

Emerging and re-emerging diseases – the threat continues

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ABSTRACT

Infectious diseases have accompanied human development from the earliest times and have often influenced it greatly. Although they were considered “an endangered species” in the second half of the 20th century, they continue to pose a serious threat to individual or public health. Diagnosis technique improvement, climate changes, increased population mobility and vaccine cover decrease are only some of the factors that have contributed lately to the occurrence and fast spreading of new pathogens or to the re-emerging of diseases already considered historical. Most of these infectious agents (Zika, Ebola, Chikungunya, MERS, SARS, new influenza viruses), for which there are few therapeutic resources, were the cause for regional or global epidemic outbreaks, which generated concern among healthcare professionals and often panic in the population, as well as significant economic losses. The international and medical communities joined their forces and got financially and logistically involved, sometimes paying with their own lives, in fighting these new threats. The fast understanding of the epidemiological process, pathogenesis and development of diagnosis and prevention methods has often helped limit the spread of emerging diseases and has laid the grounds for their future control.

Keywords: arbovirus, epidemic, zoonoses, infection

Infectious diseases have accompanied human development from the earliest times and have often influenced it greatly. Most scientists agree that the first bacteria emerged on Earth about 3 billion years ago (1), whereas the first intelligent humans date back to 100,000 years at the most (2). Nevertheless, we only found out about the existence of these living creatures invisible to the naked eye in the 17th century, when Anton van Leeuwenhoek, a rich cloth merchant, invented the first optical microscope designed to help him check the quality of the fabrics that he sold (3). This was not enough for the medical world to realize the importance of the discovery of the Dutch merchant. Two more centuries were necessary for the theory of the “spontaneous generation” (4) of diseases to be forgotten due to the discoveries of the founding fathers of microbiology, who showed that bacteria, small, yet diverse and extremely well organized creatures, were the cause of a large number of diseases – the infectious diseases.

For a rather long time, doctors did not have efficient weapons to fight these diseases, until the discovery and large scale production, after the Second World War, of the first antibiotic – penicillin. Things then evolved rather quickly, with the emergence on the market of many other classes of active antibiotics against an increasing number of bacteria (5). Thus, in the 1970’s, due to the wide range of available antibiotics, to bacteria with no significant acquired resistance and to the good response to the massive vaccination campaigns conducted at that time, many specialists predicted a short life to infectious diseases and were virtually convinced of their disappearance (6). Nonetheless, nowadays, almost half a century later, not only did they not disappear, but, on the contrary, at least 3 of the 10-major mortality causes of the first decade of the 21st century have had an infectious cause (pneumonia, acute diarrheic disease, HIV); moreover, some of them have become increasingly important (7).

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Why did this happen? Because pathogenic microorganisms have their own intelligence and ability to adjust to our various microbicidal weapons, and because humans are sometimes not so intelligent and abuse this arsenal in human and veterinary medicine, as well as in agriculture. Furthermore, we discover new infectious agents, or realize that older, already known diseases have infectious origins.

The definition of emerging (E) or re-emerging (RE) diseases varies. A disease is said to be emerging if its incidence has increased over the last 20 years or is expected to increase in the near future due to the occurrence of a new infectious agent or to the discovery of an infectious disease of an already known disease (8). Morse (9) has a different approach and sees emergence as the occurrence of a new infection in a population or the rapid increase of the incidence or geographic spread of an already known infection. Re-emergence is the reoccurrence of a known disease, which was considered eradicated or under control.

The causes of E and RE diseases are numerous and often complex: conurbations make disease transmission much easier, increased population mobility facilitates the extremely rapid spread of infectious diseases as we have witnessed on many occasions in the recent past. Climate changes and insect environment changes allow these vectors to extend their survival and associated disease transmission area. We should also mention here antibiotic resistance, vaccine coverage decrease, lack of hygiene standards and many other contributing factors.

Looking back at the last 20 years, one may notice that starting with 2008 there was at least one emerging pathogen per year (Table 1).

Among the re-emerging diseases we may list: malaria, measles, tuberculosis, cholera, whooping cough, diphtheria, plague, multi-resistant bacteria infections: *S. aureus*, *Ps. aeruginosa*, *K. pneumoniae*, *E. coli* and many more.

What is the origin of ED?

It is currently thought that about 1400 species of human pathogens have been discovered, 60% of which are transmitted from animals, 10% by environmental factors and the rest exclusively among humans (10).

When referring strictly to ED, 73% of them are zoonoses (SARS, Nipah, Ebola etc.), and this per-

TABLE 1. Emerging infections over the last 20 years

Year	Pathogen/Disease
2015	Ebola Zika
2014	D68 enterovirus
2013	A/H7N9 influenza Chikungunya
2012	Middle East respiratory syndrome (MERS) Borreliosis coronavirus
2011	<i>Escherichia coli</i> 0104:H4
2010	Huaiyangshan virus, (SFTS)
2009	A/H1N1pdm09 influenza
2008	<i>Plasmodium knowlesi</i> Lujo virus
2005	Human HTLV3, HTLV4 retroviruses
2004	A/H5N1 influenza Nipah virus
2003	SARS coronavirus
2000	<i>C. difficile</i> BI/NAP1/027
1996	West Nile virus

centage has been increasing lately. A significant part is represented by diseases transmitted by vectors – almost one third (22.8%) (10).

E and RE diseases have long ceased to be a mere regional problem in tropical or underdeveloped areas, as they emerged or spread rapidly throughout the world. The number, diversity and concentration of human pathogens increase as we approach the Equator, probably due to environmental factors (humidity, temperature) supporting their transmission and multiplication. Nevertheless, this is not the case with ED, most of which originate in NE USA, in Western Europe, Japan, Asia, SE Australia (11).

The most well-known **emerging arboviroses (ARthropod-BORne virus)** are generated by the West Nile, Chikungunia, Denga, Zika or Huaiyangshan viruses.

West-Nile virus infection is one of the most common arboviroses in the world, being transmitted by the *Culex* mosquitoes, which are also very common in Romania and for which humans are only an accidental host.

Its spread in Europe has been known as early as the 1960's, most of the infections being asymptomatic (80%) or generating an undifferentiated febrile disease.

However, the summer of 1996 witnessed in Romania one of the biggest epidemics ever known of meningo-encephalitic forms of West-Nile infection, with over 800 cases (393 laboratory confirmed) and 17 deaths (12).

Similar outbreaks followed in New York (62 cases, 1 dead) in 1999 (13), Israel (417 confirmed cases, 33 dead) in 2000 (14), Canada (1494 cases, 14 dead) in 2003 (15), USA (663 cases, 335 meningoencephalitis cases, 32 dead) in 2009 (16) and, closer to us, in Greece (262 cases, 35 dead) in 2010 (17).

After the 1996 events, Romania set up a surveillance system devoted to this disease in the National Center for Communicable Disease Surveillance and Control, which reported sporadic cases: 82 neuro-meningeal forms between 1997 and 2004, 2 in 2008, 3 in 2009, with a peak in 2010 – with 54 confirmed cases (18,19). The latest report of the NCCDSC (November 2016) shows 93 confirmed cases and 11 deaths caused by West-Nile (20).

Chikungunya is a virus isolated in Tanzania in 1952, the name of which derives from the local Kimakonde dialect and means “to contort”. The clinical manifestations of the infection resemble influenza, with a 7-to-10-day incubation period, and gastrointestinal, cardiovascular or nervous (meningoencephalitis) complications. Deaths have been reported in the elderly or in patients with comorbidities (21).

The disease is transmitted by the *Aedes aegypti* mosquitoes by daytime bites (which used to be present in Europe, but has now disappeared) and the *Aedes albopictus* mosquitoes, which still exists in southern Europe and the existence of which has also been recently reported around Bucharest (21, 22).

After the first cases reported in eastern Africa in the 1950's, the infection spread relatively rapidly and is now present on all the continents, including in Europe. The first major epidemic outbreaks occurred in the Indian Ocean islands between 2001 and 2007, with over 100,000 cases in the Réunion Island and over 1 million in India (23,24). In 2007, the virus reached Europe, more precisely northern Italy, where 247 cases were confirmed and one died (25) (it seems that the virus was transmitted by an Indian on a business trip). In France, the first case of indigenous transmission occurred in 2010, and another 14 cases were reported by 2014 (26). Since 2013 the disease has been also present in America (Brazil, Mexico, Columbia), including in the USA (Florida) (27).

Dengue has been known in Chinese medicine since the 10th century (28), whereas the first “modern” epidemics were reported around the Equator in the 18th century (29). It is another disease transmitted by mosquitoes (*Aedes* family), the main reservoir of which is man and different species of monkeys. As far as its importance is concerned, it is considered the second mosquito-transmitted disease in the world (after malaria), as it has spread in over 110 countries (30), generally between the 30° N and 40° S latitudes. Starting with the 1950's, a severe form of the disease has been reported, with hemorrhagic manifestations, especially in children (hemorrhagic dengue), which causes over 20,000 deaths per year (31).

Many infections are asymptomatic (40-80%). Often the infection produces manifestations resembling influenza. Sometimes, a severe form or dengue shock (<5% of all the cases, especially children and adolescents) with increased capillary permeability may determine life-threatening hypovolemic shock and high mortality rates (31).

The number of dengue cases has increased worldwide during the last decades (from about 1,000 in the 1950's to 1 million between 2,000 and 2007), just like the geographical area of its spread. About 2.5 billion people (2/5 of the world population) are currently exposed to the dengue risk (29). Disease prevalence estimations range between 50 and 90 million cases each year, of which up to 76 million (67-136 million) are clinically manifest (31).

In Europe, the latest epidemic occurred in Greece in the 1920's, and imported cases have been reported since. Between 2008 and 2012, their number reached 4,000 (of which 6 in Romania). In the entire EU, the number of cases doubled in 2012 as compared to 2011 (32). The latest epidemic on the quasi-European territory was in Madeira, an island in the Atlantic Ocean under Portuguese administration, in 2012, with over 2,000 probable cases (1,000 confirmed). The disease also affected the tourists, who later exported the disease to 13 EU countries. One of these cases even reached our hospital in Iasi City. There were no deadly cases reported (33).

Zika virus has made it to the front page of newspapers and has been the focus of attention of the medical community since the beginning of 2016. It has been known since 1947, the first hu-

man infection being described in Nigeria, in 1954 (34). Until 2007, it seems that there were only small African sites of infection. The first important epidemic outbreak was reported in 2007, when 73% of the population of Yap island was infected (35). The disease then rapidly spread in the entire region and many successive epidemics occurred (36). The first cases in South America were reported in Brazil, in May 2015, with over 1 million suspected cases reported so far. It then spread to other 29 American countries. Only imported cases have been reported in Europe and Canada so far (37).

The virus is transmitted mainly by *Aedes* (*Ae. aegypti*, *Ae. africanus*, *Ae. hensilli*, and *Ae. Albopictus*) mosquito bites. The virus can survive up to 60 days in the mosquito body, and the reservoir of infection is represented by monkeys and other species of wild and domestic animals, in addition to humans. Inter-human transmission (from mother to fetus, by sexual intercourse and possibly by transfusions or laboratory exposure) has been also described (37,39).

Up to 80% of the infected people remain asymptomatic. When they do occur, clinical manifestations are generally mild and self-limiting: moderate fever (37-38°C), arthralgia, myalgia, headache, conjunctivitis, centripetal pruritic erythematous maculopapular rash lasting 1-4 days.

The complications associated with the infection first attracted attention on the disease. Newborn microcephaly and other nervous system malformations are a possible consequence of infection in pregnant women. The infection was also accompanied by: Guillain-Barré syndrome, meningoencephalitis, hearing impairment, hematospermia. 11 deaths have been reported so far in connection with Zika virus infection (38).

In non-endemic areas, the disease is difficult to recognize by a mere physical examination, in the absence of solid epidemiological arguments. A positive diagnosis generally requires confirmation by molecular biology tests or by IgM antibodies determination (35).

Huaiyangshan virus is a new member of the *Bunyaviridae* family, which was discovered by a Chinese researcher (Xue-jieYu) in 2009 (40). It causes a severe fever syndrome associated with thrombocytopenia and digestive manifestations, with a fatality rate of up to 30%. The disease, which

is transmitted by tick (*Haemaphysalis longicornis*) bites or close contact with the patient's fluids, was reported in Eastern China (several thousand cases between 2011 and 2012). Several cases were also reported in Japan and Southern Korea (41).

Other emerging diseases

SARS was the first emerging disease of the 21st century. An epidemic of atypical severe pneumonia cases of unknown etiology affected China in November 2002. The disease was initially exported to Hong-Kong and then rapidly spread worldwide. The first cases were reported to the WHO in February 2003 (Carlo Urbani, an Italian doctor, was the first to have recognized SARS as a new disease; he himself died due to this infection, a month later) (42), and the (SARS-CoV) virus was identified after only a few weeks in several laboratories. More than 24 countries reported cases within only a few months from the first one. Fortunately, the epidemic was extinguished by the end of 2003, with 8096 probable cases and 774 deaths reported (9.6% fatality rate) (43).

The history of the **Middle East Respiratory Syndrome** (MERS) started in June 2012, with a 60-year old Saudi Arabia sheik, with no previous comorbidities, who died due to a severe febrile respiratory infection accompanied by renal failure, apparently with no etiology. A few months later, an Egyptian doctor (Ali Mohamed Zaki) announced the discovery of a new coronavirus (MERS-CoV) associated with this disease, which subsequently spread in Jordan and other countries in the region (44). Imported cases were later reported in Europe, USA, Africa and Asia. In May 2014, there were 697 confirmed cases and 210 dead (45). In 2015, an epidemic broke out in Southern Korea with 186 cases and 36 deaths (46). The number of cases reached 1841 in 2016 and affected 27 countries, with a significant fatality rate – 35%.

The virus comes from bats, and camels are its natural reservoir (>90% of the camels in Oman have antibodies), its transmission being mainly zoonotic. Inter-human transmission is possible, sometimes causing nosocomial epidemic outbreaks (Korea, Japan, Saudi Arabia) (47). There is currently no vaccine or specific therapy.

The recently extinguished **Ebola** (EVD) epidemic was one of the biggest so far, with 28,616 probable or confirmed cases and 11,310 dead. Over 10,000 patients survived the infection (48).

The virus was first described in 1976 after an African epidemic with high fatality rates (Congo 318 cases, 88% fatality rate, and Southern Sudan 284 cases, 53% fatality rate). The virus disappeared for 20 years only to reappear later in successive outbreaks in Central and Western Africa (Congo, Uganda and Gabon) (49).

The onset of the current epidemic dates back to December 2013 and was traced to Guinea. It rapidly extended to the neighboring countries Sierra Leone and Liberia, the highest number of cases being reported in the latter country (4809) (50).

The cases exported both to Europe (15 confirmed cases) and to the USA (11 confirmed cases), as well as the significant percentage of lethal cases, despite the modern supportive treatment and the experimental attempts of etiological therapy, have been a serious preoccupation for the specialists.

Disease transmission to the medical staff had been known since before this epidemic, considering that such cases had been reported during the previous outbreaks as well (in 1995 and 2000, 89 and 32 cases, respectively). The medical staff providing care to these patients are thought to be 21-32 times more predisposed to catching the disease than the general population. 1040 EVD cases were reported in the medical staff at the end of the epidemic (815 confirmed cases). Among the infected individuals, 50% were nurses and caregivers, 12% were doctors or students, laboratory personnel. Two thirds of infected medical staff died (51). At the beginning of the epidemic, over 10% of the patients belonged to this category, that had come into contact with the initial cases. According to a WHO report, in the three most affected African countries, between 1.5 and 6.9% of the entire medical staff died of EVD in the referenced period (1.45% in Guinea, 8.07% in Liberia and 6.85% in Sierra Leone) (51).

The disease transmission path has not been fully elucidated yet, but it seems that close contact with the patient or their secretions is necessary. It is thought that local burial rituals have significantly contributed to disease spread (51).

After a 3-to-16-days incubation period, EVD manifests itself as febrile disease with digestive and respiratory symptoms. The second week is characterized either by the patient's recovery, or by the occurrence of hemorrhagic phenomena, multiple organ failure, diffuse intravascular coagulation and often death (49).

The diagnosis is set by PCR or viral antigen detection. The specific IgM antibodies may be detected 8-12 days after disease onset.

The international community joined forces to help the affected countries and sent over 4,000 experts in 70 locations, 1.48 millions of sets of safety equipment, logistics. Several quick diagnosis tests were developed, significant progress has been made in the creation of a vaccine and expert and rapid reaction teams in case of epidemic have been strengthened (52).

H5N1 avian influenza of 2004 was one of the first serious warnings about the pandemic risk of infectious diseases at the beginning of the third millennium. This high fatality rate (61%) virus only spread in a few countries, most of them in South-Eastern Asia. 273 confirmed human cases were reported by 2007 (53). Although the disease has not had a large scale global spread, the anti-epidemic measures (especially the killing of domestic farm poultry) had a considerable economic impact.

2009 saw the emergence of the first cases of **A H1N1 virus influenza**, initially called "swine" influenza in Mexico. It rapidly spread worldwide (214 countries, 18,499 confirmed deaths (54) and 15 times more estimated cases (55)), which determined the WHO to issue a pandemic alert. As far as Romania is concerned, almost 600 cases and 82 deaths were confirmed in 2009 and 2010. There have been controversial debates about this pandemic, the magnitude and fatality rate of which were by far inferior to those specific to seasonal influenza epidemics. There were allegations of conflict of interests and abusive behavior from certain WHO experts suspected of unorthodox connections with vaccine and influenza medicine producers (56).

A new avian influenza virus – **H7N9** was detected in Eastern China in 2013, yet human cases were relatively few (419 cases, 127 dead – 22% fatality rate). There were few exported cases – Canada, Malaysia and Hong-Kong. Inter-human trans-

mission was possible, but difficult, an assumption proven by the few isolated family infections (57). There later occurred annual regional epidemic outbreaks, the latest and widest so far being the one affecting China between October 2016 and February 2017, where there were 424 confirmed cases (58).

The **Enterovirus 68** is another emerging pathogen. Identified for the first time in California in 1962 (59), this virus is responsible for an occasionally severe child's respiratory disease, especially in asthma patients. Only 26 cases were detected in the USA between 1970 and 2005; nevertheless, starting with 2013, epidemic outbreaks have been reported in Japan, Philippines, Netherlands and USA (60). An epidemic broke out in 49 American states and Canada between August and October 2014, with 1153 confirmed cases and 14 dead (61).

Nipah virus is responsible for a zoonosis transmitted from bats to humans, with epidemic outbreaks in Malaysia (1998-1999: 283 cases, 109

deaths) (62) and in Bangladesh, (2004), due to contaminated palm tree sap consumption, with a fatality rate of over 50% (30 confirmed cases, 18 dead) (63). The infection may be asymptomatic or cause respiratory symptoms, sometimes lethal encephalitis. The disease extended to Asia and Australia and corresponded to the bats' natural habitat; several cases were also reported in Mozambique and Ghana (64).

CONCLUSIONS

The events that occurred during the recent years have proven that there are no borders to infectious diseases, which may spread very rapidly.

The question that each local specialist should ask him or herself is whether they are theoretically and logistically ready to deal with such an emerging disease which we may be brought to face unexpectedly.

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