



## REVIEW ARTICLE

# Emerging and re-emerging infections at the turn of the millennium

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**Summary.** After World War II, mankind believed that infectious diseases were on the way to being defeated. Unfortunately, they still are the second worldwide cause of death. Globalization changes promote the emergence of new infections and pandemics; international deliveries and travelling facilitate the dissemination of infectious agents; man-induced environmental changes create new opportunities for contacts between species, leading to infections in aberrant hosts, including man; global warming enables insects, a major vector of pathogens, to thrive in more countries. The main pandemics have been

caused by viruses, such as HIV and novel subtypes of influenza viruses. In addition, prion proteins are a threat. The transmission of the Creutzfeldt Jakob disease variant through blood transfusion and the recent discovery of prion protein in the spleen of a haemophilia patient are a matter of further concern. The end of the war against infectious diseases is not in sight. Mankind's battle with pathogens has lasted millennia and is destined to continue.

**Keywords:** emerging, infections, prion, re-emerging pathogens, virus

## Introduction

Throughout history man has periodically been the victim of epidemics: we have historical reports that vividly report these calamities, such as *'the plague of Justinian'* [1] dating back to the Roman empire, *'the Black death'* in the Middle Ages [2], the *'Spanish flu'* in 1918 [3], the emergence of acquired immunodeficiency syndrome (AIDS) in the early 1980s and the more recent severe acute respiratory syndrome (SARS) at the beginning of the XXI century [4]. After World War II, the extensive knowledge on infectious agents and their hosts, environmental factors involved in their transmission, improvements in hygiene, healthcare and socioeconomic status and, last but not least, the discovery of effective antimicrobial therapy and the availability of vaccines, lulled man into believing that *'the war against infectious diseases had been won'* and that epidemics were a phenomenon of the past [5,6].

Nothing could have been further from the truth. At the beginning of the third millennium, infectious diseases still are the second cause of death in the world (the first in developing countries). Fifteen million humans die every year of infectious diseases, the five *'big killers'* being AIDS, tuberculosis, malaria, respiratory infections and infantile diarrhoea [6,7]. In the last decades, a number of new pathogens responsible for emerging infectious diseases, such as avian and swine flu, AIDS, SARS, West Nile, Ebola and variant of Creutzfeldt-Jacob disease (vCJD) have been identified and other infectious diseases are re-emerging after a period of quiescence, such as malaria and tuberculosis caused by multi-drug resistant strains [2,5,6,8,9]. The picture is compounded by the so-called *'deliberately emerging'* pathogens, such as anthrax and smallpox – biological weapons that humans might plan to spread deliberately as an act of bioterrorism [2,6,9].

### *Facilitating factors for emerging infectious diseases in the third millennium*

In the world of globalization, regular exchanges of enormous amounts of goods throughout the world and low-cost frequent travelling, whereby hundred thousands of people move from one side of the earth

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to the other within a matter of hours, facilitate the dissemination of infectious agents (microbial traffic). Infectious diseases that once upon a time would have remained confined to their ecological niche can now potentially spread rapidly to every corner of the earth before preventive measures can be implemented [5,10].

What is more, a number of other factors promote not only the dissemination but also the emergence of new infectious diseases: intensive farming and breeding associated with crowding promote the development of foci of infection; global warming has modified the climate, making insects, a major vector of pathogens, able to thrive in countries where the climate was previously hostile; the exploitation of natural resources has produced environmental changes that create opportunities for new contacts between species leading to emergence of infections in new hosts. The ability of an infectious agent to mutate and to jump the barrier species from animals to humans contributes to the emergence of zoonotic diseases. Indeed, most of the outbreaks in the last 30 years have been caused by infectious agents normally hosted by wild animals (reservoir hosts).

Following the loss of their normal habitat (e.g., climate changes, ecological changes in land use), these animals can move closer to farms where they infect livestock (spillover hosts). In parts of the world characterized by crowding and low hygiene standards, the livestock then infect man. In some cases, man results to be a 'dead-end' host (aberrant host), who does not transmit the infection any further.

For instance, in the 1990s, an unexplained epidemic of acute cardiopulmonary syndrome occurred unexpectedly in a Navajo tribe living on the border of the four corners region (New Mexico, Arizona, Colorado, Utah) of the southern-western United States [11]. This potentially deadly disease caused by an unknown virus (*Sin nombre* virus or 'nameless virus') subsequently identified as a member of the *Hantavirus* genus (*Bunyaviridae* family) is transmitted from mice to humans by inhalation of aerosolized virus-contaminated rodent excreta (saliva, urine, droppings). During the 1993 Navajo outbreaks, the wet and mild conditions as a result of changes in climate caused by *El Niño* favoured an abundance of mice food allowing a significant increase in the deer mouse population (*Peromyscus mariculatus*), the natural reservoir of this virus [12]. The migration of infected rodents near human settlements created the ideal conditions for the outbreak onset.

The deforestation that occurred in Australia and Malaysia in the late 1990s forced fruit bats (flying foxes), the reservoir of *Nipah* and *Hendra* viruses

(*Henipavirus* genus, *Paramyxoviridae* family), to move closer to human dwellings creating the conditions for the emergence of focal outbreaks of encephalitis with high fatality rate in humans [13]. In this case, viruses were transmitted from bats to livestock animals (pigs and horses) and from these to humans.

In other cases, however, zoonotic transmission is followed by viral adaptation to the new host that makes human-to-human transmission feasible. This is the case of several mutated viruses [10,14,15].

### *The viral threat*

Most of the emerging infections are caused by viruses, which, according to Nobel Prize winner Peter Medawar, are 'bad news inside a protein envelope'. The 'bad' news consists of strands of DNA or RNA that are able to penetrate mammalian cells, obliging them to reproduce the viral components instead of their own. The bad news can get even worse as viruses adapt continually to the environment by mutation, recombination or gene reassortment [2,15]. The two key features of intracellular replication and genetic evolution make viral infections particularly difficult to combat: currently available anti-viral agents block viral replication by various mechanisms, but hardly remove dormant viruses that have already penetrated inside host cells and the protection conferred by vaccination can be made fruitless by genetic evolution of the pathogen, which may enable it to escape previously induced immunity.

### *HIV and SARS: local zoonotic transmission with worldwide consequences*

An example that shows why zoonotic transmission must be avoided is the infection by HIV. Its natural reservoir is a non-human primate, called *Pan troglodytes troglodytes*, in which it is fairly harmless. Man became probably infected through contacts with infected blood during hunting and slaughtering processes ('bush meat', hunter's cut) about 60–70 years ago [16]. The infection remained confined to areas of Africa up to about 40 years ago when international travelling and exchanges became more widespread. Infected subjects moved from Africa to Haiti; from there, the infection then spread, as a result of sex tourism, first to gay communities in cities of North America (Los Angeles, San Francisco, New York) and then to Europe. At first, it spread in high-risk groups, such as male homosexuals, intravenous drug abusers and recipients of multiple

transfusions; then, it extended to the general population. The outcome is the current pandemic: in 2008, WHO estimated that 33 million adults and children were living with HIV infection/AIDS worldwide, that more than 40 million people have died of the disease so far and that the number of deaths in the last year amounted to 2 million [17].

Another well known example of recent worldwide pandemic is the SARS. This emerging airborne viral disease had a great impact on account of its rapid international spread under favourable conditions created by our highly mobile, closely interconnected world. The origin of SARS was in areas of dense population in southern China, where humans and animals are packed side by side providing ideal conditions for a new virus to emerge by jumping across species. The natural reservoir of SARS virus (SARS-CoV) is the horseshoe bat, the spillover host is the masked palm civet or raccoon dog; man is an aberrant host [18]. The pandemic originated in Guangdong, in Southern China, where families often cohabit with the animals they rear. The promiscuity enabled the SARS-CoV to skip across species and find a new host – man. It has been documented how the first identified infected human (index case) unintentionally infected another 13 humans in the Metropole hotel in Hong Kong, who then travelled to five different countries (Germany, Canada, Thailand, Vietnam and Singapore), giving rise to new foci of infection. This ultimately led to a worldwide epidemic affecting more than 8000 people, with a death rate of 9.6% [19]. This event showed how modern transport systems can enable an emerging infection in one part of the earth to spread rapidly throughout the globe. However, it also showed how international healthcare co-operation can achieve control of a rising pandemic within less than a year.

#### *Ebola and Marburg: 'hit and run' viruses*

However, not all viruses behave this way. Some viruses adopt the so called 'hit and run' strategy as they cause recurrent, geographically confined, usually self-limiting outbreaks. This is the case of Ebola and Marburg viruses, both members of the family *Filoviridae*, causing severe and often fatal haemorrhagic fevers in humans and non-human primates. In 1976, transmission of Ebola virus from its natural reservoir, which is still unknown, to man resulted in two simultaneous but separate, explosive outbreaks of human disease caused by two distinct virus subtypes in Zaire and Sudan with a case-fatality rate of approximately 90% and 50% respectively. The disease was self-limited both in space and time: it

remained confined to well-defined geographical areas and mysteriously resolved [20]. Since then, recurrent outbreaks have been reported in African countries including Sudan, Gabon, The Democratic Republic of Congo, Republic of Congo and Uganda. A variant of the African Ebola virus, the Reston virus, was first identified in 1989 in Reston, Virginia, USA and in 1992 in Italy (Siena) in colonies of *cynomolgus macaques* imported from the Philippines [21]. Despite its high pathogenicity in non-human primates, this virus does not seem to cause disease in humans. The infection by the Marburg virus followed a similar course: in 1967, German laboratory workers were infected by African green monkeys belonging to the *Cercopithecus aethiops* species imported from Uganda and developed fatal haemorrhagic fever [22,23]. Since then, sporadic cases and outbreaks have been reported in the Democratic Republic of Congo in 1998–2000, Angola in 2004–2005 and Uganda in 2007. In July 2008, an imported case of Marburg haemorrhagic fever was diagnosed in the Netherlands in a Dutch woman who became infected by visiting a bat cave while travelling in Uganda [24].

#### *West-Nile, Dengue and Chikungunya viruses: vector-borne throughout the world*

Arthropod-borne viruses are very common (more than 600) and more than 150 cause diseases in humans in more than 100 countries world-wide, with a disease burden as high as a hundred million cases every year. Ecological factors, such as new routings of long-distance bird migrations and the increased long-distance air travel facilitate the movement of infected persons, livestock and exotic arthropod vectors around the world contributing to the spread of vector-borne diseases from the original niches to new geographical areas. Changing in public health policy, insecticide and drug resistance are additional factors which can contribute to the emergence or resurgence of vector-borne infectious diseases [25]. An example is the West Nile Virus (WNV) infection, originally confined to Africa (along the Nile), Southern Europe, parts of the Middle East and India, which has recently modified its epidemiological picture. In 1999, WNV was firstly imported into the New York area and, thanks to the presence of specific vectors (*Culex* mosquito) and natural susceptible hosts (crows, jays), the infection rapidly spread coast to coast.

Man is a dead-end incidental host: it has now been estimated that 1–3 million people have been infected by WNV in North America.

West Nile (WN) is a potentially serious illness whose symptoms may range from mild to severe. In about 80% of cases, infection is asymptomatic and asymptomatic carriers may be infectious via blood transfusion or through organ and tissues donations [26]. In 2002, there were 23 documented cases of WNV transfusion-transmitted infections, which induced the USA blood collection agencies (BCAs) to implement blood screening for this virus [27]. From June to September 2003, several hundred potentially infectious components were identified by the tests.

In the last 50 years, outbreaks of WNV have been reported in some European countries both in horses and humans. In September–October 2008, the first two cases of WNV neuroinvasive disease have been reported in northern Italy [28]. To prevent infection through blood donations by infected donors during the viremic peak, screening programmes have been introduced during the seasonal mosquito activity in the affected area.

Other examples of vector-borne diseases that have extended elsewhere in view of the climate changes and global warming is the re-emergence of Dengue virus (DV) infection transmitted by *Aedes aegypti* mosquito in tropical and subtropical countries. The susceptibility of *Aedes albopictus* also known as ‘Tiger’ mosquito (a mosquito of Asian origin currently widespread in countries with a temperate climate) to serve as a new vector of DV gives new opportunities to the virus to extend its area of spread. The tiger mosquito which is the vector of *Chikungunya* virus (CHIKV), a virus that caused several epidemics in Africa, Southeast Asia, the Western Pacific and India, was first introduced in Italy in the early 1990s by importing used tyres. In 2007, the CHIKV transmitted by this mosquito caused the first autochthonous epidemic outbreak in Europe, in the north-east of Italy (Emilia Romagna Region) which involved more than 200 cases [29,30]. This prompted the National Blood Centre and regional health authorities to take specific precautionary measures to ensure the safety of blood supply.

*Influenza viruses: unpredictable behaviour because of unique capacity for genetic variation*

Influenza A is an airborne virus that repeatedly produces epidemics every year during the cold season. Its hosts include birds (natural reservoir) and a number of mammals, including whales, seals, horses, pigs and man. It is particularly able to adapt to new hosts, thanks to its unique capacity for genetic variation: its surface proteins are able to

mutate up to 50% of their amino acid sequence without losing their capacity to infect mammalian cells and its genome is made of eight RNA segments that are genetically independent and that can therefore randomly reassort, forming antigenically novel subtypes [31]. Such novel strains have caused a number of dangerous pandemics in the past, such as the Spanish flu in 1918, Asian flu in 1957 and Hong-Kong flu in 1968. Currently, Avian flu is a real threat caused by mutated strain H5N1, which continues to spread in humans. The cumulative number of human cases of Avian Influenza H5N1 reported by WHO by 11 August 2009 amounted to 438 cases and 262 deaths [32]. The issue is whether this virus or other avian viruses (H9N2, H7N7) will cause a novel pandemic or not [33]. To cause a pandemic, three characteristics are required: (i) the ability of the virus to replicate in a human host, (ii) the population has to be susceptible to it, and (iii) human-to-human transmission has to be possible. At present, for H5N1, the first two features are satisfied, but not the third. However, it cannot be excluded that it will develop the third feature in the future.

On the contrary, human-to-human transmission has been proven for the novel swine Flu caused by the influenza A (H1N1) virus (S-OIV) isolated for the first time in March–April 2009 in Mexico [34]. This novel strain is a cause for concern as it has resulted from the unique reassortment of genetic elements of influenza viruses that normally infect three different kinds of host – swine, birds and human beings. The study of its structure has revealed that it differs considerably from its predecessors, isolated in human beings: its H antigen, which enables it to bind and infect cells of different species, has changed in terms of amino acid sequence alignment by approximately 27% and its N antigen, which enables it to digest sialic acids (neuraminidase activity), ensuring better access and spread in the organism, has changed by about 18%. This means that exposure to its predecessors may not provide any immunity to this unique strain and the whole population on earth is theoretically at risk [35]. Indeed, in April 2009, WHO declared a phase-5 alert indicating that a pandemic was imminent and that it was urgent to finalize the organization, communication and implementation of the pandemic preparedness plans. On June 11, 2009 WHO then announced the beginning of a flu pandemic with a total of 29 669 cases worldwide and 145 deaths. Only one month later, on July 6, 2009, WHO reported that the number of infections had increased up to nearly 100 000 with 429 deaths. Laboratory-confirmed cases as officially reported to WHO as of 14 August 2009 amount to 182 166 with

1799 deaths. Given that countries are no longer to test and report individuals, we can estimate that the number of cases reported actually understates the true number of cases.

At the time of writing (mid-August 2009), WHO considers the pandemic to be moderate. The speed at which the infection is spreading is such that infection of millions of people worldwide is considered to be inevitable. However, symptoms are mild and most people recover from the infection without the need for hospitalization or medical care. The rate of severe infections is currently similar to what is generally seen during local seasonal influenza. However, monitoring is essential as it is not possible to predict how the pandemic will evolve. H1N1 might disappear spontaneously, cause a mild pandemic or a severe pandemic after virus mutation/re-assortment.

Concerning blood transfusions, the risk of direct transmission of influenza via blood or blood products is extremely low. The major issue will be a temporary loss of blood donors during the pandemic peak, with impact on blood supply, as donors may not attend blood collection services on account of illness.

### *The prion threat*

An atypical infectious agent is the prion protein, a conformational variant of a naturally occurring protein that cannot be removed by normal degradation processes and accumulates forming fibrous aggregates that are believed to be involved in the pathogenesis of the disease [36]. The new prion disease that emerged in man in the UK in 1996 was a food-borne infection caused by modern intensive meat production based on 'industrial cannibalization': a prion disease that has been known to affect sheep and goats for more than 200 years (scrapies) had been transmitted to cattle via inadequately sterilized fodder of animal origin, giving rise to an epidemic of Bovine Spongiform Encephalopathy (BSE), also called 'mad cow disease', which in turn was then transmitted to man via meat consumption. Prion-infected humans develop a variant of classic sporadic Creutzfeldt-Jakob disease (vCJD), an invariably fatal neurodegenerative disease. It is not known what proportion of prion-infected humans develop symptomatic disease. Also, the mean latency period from prion infection to the development of overt disease remains unknown. Over the period 1996–2007, a total of 161 cases were reported, nearly all in the UK and attributed to dietary exposure. Possible transmission of vCJD by blood transfusion has been documented in the UK [37]. The emergence of prion

disease has led to a reduction in the number of donors as people with a history of visiting the UK during the cattle BSE epidemic are excluded. Recently, the prion protein has been found in the spleen during the postmortem examination of a 70-year-old patient suffering from haemophilia who died of causes unrelated to vCJD. Indeed, this patient did not have any neurological symptoms before death [38]. Of some concern is the fact that in 1996, this patient received a batch of factor VIII manufactured using plasma from a donor who developed symptoms of vCJV 6 months after donation. Although the mode of transmission has not been confirmed, the UK Health Protection Agency together with the Haemophilia Centre Doctor's Organization alerted haemophiliacs about this finding.

A related alert had been made a few years earlier: in 2004 patients with bleeding disorders who had been treated with plasma-derivatives made with blood collected in UK between 1980 and 2001 were told that they were potentially at risk of vCJD and excluded from donating organs. However, although patients exposed to contaminated products in the past may be at risk for vCJD, this does not mean that currently available plasma-derived products (manufactured with UK free plasma) still carry such risk. [39].

An important treatment option for patients with bleeding disorder is the administration of recombinant factors VIII, which is not derived from plasma and undergoes several processing steps to remove any contaminating viruses and prions [40].

### Conclusions

The development of new antimicrobial drugs and antibiotics together with the availability of safe and effective vaccines led to a spirit of optimism towards the definitive control and prevention of several infectious diseases. Man may have won some battles against infectious diseases, but the war is still raging and the end is not in sight. In general, there is no way to predict when or where the next pathogens will emerge. Emerging and resurging diseases are common in areas rich in wild animals and where natural and social environmental factors, including man's activities, increase the opportunities for the pathogens to extend their ecological niches and to be transferred to and from humans and other animals. The continual emerging of new infectious agents and re-emerging of drug resistant strains of old ones are issues with far reaching consequences. Infectious diseases have always been present in society and are destined to remain part of human life in the future.

## Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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