thanks largely to the fact that a few effective drugs were finally developed, including in particular the protease inhibitors, incidence of HIV has plateaued and is now decreasing. It is now a treatable disease, with many lives saved among those who can afford the medication.

But the disease remains worrisome. Virologists have already identified growing antiviral resistance in some patients. Perhaps more worrisome, the advent of interventions has led some younger people to regard HIV/AIDS with less seriousness than those who lived through the scare in the 1980s might, unaware of the devastation the virus caused before effective treatments were available. So society has come full circle, facing complacency again.

If there is a bottom line to the theme of this discussion, it is that society can no longer afford to become complacent. In much of the world, infectious diseases remain major causes of disease and death, even if we sometimes seem unaware of this.

### **The Effects of Pandemic**

The 1918 Spanish Flu is an example of a nightmare scenario involving an emerging infectious event. It may very well have been the greatest natural disaster in history. Even today, the death toll associated with this pandemic – which happened almost a century ago – keeps going up as investigators uncover data from nations further from its pathogenesis, in developing countries and more remote places. But that pandemic (by definition, a global epidemic) is estimated to have caused at least 50 million deaths, depending on various sources. Repetition of such an event, even on a smaller scale, is obviously a matter of great concern.

## 2. Re-Emerging vs. Emerging Infections

Of course, forgotten or controlled infections may reappear. These are sometimes referred to as re-emerging infections. In today's highly mechanized modern societies marked by relatively high standards of living, these infections have been pushed to the margins but have never been entirely eliminated. When public health measures are relaxed or are abandoned because of higher priorities, lack of money or complacency, the forgotten infections reappear, as diphtheria did in the former Soviet Union and Eastern Europe, when they could no longer financially maintain their immunization programs. Events such as this should remind us that although many of these diseases may be forgotten, they have not been eliminated.

In contrast are emerging infections, ones that are not previously recognized and seem to appear suddenly or mysteriously as in The Andromeda Strain. A proper definition of emerging infectious disease could be: those infections that are rapidly increasing in incidence or geographic range.

In some cases, these are novel, previously unrecognized diseases. But, as discussed below, many of them are not of The Andromeda Strain variety. They don't come from space. In many cases, they have existed in nature for some time. Very often, anthropogenic causes – often unintended consequences of societal development – are important to the emergence of these infections.

There are many examples – Ebola, Hantavirus pulmonary syndrome (discussed more below), Nipah, which originated in fruit bats, SARS and, of course, influenza, whose adaptability still continues to surprise us. In a way, one could consider these and other infections as stars in the sky, “a thousand points of light.” But they are actually more like many little fires all over the world, most of which epidemiologists did not recognize before they became big brush fires: for example, the introduction of the West Nile virus to the United States in 1999, enteropathogenic *E. coli* etc.

Ebola is another case in point. From 1976 on, when it was detected for the first time in Congo-Zaire, Ebola left a trail of smoldering fires that quickly blew out because of the high lethality rate. Suddenly, in 2014, a wildfire of infection spread in West Africa (first case in December 2013, misdiagnosed at the time). Ebola used to be a bush epidemic, and now it was hitting urban zones too.

The alarm caused was maximum. The “deadliest Ebola outbreak the world has ever seen”, to quote Médecins sans Frontières, wreaked havoc in three countries, Guinea, Liberia and Sierra Leone, destroying lives and families, casting a blight on the already very poor health services and even putting in danger the security of the state. In one year, Ebola killed more than 10,000 people, whereas the same virus had killed 2,000 individuals in the preceding four decades. Despite weeks of panic in the West, international action proved rather defective and tardy. The World Health Organization, in particular, suffered lasting discredit and now appears to be crying out for reform.

## 3. Disease Emergence

The process of infectious disease emergence can be broken down into two steps for analysis:

- Introduction – where these “Andromeda-like” infections originate; and
- Establishment and Dissemination, which fortunately for us is much harder for most of these agents to achieve.

The basic lesson here is that many may be called, but few are chosen.

In this two-step process, the “opportunities” for a pandemic event are increasing, thanks to ecological changes and globalization, which give the microbes greater opportunities to travel and to do so very quickly. Even medical technologies have played an inadvertent role in helping to disseminate emerging infections.

### *Introduction*

Perhaps the most mysterious step – one hopefully demystified a bit here – is Introduction. Many of these infections, exotic as they may seem, are often zoonotic: infections of other species that pass to humans. Some of these transfers are relatively benign. Some of them cause no impairment at all. However, some can cause truly dramatic conditions, like Ebola.

This zoonotic pool is a rich source of potential emerging pathogens. So much biodiversity exists, including a tremendous biodiversity of microbes. Some unknown amount of that biodiversity remains untapped.

Changes in the environment may increase the frequency

of contact with a natural host carrying an infection, and therefore increase our chances of encountering microorganisms previously unknown to humans. Of course, the role of food animals, as well as wildlife, has come very much to the fore in recent years.

A number of ecological changes, many of them anthropogenic, provide new opportunities for pathogens to emerge and gain access to human populations. These bacteria, viruses and other organisms may be considered as microbial explorers, discovering new niches – humans – and exploring new territory. Examples associated with environment-based transference activities include agriculture, food-handling practices, and, for the vector biologists, changes in water ecosystems.

#### *Evolution at work*

In addition, evolution has played an important role. Evolution almost by definition continually leads to the biodiversity of pathogens that develop independently in nature. Conceptualizing the vastness of biodiversity can be challenging, even within a single genus. We don't know how many viruses humans are exposed to, or even how many inhabit the typical human at any given moment.

Analysis of herpesviruses, which have been subject to numerous studies, can provide some context. Eight human herpesviruses are known to exist, and at least six of them are ubiquitous in the human population (the exception being Human herpesvirus 8, which causes Kaposi's sarcoma).

Herpesviruses can be found worldwide. Several of them are present at very high rates in the human population. Again, these herpesviruses discussed here are present exclusively in humans. Other herpesviruses exist for other species. This indicates a high level of co-evolution between host and pathogen.

Additionally, these organisms have demonstrated the ability to adapt to new hosts and environments through natural selection. The most notable example is influenza, but many others – the coronaviruses, like SARS – exist as well. Of course, antimicrobial resistance has been mentioned many times and offers one of the rare examples where the real world can be replicated in vitro, just on a different scale.

*Globalization at work – Hantavirus pulmonary syndrome*  
Hantavirus pulmonary syndrome was one of the first infectious outbreaks to happen suddenly in the United States after the original Institute of Medicine (IOM) Emerging Infections report was published in October

1992: during the spring and summer of 1993, Hantavirus pulmonary syndrome suddenly appeared in the US Southwest. Starting in the late spring of 1993, people started appearing at emergency departments and clinics with respiratory distress. Many of them were hospitalized. The case-fatality rate was about 60 percent, even with treatment. It's a little lower now, but still high, near 40-50 percent.

The health departments conducted a typical investigation:

- There was a pocket of plague in that area, so the local health departments tested for it
- Another possibility was influenza out of season. These and other likely possibilities were ruled out
- The state health departments then called in the Centers for Disease Control (CDC), which performed a number of tests and identified, perhaps surprisingly, a Hantavirus as the most likely culprit

This was tested both by serology and, later, by Polymerase Chain Reaction (or PCR), a technology in molecular biology used to create millions of copies of DNA strands quickly. Rodents are the most common carriers of Hantavirus. Thus, a number of rodent species were trapped near patients' homes and tested.

The most frequently trapped rodent was apparently also the most frequently infected: *Peromyscus maniculatus*, the white-footed deer mouse. This mouse is local to the area and is prolific, making it essentially the major wild rodent in this region.

Once the origin was identified, a test was developed and clinicians were alerted to look for the virus. They discovered the virus in a number of other places, including serum and tissue samples from deceased patients whose cause of death was unknown but odd – in cases of acute respiratory distress for example. Some cases also occurred outside the range of *Peromyscus maniculatus*, which were traced to natural infections of other rodent species.

Before 1993 the US had reported one known case of Hantavirus, which was not associated with human infection (Prospect Hill virus). Another variant appeared in rats, the Seoul virus and related variants that could be found in port cities, but these are not associated with major disease. Doctors in 1993 added the first Hantavirus that affects humans: the virus that causes Hantavirus pulmonary syndrome. Once the medical community started looking for Hantaviruses, there was no shortage



of previously unrecognized Hantaviruses. Throughout North and South America, an entire string of Hantaviruses were discovered that nobody had known even existed.

Most if not all of these Hantavirus variants likely had long been present. Their diversity represents evolution at work, though exactly how long these types have been evolving is not clear. It's possible that specialization could have begun as far back as 2 million years ago, when the numerous rodent species separated, though mammalogists may be able to shed more light on this.

Some of these viruses have been associated with human disease. Many others have not. As with the emergence of HIV, it first seemed that Hantavirus was an orphan, but, of course, it has its relatives; they just haven't been discovered yet.

But this example indicates that an emerging infection can occur anywhere. Even dry and arid areas of the world that seem to be inhospitable to life, such as the US Southwest, have their share of infectious diseases, different from the rainforest but just as significant. Infections are now shifting from one part of the globe to another very rapidly. In the spring of 2014 the Chikungunya virus reached Puerto Rico: an East African parasite is now thriving in the Caribbean (there would be also cases in Polynesia). Moving easily across continents, masses of people bring mosquitos and microorganisms along with them. Gone forever are the days when to bound an epidemic within a

As another brief example, monkeypox is generally considered to be "exotic." It is a virus found in African forests and is a close relative of smallpox. Despite its name, its natural reservoirs are actually rodents. Given this natural habitat, discovering a case in Wisconsin (and in five other Midwestern states) in 2003 was surprising. Even more interesting was how it got there: through the trade in exotic pets.

geographically narrow zone was deemed possible.

#### *Avian sources - Influenza*

Recently virologists have been considering respiratory viruses a great deal. Some of our most serious historical examples – influenza, measles, smallpox, and many others – have been respiratory viruses. Right now the recent H1N1 influenza pandemic is very much on our minds, as well as avian flu.

The increasing opportunities – and rates – of globalization in fact can be illustrated by pandemic influenza. Flu may be familiar, but should not be taken for granted. Clinicians

who work with it view it with great respect. The 1918 pandemic is one reason.

Although general mortality trends have been downward, there are no guarantees. Several flu pandemics have been documented in the last century beyond the Spanish Flu. Still, the 1918 pandemic was by far the worst. It took several years to circumnavigate the globe.

The Asian flu of 1957 (as it happened, this author lived through the next two 20th Century influenza pandemics) was particularly virulent, to put it mildly, but was nowhere near as destructive in terms of attributable deaths as the 1918 flu.

Later, the pandemic Hong Kong flu of 1968 appeared but was relatively mild compared with the 1918 and even 1957 flu outbreaks (and even more so in comparison to the H1N1 of the past year, whose full story is yet to be told). Other pandemic events have occurred along the way: the reappearance in 1977 of the "old" H1N1, and the famous swine flu case, about which IOM president Harvey Fineberg wrote when he was at Harvard (since dubbed "the pandemic that never was").

Many photos – the high technology of the time – show graphically the impact that an outbreak like the 1918 flu can have. The CDC has since recalculated the case-fatality rates to today's population to estimate the expected deaths under a similar scenario. If it happened with today's population, a 1918-like pandemic would probably cause almost 2 million deaths in the US alone. An outbreak similar to the 1957 or 1968 pandemic, much milder pandemics, could cause around 100,000 deaths. In any case, the flu is not something to take lightly.

Novel or new genes tend to come from avian sources that reassort, somehow, often with mammalian genes. In other cases the virus sometimes may transfer directly from avian to human, although that seems to be a relatively rare event.

Pandemic flu begins its globalization by emerging from other animal species. Rob Webster and Virginia Hinshaw discovered in the 1970s that water fowl appear to be natural reservoirs for influenza viruses. Therefore, there is certainly open territory for influenza virus dissemination along any of the Old World migratory paths.

As a result of all of those movements of birds, for both migratory fowl and domestic poultry, a number of outbreaks of H5N1 avian influenza have occurred, starting in Asia and extending into Europe and Africa as well. There have been some human cases, mostly (although

not all) occupational, and with a high case-fatality rate. Fortunately, only a few instances of human-to-human transmission have been recorded so far, all apparently quite limited. Obviously everyone is monitoring this closely, just in case there is a change in the H5N1 virus's ability to transmit from person to person. If this virus were able to infect people readily and transmit itself as well as ordinary seasonal influenza does, then it could well become a pandemic.

Could the currently pandemic H1N1 and the rather limited H5N1 combine, to create a really deadly pandemic? Honestly no one knows. Like earthquakes, influenza pandemics happen, but also like earthquakes so far nobody in this business can predict exactly when, where or with what magnitude. The only people who claim they can, at least as of now, are either charlatans or great risk takers.

The H1N1 pandemic is an example of how easily influenza can still fool us: while we had our eye on chickens in Asia and H5N1 (and wisely so), we didn't notice H1N1 emerging from (apparently) pigs in North America. Even the very origin of a flu pandemic in the Western Hemisphere flies in the face of established expectation: flu pandemics traditionally originate in Asia.

## 4. Establishment and dissemination

The second step in emergence is establishment and dissemination. Luckily, this is much harder for a pathogen to accomplish. Many infections that can infect humans from time to time may not have a good method of transmitting or propagating themselves. Society has helped in this regard – HIV, for example – and provided some paths for “microbial traffic”: pathogens moving into new areas or new populations.

Environmental changes can be important as well. It used to take a long time for a person to travel around the world. Now it can be done within 24 to 48 hours, with proper timing between flights. If the frequent flier doesn't make all the connections, as often happens, then they spend time in a usually crowded airport, where they will have even more opportunity to infect others.

### *Dissemination – SARS*

Consider SARS. Ironically, right before the SARS outbreak, Hong Kong launched a new promotional campaign with the slogan “Hong Kong will take your breath away.” Perhaps they are good prognosticators

of flu and other respiratory disease outbreaks. They certainly have had much more direct experience.

The spread of SARS was a remarkable event. One infected individual – a physician, in fact – from south China treated a patient, along with several others, who had an unusual pneumonia. Clinicians usually assume community-acquired pneumonia is not very transmissible. In this instance this assumption turned out to be a major mistake. The physician then travelled to Hong Kong, where he stayed at the Hotel Metropole, a popular business hotel, and became sick.

He believed he had the same disease that had killed the patient he had treated earlier. He went to the hospital, told his health care providers about his odd patient, and warned them to be careful. Apparently they didn't heed his advice: 99 health care workers were infected in Hong Kong. At the same time another dozen people were infected in the Metropole. This dispersion is what was responsible for the dissemination of SARS essentially worldwide.

SARS actually created a few near-misses that could have made the infection even more widespread. A New York businessman travelled to Vietnam but didn't return directly to New York. A doctor from Singapore did travel to New York, but didn't present symptoms until he was on his way home. He was quarantined in Germany.

However, the consequences of SARS on global travel were enormous. The usually bustling Hong Kong airport was deserted at the height of the pandemic. Ten years later, MERS (Middle East Respiratory Syndrome) would cause analogous disruptions. The infection spread as of the spring of 2012 over the Middle East (mainly Jordan and Saudi Arabia). Between spring 2012 and winter 2015, there have been 502 deaths out of 1,413 confirmed cases. Compared with SARS, MERS appears more lethal (35 percent) while being less contagious. The infection hit South Korea in June 2015. Out of 182 confirmed cases, 32 patients died. Despite a lethality rate lower than expected (17.6 percent), the Seoul authorities panicked. More than 2,000 schools were closed, and 3,439 people were quarantined. China became fairly nervous (the first confirmed case was detected in Guangdong on May 29), planning to close its borders to possibly infected people coming in from South Korea or the Middle East. Like SARS, MERS is a rather politically sensitive disease. In order not to frighten pilgrims, Saudis were prone to deny the spread of infection, at least during the first ten months, when the epidemic rambled over the Peninsula, whereupon they showed a more open attitude towards international cooperation.

### *Tracking the vector*

ProMED-mail is a listserv for the reporting and discussion of emerging infections. A little item appeared in February, questioning whether something odd was going on in China due to reports of deaths. The next day China reported 305 cases of SARS.

Yi Guan, as first reported at an IOM Forum meeting on SARS a few years ago, actually uncovered earlier cases, documented to at least November, 2002, involving several different cases in perhaps five cities in south China. But they weren't reported or recognized at the time.

He conducted a survey and determined that animal slaughterers and wild animal handlers had a much higher chance of becoming seropositive. The link to humans was determined to be *Paguma larvata*, the palm civet, which is a prized food animal in south China, particularly during the winter. It appears that the civets became infected in the live animal markets, probably from contact with bats (according to work by Peter Daszak and colleagues). Wild-caught and farmed civets that were tested were all negative for the SARS coronavirus.

Eventually SARS reached Canada, and created heightened epidemiological concern. In total, there were about 8,000 SARS cases, most of them in the original area in Asia, but a few in other scattered places. SARS is attributed as the cause of 700 deaths, or about a 10 percent case-fatality rate, which is quite high. The SARS outbreak also marked the first time the World Health Organization (WHO) had acted aggressively. As a result, they were able to effectively solve some of the scientific and disease-control problems.

HIV presents a similar story. We don't know how it entered the human population, though it may have been through a similar mechanism. The virus originated in chimpanzees most likely, and humans may have become infected by preparing or handling infected non-human primates for the "bush meat" trade.

Hospitals also provide opportunities for spreading infections. For example, contaminated injection equipment can be important in transmission. Most of the Ebola cases developed in this way.

## Conclusion

Some recognizable factors, such as ecological factors or globalized travel and trade, contribute to the spread of infectious disease. This was the framework used in the original IOM report. These factors have since been augmented and refined in the new version of the IOM report in 2003, but in general the newer version retains the same findings.

We know what is responsible for pandemics. The question then becomes: what are we going to do about it? One thing that can help is better surveillance. We can also consider whether we can focus efforts on "hotspots," areas where the key factors in terms of emergence are most active.

The reality is that we need better early-warning systems and more effective disease control, to be implemented without delay.

To summarize:

- Several factors are responsible for the emergence of infectious disease;
- Interspecies transfer is often responsible for or facilitates infectious disease transmission;
- We do things (anthropogenic changes) that often increase the risk of transmission, by altering the environment and interposing ourselves into an environment with pathogens unfamiliar to humans.

We can manage those risks in some ways using our wits. You could ask, what should we be doing to make the world safer? Effective global surveillance is one answer, along with better diagnostics, the political will to respond to these events, and research to help understand the ecology and pathogenesis of these "new" infections and to help develop effective preventive or therapeutic measures.

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