



Emerging Infections and Future Threats

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ABSTRACT

Emerging infections represent a concern especially when their increase is rapid and their mortality is high. They can be caused by previously undetected or unknown pathogens, by known agents affecting new geographical sites or new populations, or by re-emerging agents whose incidence of disease had significantly declined in the past. The main causes of emerging infectious disease (EID) spread include crowding; mobility (tourism, migration, asylum seekers, and refugees); centralization of food production and supply and new food vehicles; war, famine, and displacement; and change in vector distribution and susceptibility. Another important issue regarding EIDs is the source of pathogens, with 60.3% of cases from a non-human animal origin (zoonotic pathogens). If emerging viral infections represent a concern mainly in underdeveloped areas of the world, the emergence of antimicrobial resistance is a growing concern worldwide especially in developed and high-income countries, where misuse and overuse of antibiotics among humans and in the veterinary setting, including animal feeding, artificially created the selection of resistant strains. Future threats include not only diseases caused by viral agents, such as the case of Ebola virus disease periodical re-emergence, but also infections with antibiotic-resistant bacteria. It is estimated that in 2050, deaths due to antimicrobial-resistant infections will be higher than those due to cancer.

Keywords: Emerging infections, ebola virus disease, antimicrobial resistance, zoonosis

INTRODUCTION

The history of humankind has been greatly determined by infectious diseases. In the past, epidemics of plagues and undetermined infections have changed the face of the world. The Black Plague, one of the most ravaging pandemics in human history, resulted in an estimate of 75–200 million deaths in Europe and Asia, peaking in Europe from 1347 to 1351, finally killing approximately 30% of the population (1).

In the past century, there was a decline in infectious diseases, including cholera, tuberculosis, and smallpox, due to vaccination, clean drinking water, improved sewage system, and a wider improvement in living conditions and social infrastructure. Indeed, a decrease in infectious diseases was strongly related to a decrease in host susceptibility and in disease transmission. Host susceptibility was in turn decreased owing to better housing, better nutrition, and use of antibiotics as seen in developed countries in the past century (2).

In the beginning of the second half of the past century in developed countries, there was an optimistic wave about the defeat of infectious diseases; this optimistic attitude was mainly determined by the introduction of antibiotics, immunization, and a better quality of life. As seen many times in history, things went differently. A series of outbreaks and epidemics, emerging infections, and the appearance of resistance to antibiotics proved that the war was far from being won.

The Ebola virus infection epidemic in 1976 in central Africa, the Legionnaire disease epidemic in 1977 in Philadelphia, and the human immunodeficiency virus (HIV) pandemic in 1981 first identified in San Francisco were the alarm bells that infectious diseases were far from being eradicated. Moreover, another challenge was represented by the fact that these diseases occurred in both developing and developed countries, thus indicating that much was still unknown about infectious diseases. A new world became familiar to scientists and media, i.e., “emerging infectious diseases,” largely occurring because of changing demographics and behaviors, changes in industry and technology, change of environment and land use, international commerce and travel, collapse of public health measures, and microbial adaption and changes; all of these conditions were linked to industrialization, urbanization, globalization, and political/economic changes seen in the last decades (2). The 2013 Ebola virus outbreak in West Africa was indeed sustained by a change in travel, urbanization, and economic conditions; previous Ebola virus outbreaks were bound in rural villages and terminate quickly. During the 2013 Ebola epidemic, owing to scarce health infrastructure in their villages and a wider attitude to travel, sick people were more prone to migrate from rural villages to big cities, thus determining a wider spread of infection. In those conditions, poor, crowded city provided an “ideal incubator for outbreaks” (3).

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EIDs

The definition of emerging infectious disease (EID) is complex because it includes the following:

- events caused by newly evolved organisms, such as multidrug-resistant tuberculosis and plasmid-mediated colistin-resistant Gram negative bacteria;
- organisms that recently emerged in the human population for the first time, such as HIV-1 infection in 1981, severe acute respiratory syndrome (SARS) coronavirus in 2003, and Middle East respiratory syndrome caused by a novel coronavirus (Middle East respiratory syndrome coronavirus or MERS-CoV) that was first identified in 2012 in Saudi Arabia;
- pathogens present in humans historically, but with a recent dramatic increase, such as Ebola virus disease (EVD) in Western Africa in 2014.

The main causes of EID spread include the following (Table 1):

- crowding: this is valid for both community (SARS and MERS-CoV) and healthcare-associated infection;
- mobility that includes tourism, migration, asylum seekers, and refugees. Travel can model infectious disease dynamics by introducing potential pathogens into susceptible populations or by modifying the rate of contacts and exposures between infected and susceptible individuals, such as HIV, tuberculosis, and multidrug-resistant organisms;
- centralization of food production and supply and new food vehicles, such as *Cyclospora cayentanensis* outbreaks linked to fresh express salad mix sold at a chain of restaurants in the US in 2018 (<https://www.cdc.gov/parasites/cyclosporiasis/outbreaks/2018/b-071318/index.html>) and hemolytic uremic syndrome clusters of cases caused by Shiga toxin-producing *Escherichia coli* O157 in Germany in 2016–2017 possibly associated with packaged minced meat consumption (4);
- war, famine, and displacement: infectious diseases ruthlessly exploit the conditions created by these circumstances. War often determines a deterioration or a stop to ongoing prevention and control programs, and as a consequence, an increase of infectious diseases highly dependent from these programs occurs (5). This is the case of the re-emergence of malaria by *Plasmodium falciparum* in Afghanistan, trypanosomiasis in the Democratic Republic of Congo (DRC), acquired immune deficiency syndrome, and vaccine-preventable diseases, such as measles (5);
- change in vector distribution and susceptibility: the emergence of Zika and the spread of dengue, chikungunya, and West Nile fever in countries were not present in the past, clearly documenting an ecological change especially involving vectors.

Jones et al. (6) reported the emergence of 335 infectious diseases in the human population between 1940 and 2004. Viral agents, especially RNA virus, such as Ebola, pose a major threat owing to the high rates of nucleotide substitution, poor ability of mutation error-correction, and, as a consequence, better capacity to adapt to humans (7). EID events in the last decades were due mostly to bacteria, i.e., vancomycin-resistant *Staphylococcus aureus* or

Table 1. Main causes of emerging infectious disease spread

Crowding in the community and healthcare setting
Mobility: tourism, migration, asylum seekers, and refugees
Centralization of food production and supply and new food vehicles
War, famine, and displacement
Change in vector distribution and susceptibility

rickettsiae (54.3% of cases) (6). Indeed, viral and prion pathogens constitute only 25.4% of EID events. It is likely that in recent years, this proportion has been stable owing to the spread of high multidrug-resistant Gram negative bacteria.

Sources and Mode of Transmission of EID

Another important issue regarding EIDs is the source of pathogens, with 60.3% of cases from a non-human animal origin (zoonotic pathogens). In many cases, these pathogens have a wildlife origin, such as Nipah virus in Perak, Malaysia and SARS in Guangdong Province, China. More recently, Anthony et al. presented a new framework for the discovery of wildlife novel viruses for estimating the number of viruses that exist in a mammalian host. They estimated the existence of at least 320,000 mammalian viruses to be discovered within nine families. According to an economic analysis, the cost for discovering these viruses would represent a minimal part of the total expenses owing to many pandemic zoonoses (8). This supports the suggestion that zoonotic EIDs represent a major and increasing threat to global health (9–11).

More than 10,000 years ago, in the Neolithic Age, the human-domestic animal sphere was 0.1% of the total mammalian mass, whereas currently, it is 90% (12). The transformation of the Earth's biomass has greatly conditioned the modes of transmission of pathogens, from showing only animal-to-animal transmission gradually evolving to being only human-to-human transmission (13). This transformation is hypothesized to be caused by repeated short introductions of these agents in humans, initially without the ability to sustain human-to-human transmission; for HIV, this “viral chatter” has been estimated to be consistent in at least 10 entries (14).

Another interesting chatter occurred in the 2002 SARS epidemic. In this outbreak, the viral agent was introduced into humans from civet cats that represent a “bushmeat” sold for human consumption, with approximately 4.5 million tons of bushmeat sold from West and Central Africa annually (15). However, the original reservoir was not the civet cat, but the horseshoe bat (16). Bats harbor many viruses that can sometimes infect people, including Ebola and Marburg; genetic studies of viruses from horseshoe bats in one cave in China suggested that the animals are reservoirs of SARS coronaviruses (17).

Another interesting model of “viral chatter” is represented by Henipavirus, a genus of the family Paramyxoviridae with two members, including Hendra virus and Nipah virus. Hendra virus was identified in Australia in 1994 as the cause of an outbreak of acute and highly lethal respiratory disease among horses in a racing stable, also causing a lethal disease in humans in contact with the stable (18). In the following 17 years, Hendra spilled from its natural host (fruit bat) on 14 known episodes, infecting at least 45 horses and 7 people in close contact with horses (19).

Nipah virus was first described in Malaysia in 1999 as the cause of respiratory/neurological syndrome in farm pigs with a fatal infection in attendant pig farm workers (20). In addition, for this virus, the natural host was identified in fruit bats; the difference was that the virus spilled from bats to pigs to people. Another peculiar characteristic of this virus is the possibility of transmission from bat-to-human to human-to-human. Both Hendra and Nipah viruses have a high fatality rate, sometimes exceeding 70% (19).

Viral spillover was the cause of the spread in the human population of another virus, the Rift Valley fever (RVF) virus, a member of the genus *Phlebovirus* in the family *Bunyaviridae*. This virus is transmitted by mosquitoes and blood-feeding flies affecting mostly cattle and sheep; however, humans can also become infected. During the construction of the Senegal River Project in West Africa in 1987, owing to flooding in the lower Senegal River area, ecological conditions and interactions between animals and humans were altered, resulting in a large RVF outbreak that occurred in humans and animals (21).

If emerging viral infections represent a concern mainly in underdeveloped areas of the world, the emergence of antimicrobial resistance is a growing concern worldwide especially in developed and high-income countries, where misuse and overuse of antibiotics among humans and in the veterinary setting, including animal feeding, artificially created the selection of resistant strains. Over the past decades, bacteria with specific clones expressing resistance to several antimicrobials spread worldwide. This is the case of *Enterobacteriaceae*, mainly *Klebsiella pneumoniae* resistant to carbapenems with different resistant enzymes including *K. pneumoniae* carbapenemase, New Delhi metallo-beta-lactamase 1, and other metallo-beta-lactamases. More recent pan-resistant strains, also expressing resistance to polymyxins, have been identified as the cause of severe diseases; some colistin-resistant strains had a chromosomal resistance, likely induced by antibiotic pressure, but in other cases, colistin resistance was linked to mobile elements, plasmids, such as mobilized colistin resistance. This emerging resistance represents an important concern owing to its potential for spreading among bacteria of different species; as evidenced recently in China, the environment is one of the main sources of these mobile elements, likely owing to the wide use of colistin in agriculture (22).

Surveillance of EID: A Room for Epidemiology, Diagnostics, and Clinics

The first and essential step in facing an EID is prompt recognition and identification. Before any response can be implemented, the event must be detected, recognized, and then identified as needing special attention. Detection indeed requires surveillance. Traditional surveillance systems often operate with considerable delay; syndromic surveillance systems may overcome these problems, thus providing the necessary lead time. Syndromic surveillance uses clinical characteristics that are detectable before the confirmation of diagnosis or activities suggested by the onset of symptoms as a signaling of modification of the activity of diseases. Information may be obtained from various existing sources, such as emergency department records and counter medication sales. These systems can act as an early warning system by furnishing data close to real time, thus allowing the detection of sporadic EIDs or naturally occurring outbreaks.

Indeed, the list of potential EID is alarming, and laboratory panels do not cover every potential infectious agent. Syndromic surveillance coupled with targeted diagnostic assessment is the best way for detecting EIDs. Recently, Petersen et al. described the “diagnostic pyramid” with the tip of the iceberg represented by what we know (Theranostics), i.e., diagnosis of treatable etiologies and routine and commercial applications, the submerged part of the iceberg represented by what we should know, i.e., differential diagnosis of known etiologies and less common diagnostics that may not inform the treatment, and much deeper, what we may never know, i.e., unknown pathogens, EIDs, and novel platforms for discovery (14). This is the challenge of syndromic surveillance associated with extensive diagnostic assessment. It appears unrealistic that diagnostic assessment based on syndromic surveillance should be expanded on a routine basis. However, increased surveillance and assaying for unusual infectious diseases should be developed and available, hopefully inside novel platforms that allow for a broad range of diagnostics.

Future Threats

The 2014 Ebola virus outbreak in West Africa was the widest outbreak since the virus was first discovered in 1976, with a total number of cases and deaths higher than all others combined. Indeed, a total of 28,616 confirmed, probable, and suspected EVD cases were reported with 11,310 deaths up to the end of the epidemic in April 2016, with a case fatality rate of 39.5%. The countries involved in the epidemic were principally Guinea, Liberia, and Sierra Leone; however, Nigeria (20 cases and 8 deaths), Mali (8 cases and 6 deaths), and Senegal (1 case and no deaths) were also involved (<https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/index.html>). This epidemic was also characterized by some EVD cases evacuation from West Africa to Western countries. A total of 26 cases, of which 4 were fatal (Center for Infectious Disease Research and Policy), were treated in Europe (23–25) and North America (26, 27) during the outbreak. A without equal number of healthcare workers, including physicians, nurses, housekeepers, epidemiologists, psychologists, sociologists, statisticians, experts in ethics, and especially personnel dedicated to logistics and administrative problems, from different countries and settings were involved in caring for patients with EVD. Well-renowned organizations with EVD experience provided guidelines, recommendations, and guidances on infection prevention and control and the clinical management of suspected or confirmed patients with EVD (28, 29). The EVD epidemic reminded the people of the hazards of pathogen transfer from animal reservoirs and highlighted the importance of drivers for the emergence of new infectious diseases or re-emergence of well-known ones, such as global travel and trade and demographic and climate changes. Another lesson from this outbreak was the fact that its beginning was sustained by the lack of infection control measures in the healthcare facilities where patients were admitted. EVD outbreak also pointed out the weaknesses of healthcare systems across the three countries involved (Liberia, Sierra Leone, and Guinea) and other neighboring areas, including the lack of reliable public health surveillance systems (30).

The recent EVD outbreak in the DRC further highlighted the same problems seen in the 2014 outbreak, with the addition of the challenges the government and health organizations face in tackling Ebola in an area where years of instability and war have under-

mined the locals' confidence in the authorities.

Strengthening the healthcare systems, including laboratory facilities and clinical centers, surveillance, and awareness in countries where emerging infections are more common represent some barriers for minimizing the spread of these agents.

However, the struggle is inconsistent if we do not overview the global health animal situation (One Health approach), with particular consideration to those zoonoses of particular relevance for human health (Table 2), as reported in the 86th General Session of the World Organisation for Animal Health in 2018 (<http://www.oie.int/en/for-the-media/press-releases/detail/article/state-of-play-of-the-global-animal-health-situation/>).

Moreover, there is a need to limit the use of antimicrobials in the veterinary/animal setting. Indeed, the drivers of antimicrobial resistance include antimicrobial use and abuse in human, animal, and environmental sectors. It is noteworthy that most of the classes of antimicrobials used to treat bacterial infections (cephalosporins, fluoroquinolones, polymyxins, tetracyclines, and macrolides) in humans are also used in animals as mass medication or for growth promotion (31).

The burden of infections with antimicrobial-resistant bacteria is a current and future concern. It is estimated that deaths due to antimicrobial-resistant infections will be higher than those due to cancer in 2050 (32). Recently, the European Centre for Disease Prevention and Control (ECDC) published in *Lancet Infectious Diseases* a study in which the authors estimated >670,000 infections with antibiotic-resistant bacteria between January 1, 2015 and December 31, 2015 (33). The infections caused an estimated number of >33,000 deaths. In addition, for the first time, the health burden of five types of infection with antibiotic-resistant bacteria was expressed in disability-adjusted life years that was estimated to be >870,000. The burden for the European Union (EU) and European Economic Area (EEA) appeared to be the highest in infants aged <1 year and people aged ≥65 years. The authors further stated that “the contribution of various antibiotic-resistant bacteria to the overall burden varies greatly between countries, thus highlighting the need for prevention and control strategies tailored to the need of each EU/EEA country.” As >63% of infections were associated with healthcare, it was stressed once more the importance of proper infection prevention and control measures, as well as antibiotic stewardship, to reduce the number of healthcare-associated infections. This is even more important when considering that 39% of the burden is caused by infections due to bacteria resistant to antibiotics, such as carbapenems and colistin, that represent the last-line treatment options.

Up-to-date information on EIDs is possible on the sites of the main international (World Health Organization, Centers for Disease Control and Prevention, and ECDC) and national organizations and on those of scientific societies (Program for Monitoring Emerging Diseases for the International Society of Infectious Diseases).

The European Society of Clinical Microbiology and Infectious Diseases in March 2017 established an Emerging Infections Task Force (EITaF) to evaluate the possible role of clinical virology and microbiology at the forefront of disease detection; moreover, EID preparedness, in light of the challenges posed by the budgetary re-

Table 2. Zoonoses of particular relevance for human health, as reported in the 86th General Session of the World Organisation for Animal Health in 2018

Highly pathogenic avian influenza in birds: the data collected since 2017 show that the world is experiencing a massive spread of avian influenza in animals. Accurate and real-time information is crucial to continuously monitor virus behavior.

Rabies was reported to be present in 57% of the 183 countries and territories that notified information to the World Organisation for Animal Health and continues to cost the lives of thousands of people annually mainly in Africa and Asia. A global business plan for the elimination of dog-mediated human rabies was launched in 2017 under the initiative of the “United against rabies.”

Bovine tuberculosis: in 2017 and early 2018, the disease was reported to be present in 43% of the reporting countries and territories and is distributed in every region of the world. A Roadmap for Zoonotic Tuberculosis was launched in 2017 to support the worldwide effort needed to end the global tuberculosis epidemic.

straints to laboratory medicine, was among the scope of this task-force, together with the creation of a network of infectious disease and clinical microbiology experts. Indeed, EITaF aims to establish a network of experts who can raise awareness on EID within the society and beyond, collaborate with other networks targeted on emerging diseases, develop knowledge on EID early detection and diagnosis, and stimulate research on EIDs in the field of surveillance, diagnostics, prevention, and clinical management. One of the activities EITaF had was to update the outbreak occurrence worldwide; in 2018, 38 news were posted, ranging from Yellow Fever in Sao Paulo, extensively drug-resistant *Salmonella enterica* serovar Typhi outbreak in Pakistan, colistin-resistant bacteria in humans and animals, EVD in the DRC, monkeypox in Nigeria, and Marburg in Sierra Leone (https://www.esamid.org/research_projects/emerging_infections_task_force/).

CONCLUSIONS

Mobility, people traveling much more frequently and far greater distances than in the past; living in more densely populated areas; centralization of food production and supply and new food vehicles; war, famine, and displacement; change in vector distribution and susceptibility; and more opportunities to come into closer contact with wild animals all represent a potential for EIDs, either caused by new or well-known viral agents or by antimicrobial-resistant bacteria, to spread rapidly and cause outbreaks locally or globally.

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