

EMERGING AND RE-EMERGING VIRUSES IN THE ERA OF GLOBALISATION

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Introduction

During their evolution, human beings, as every other animal and vegetable species, have had to face innumerable challenges from the world of micro-organisms. Indeed, the history of mankind is littered with 'scourges', that is, epidemics and pandemics characterised by high rates of morbidity and mortality. There have been numerous examples of major epidemics in the past centuries.

In the Middle Ages *Yersinia pestis* was the cause of the *Black Death*, a plague that devastated the countries of the Mediterranean basin reaching as far as China^{1,2}. In the 1500s after the colonisation of the New World by Europeans, epidemics of *smallpox* and *measles* contributed to the decline of the Aztecs^{1,3}. In exchange for having spread such epidemics, the European population was exposed to *syphilis*². At the end of the 1800s there was a spread of *tuberculosis* or '*industrial disease*', this name so-called because its emergence coincided with the beginning of industrialisation in the Western world. Finally, there was what has been defined as the mother of all pandemics, the *Spanish flu* of 1918-19, which infected a third of the world's population and was responsible for the death of about 40-50 million people⁴.

Half way through the 20th century, after the end of the Second World War, the perception that infectious diseases were under control began to spread. This was due to a series of improvements in social factors and health care, to the cleansing of the environment and water and to the availability of ever more effective vaccines and antibiotics^{3,5}. Indeed at the time it was said that "it is time to close the book on infectious diseases", claiming that the battle against infectious diseases could finally be considered to have been won^{5,6}. Unfortunately, this optimistic view was to be

proven unfounded in the following years owing to the emergence of new infectious diseases and the re-emergence of old ones in the last decades of the century and the beginning of the new one³.

According to the WHO (World Health Organization), infectious diseases are still the second cause of death in the world (and the first in developing countries), being responsible for about 15 million deaths each year⁷. High mortality rates are found above all in countries with limited economic resources, countries in which AIDS, tuberculosis, malaria, acute respiratory infections and infantile diarrhoeal diseases represent the five so-called 'big killers'^{6,7}. In the latter 25-30 years various new pathogens causing newly emerging infections have been identified, while several diseases supposedly under control in many areas of the world, are reappearing (re-emerging/resurging diseases) and causing multiple epidemic outbreaks². Furthermore, thanks to the selection of drug-resistant strains, diseases such as malaria and tuberculosis, have conspicuously reappeared among some populations^{3,5}. Finally, this picture is completed by the so-called 'deliberately emergent' pathogens (for example, anthrax and smallpox), whose spread could be intentionally planned by humans through bioterrorism³.

Variables brought into play

The variables involved in the development of new outbreaks of infections are influenced by complex interactions between the host, the pathogen, and the natural and social environment^{2,8,9}. Environmental modifications and imbalances caused by changes in

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the climate and alterations to the ecology caused by man have increased the chances for new contacts between the various factors involved, bringing about conditions for the emergence of new infections². In the globalised world of the new millennium, with huge amounts of merchandise and millions of people transported by air from one part of the planet to another, the 'traffic' of microbes and the diseases they cause are facilitated to such an extent that infectious agents, previously confined to limited ecological niches, are now capable of spreading rapidly to every corner of the earth^{1,5}. Among microorganisms, viruses have the best characteristics to become emerging pathogens. As Peter Medawar, winner of the Nobel prize for Medicine, said: "viruses are bad news inside a protein envelope". Viruses are extremely sophisticated. They are able to acquire new biological characteristics in order to survive, exploiting the phenomena of gene mutation, recombination and reassortment so as to become able to infect new hosts and to adapt to new ecological niches^{1,10}. In the last 30 years more than 40 outbreaks have been identified in the world. Most of these were of zoonotic origin and caused by viruses, some of which were previously unknown, capable of rapidly overcoming their original geographical boundaries and spreading among the human population⁹.

The HIV/AIDS paradigm

The most important of the recently emerged infectious agents is undoubtedly human immunodeficiency virus (HIV), responsible for the largest behavioural-type pandemic in the history of mankind. The origin of HIV/AIDS can be traced back to about 60-70 years ago to sub-Saharan Africa where the virus jumped species, passing from the chimpanzee to man through contact with infected blood, probably during hunting and slaughtering processes ('bush meat', 'hunter's cut' hypothesis)¹¹. Internal migration of rural populations to the shantytowns of large cities, accompanied by poverty, sexual promiscuity and prostitution, facilitated the transmission of the virus and the spread of the infection. In the 1970s, following the commercial trading routes between some African countries and the Caribbean Islands, the virus arrived in Haiti from which country as a result of sex tourism, it was subsequently introduced into the gay community in large American cities (Los Angeles, San Francisco, New York). From here, HIV reached Europe and initially spread in particular high-risk

groups (intravenous drug abusers, male homosexuals, recipients of multiple transfusions) before propagating rapidly throughout the world, assuming the characteristics of a pandemic^{11,12}. According to WHO estimates, there are about 33 million HIV-positive subjects in the world and more than 40 million people have so far died of the disease, of whom 2 million in 2007¹³.

The lesson learnt from severe acute respiratory syndrome (SARS)

As with HIV/AIDS, the first pandemic of the new millennium also had zoonotic origin. This pandemic started in Guandong, a region in the south of China, where the high concentration of stock farms and markets of live wild and domestic animals had always facilitated great promiscuity between animals and humans. It was here that the aetiological agent, subsequently identified as SARS-Coronavirus, found the suitable ecological and epidemiological conditions to make the jump across species and spread in a new host population. Two cross-species passages were sufficient to reach humans: from the bat (the natural 'reservoir') the virus passed to susceptible animals such as the civet and raccoon ('spillover' hosts) and then, through them, to man¹⁴. The event that aided the spread of the disease among humans was the overnight stay of a nephrologist from Guandong, at the Metropole hotel in Hong Kong. During his stay, this doctor, who had SARS at its incubation stage, unwittingly infected 13 foreign guests, who, returning to their countries of origin, were to give rise to new foci of infection far from the epicentre of the pandemic^{15,16}. The lesson learnt from SARS highlights two facets of globalisation: on the one hand it showed how a new infectious disease, which emerged in a remote corner of the earth, was able to spread quickly across the planet causing about 8,000 cases and 900 deaths in 30 different countries. On the other hand it also demonstrated how scientific co-operation and active surveillance at a worldwide level was able to control the burgeoning pandemic within eight months^{17,18}.

Influenza pandemics: "the big one"

On the basis of chrono-epidemiological models, an influenza pandemic can be expected on average three to four times every century. Since 40 years have passed since the last pandemic, the arrival of a new one seems possible and perhaps imminent, even if the bizarre behaviour of influenza viruses makes it

difficult to make precise predictions as to when this will occur, as to what its impact will be in terms of morbidity and mortality and as to the biological characteristics of the causative virus. In recent years, there have been reports of human infections caused by highly pathogenic avian viruses (H5N1, H7N7, H9N2) contemporaneously with huge influenza epidemics in poultry farms, especially in countries in south-east Asia (but also in The Netherlands and Canada)^{1,3}. In particular, the H5N1 virus, following the routes of migratory birds, is currently present in various areas of the world, including Egypt, Nigeria and several European countries. The geographic spread of the H5N1 virus, which has become a panzootic, and its ability to infect –albeit occasionally, humans and other animals (pigs, cats) are sources of concern to world health authorities. At present, H5N1 lacks the capacity for efficient transmission from an infected person to a susceptible person –transmission which is necessary to cause a pandemic. It is currently considered possible, but not certain, that this virus will manage to acquire, through adaptive genetic mechanisms (mutations, reassortment), the ability to trigger a rapid chain of human-to-human infection. Other, currently unknown, viruses besides H5N1 could theoretically emerge suddenly by jumping species (as happened with the Spanish flu) or by genetic reassortment between avian and human agents (as occurred at the outset of Asian flu and then the Hong Kong pandemic) and become the cause of the first influenza pandemic of the new millennium^{19,20}. However, we must expect the unexpected from influenza. Since April 21, 2009, the CDC (Centers for Disease Control and Prevention) has reported cases of respiratory infection with a swine-origin influenza A/H1N1 virus which can be efficiently transmitted through human-to-human contact²¹. We know so far that such a new virus contains gene segments from four different virus sources: one derived from human influenza viruses, one from North American avian influenza viruses, one from North American swine influenza viruses and one from swine influenza viruses normally found in Asia and in Europe²². This new, potentially pandemic, "quadruple reassortant" virus was firstly detected in Mexico and is now rapidly spreading in different countries including the USA, Canada, Europe and Asia^{22,23}. Based on currently available data (April 2009), the WHO has raised the current level of influenza pandemic alert to phase five²³. This means that a pandemic is imminent and that the time for the implementation of the planned

measures to control at national and at global level its impact is short.

Climate and habitat changes as causes for emerging infections

In the 1990s there was an epidemic of an acute cardiopulmonary syndrome in people living in four states (New Mexico, Colorado, Utah and Arizona) in the south-west of the USA. The virus responsible for the disease, then unknown (*Sin nombre virus*, literally 'nameless' virus), was subsequently identified as a member of the *Hantaviridae* family, whose natural reservoir is the cotton mouse that lives in the cultivated fields of the prairies of the four adjacent states. The increase in the number of these rodents, due to the abundance in food favoured by the heavy rains resulting from changes in climate caused by *El Niño*, led to their migration to areas near human settlements where the virus is passed from rodents to humans through exposure to infected urine and faeces²⁴. In the same way, at the end of the 1990s, deforestation in Australia and Malaysia forced fruit bats (flying foxes), natural reservoirs of the *Hendra* and *Nipah* viruses (*Henipavirus* genus), to look for new habitats closer to human dwellings. By jumping species, these viruses were transmitted from the bats to livestock animals (horses and pigs which serve as spill over hosts) and from these to humans, causing focal outbreaks of encephalitis with high fatality rate²⁵.

"Hit and run" viruses

Ebola and *Marburg* are zoonotic infections caused by viruses belonging to the *Filoviridae* family which can jump species, probably from small mammals to humans. These viruses, responsible for haemorrhagic fevers adopt (we can say) a "hit and run" strategy. They cause sudden, explosive, geographically circumscribed (Sudan, Zaire, Uganda) epidemics endowed with a very high mortality rate (70-90%). Such deadly outbreaks are usually self-limiting and viruses disappear in the same mysterious way as the way in which they arrive in a still unknown animal reservoir until the next attack. *Ebola* disease was first described in 1976 in the equatorial regions of Sudan and Zaire, while the *Marburg* virus was identified in 1967 at Marburg, in Germany, where some laboratory workers developed a fatal haemorrhagic disease, at that time unknown, after contact with sick monkeys (*Cercopithecus aethiops*) imported from Uganda²⁶.

Vector-borne infections

Vector-borne diseases occur in more than 100 countries worldwide, affecting about half the world's population. The disease burden is high with more than 500 million cases each year. There are more than 600 known Arboviruses (arthropod-borne viruses), of which at least 150 cause disease in humans. Despite various vector control measures, there continues to be emergence and resurgence of such diseases²⁷. Mosquitos and ticks are indispensable vectors for their propagation. Changes in the climate affect the epidemiology, facilitating or hampering their diffusion in particular areas of the world. The epidemiological profile of infections by West Nile virus (WNV), for a long time limited to some regions of Africa (West Nile), Asia and the Middle East, has recently changed²⁸. Alterations in the migratory routes of birds, induced by changes in their habitat brought about by man, or importation of the virus (facilitated by intercontinental flights) either by infected people or by infected mosquito or infected exotic animals from endemic areas are the most probable explanations for the arrival of WNV, at the end of the 1990s, on the east coast of the USA. Within a few years span, as a result of the presence of specific vectors (a mosquito of the *Culex* genus) and natural susceptible hosts (crows), the infection spread rapidly to the west coast and became endemic²⁸. In 2003, the CDC recorded a peak of 9,186 cases of human infections with 231 deaths. In the same year, the confirmation of 23 transfusion-transmitted cases of infections (7 of which were fatal) led health authorities to subject all blood donations made in the USA to specific screening with nucleic acid testing²⁹.

In the last 15 years, WNV has been identified in horses in several European countries. In September 2008, WNV infected several horses in Northern Italy (Veneto, Lombardia, Emilia Romagna) and caused three cases of human neuro-invasive diseases in the Emilia Romagna region³⁰. Programmes aimed at the screening of blood and organ donations in the affected areas during the peak of mosquito activity (May-November) are currently being planned.

The re-emergence of Dengue, transmitted by the *Aedes aegypti* mosquito in tropical and subtropical regions, is also, in part, due to climatic changes²⁸. The adaptation of the Dengue virus to a second, more widely spread vector, such as *Aedes albopictus* (tiger mosquito), is certainly not good news since this vector provides the disease with new opportunities to enter

even countries with a temperate climate such as those of the Mediterranean basin. In Italy, the tiger mosquito (present since the beginning of the 1990s) has not yet led to transmission of Dengue fever, but did facilitate, in 2007, the spread of the first imported epidemic of *Chikungunya* in Emilia Romagna³¹. Following this outbreak, the health authorities of this region took precautionary measures with regards to blood transfusion, ordering the suspension of blood collection from donors resident in the infected area and from those who returned from epidemic areas during the 21 days prior to donation.

Changes in the climate with less rigid winters, as well as the cessation of certain agricultural and forestry practices for economic and social reasons, such as cleaning woods and scything meadows, seem to be factors that have favoured greater diffusion of ticks and the consequent enlargement of areas at risk. *Tick-borne encephalitis* (TBE) is a relevant public health problem in central-eastern Europe, in some countries of the former USSR, in China and in Japan. In Italy, most cases of TBE occur in alpine and sub-alpine areas of the north-western part of the country (Friuli, Trentino, Alto Adige)³².

Our wits against their genes

When Darwin wrote that the 'fittest' species survive in adverse conditions, he was not referring to the healthiest or strongest species, but rather those that are best able to adapt. Evolution selects the individuals most successful at producing progeny and ensuring their survival. For a microorganism this success can be translated as the capacity to adapt to new hosts and new environmental conditions. Infective agents have numerous possibilities to adapt rapidly to changes in the habitat. On the other hand, mankind has various 'weapons' with which to tackle new and old emergencies. The availability of effective drugs and vaccines has led to great victories, such as the eradication of smallpox, the elimination of poliomyelitis and the worldwide control of hepatitis B. Vaccination against papilloma virus is a winning strategy to prevent cervical cancer, the second most common malignancy in women worldwide. The use of antiviral drugs, including highly active antiretroviral therapy (HAART) has changed the natural history of HIV in infected subjects. Interferon, nucleoside and nucleotide analogues, combinations of PEG-interferon plus ribavirin and, more recently, protease inhibitors are drugs used successfully in the

treatment of carriers of hepatitis B or C virus, who represent, respectively, 6% and 3% of the world's population.

Mankind's battle with viruses has lasted millennia and is destined to continue. The awareness that the appearance of new transmissible pathogens is a global risk and highlights the need to adopt shared policies for the prevention and control of infectious diseases. From a WHO health report in 2007, it appears that international co-operation is the strategy of choice for the surveillance and fight against emerging infections.

"The future of microbes and mankind will probably unfold as episodes of a suspense thriller that could be entitled Our wits versus their genes".

J. Lederberg, Science 2000³³

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