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Definition of emerging infectious diseases

S. Laperche

Unit of expertise in Virology, National Reference Center for Hepatits B and C and HIV in transfusion, Institut National de la Transfusion Sanguine, Paris, France

Throughout history, humanity has been challenged by outbreaks of infectious diseases and other health emergencies that have spread. With time, scientific knowledge evolved and more and more sophisticated measures taken to fight against infectious diseases led to gradually put under control some infectious outbreaks. Therefore, in this starting 21st century, the emergence of new infectious diseases or the re-emergence of old scourges, is surprising and worrying, owing the increasing understandings and progresses done in hygiene and vaccination. The optimism provoked by the eradication at the end of 1970s, of smallpox thanks to the extensive vaccination campaign, did not persist due to the increased number of infectious diseases observed especially in areas with precarious socio-economical conditions. Moreover, the world-wide spread of AIDS as the beginning of 1980s, has deeply changed the dogma that only poor-resource areas are involved in emerging disease phenomenon. The changing exposures of populations to toxic substances or environmental and occupational challenges not only cause newly emerging diseases but also may change the susceptibility of populations to infectious agents. Emerging infectious diseases (EIDs) are a crucial challenge to the organization of human public health policies, especially in transfusion medicine [1]. On the other hand, the development of new molecular tools that have played a pivotal role in discovering and characterizing several emerging infectious agents in the past two decades, will certainly increase the number of discovered emerging agents in the near future.

The concept of EIDs

The concept of EID can be applied to infections that newly appear in a population, or have existed but are rapidly increasing in incidence. Different heterogeneous epidemiological and/or clinical situations can be classified as emergence events, which are usually identified in three circumstances.

A newly described clinical entity

This was the case with AIDS, described at the end of 1970s as a previously unknown syndrome associating severe opportunistic infections (*Pnemocystis carinii* pneumonia, toxoplasmosis… and malignant tumours (Kaposi syndrome, lymphomas etc.) and occurring in young adults. Its rapid spread in human population suggested the appearance of a novel infectious agent which has been identified as a retrovirus a few years later [2]. The Lyme disease described in 1975, due to *Borrelia burgdoferi* transmitted by ticks [3] or the Creutzfeldt-Jakob disease occurring in young adults and associated with the mad-cow in UK are other examples [4]. The severe acute respiratory syndrome caused by the SARS-CoV coronavirus is one of the most recent such an event, becoming pandemic within a matter of weeks in early 2003 [5]. SARS spread from the Guangdong province of China to rapidly infect individuals in some 37 countries around the world. The spread of SARS has been fully contained but not eradicated and may potentially return into the human population in the future.

The unexpected reappearance of a known disease

This is the case of the re-emergence of a known disease, which usually has a rare or endemic expression, but suddenly exhibits an increased incidence in a geographical area. The majority of EIDs observed in the past decades enters in this category of events. We can mention the reemergence of Cholera in South America in 1991 after almost one century of absence [6], the dramatic epidemic caused by Dengue virus due to the global expansion of Aedes albopictus [7], or those due to Chikungunya virus, another mosquito-borne transmitted firstly identified in 1952 during an outbreak in Tanzania, then responsible for many outbreaks in Africa and in Asia between 2005 and 2007. Chikungunya virus that has a major health impact in humans, caused a massive epidemic on Reunion Island with a major peak in the number of cases in February 2006 [8]. Another example is those of West Nile disease epidemic,

Correspondence: Syria Laperche, Unit of expertise in Virology, National Reference Center for Hepatits B and C and HIV in transfusion, Institut National de la Transfusion Sanguine, 6 rue Alexandre Cabanel, 75015 Paris, France
E-mail: slaperche@ints.fr

which has affected the United States at the beginning of 2000. Since its introduction to the Western Hemisphere in 1999, WNV had spread across North America, Central and South America and the Caribbean, although the vast majority of severe human cases have occurred in the US and Canada. By 2002–2003, the WNV outbreaks have involved thousands of patients causing severe neurologic disease and hundreds of associated fatalities in USA [9]. This was also the case in Europe [10], especially in 2008 in Italy with a re-occurrence of the infection in 2009. The high identity between 2008 and 2009 WNV strains [11], the earlier virus circulation in 2009 and the re-occurrence of the disease starting from the bordering infected areas reached by the infection in the previous year, strongly support the hypothesis of the overwintering of the virus and the endemisation to local host populations and show the failure in the eradication of the virus.

The identification of a new agent or an agent with new properties

In this category are included: Hepatitis C virus, discovered as the agent causing non A–non B hepatitis [12], Herpès human 8 (HHV-8) responsible for Kaposi syndrome [13]. Influenza viruses constitute the classical model of emerging pathogens due to the high level viral variability caused by their segment RNA genome favourable to point mutations and reassortments. The avian flu due to A/H5N1 and the recent pandemic flu caused by A/H1N1 2009 [14] are two examples of unexpected flu outbreaks. In addition, new or pre-existing and recognized infections can emerge (vaccination escape G145A HBV mutants) [15]or re-emerge (HIV drug resistant strains) due to drug resistance of their agent or to a breakdown in public health (e.g. tuberculosis).

Mechanisms of infectious disease emergence

Infectious diseases in humans, generally result from two combined factors. Firstly, a fortuitous contact with the environment (gangrene due to *Clostridium,* tetanus on injury occasions), arthropod bites (Lyme disease, malaria, WNV…), ingestion of contaminated food (Hepatitis E virus, *Listeria*,…), accidental inhalation (*Legionella..),* or an unknown mechanism (Ebola), and secondly a long adaptation of micro organisms to human or animals (for example retroviruses coming from primates before being adapted to humans). The main mechanism leading to the emergence remains the cross-species transmission. Three schematic outcomes of such an event can be described: the human infection is abortive without propagation and animals remain the exclusive hosts, the human infection is severe and inter-human transmission is possible but animals remain the principal reservoir (SARS-CoV), the human infection is completely successful and humans become a reservoir through inter-human transmissions (HIV). Nevertheless, an agent, once classified into one these groups, may move into another category due to viral, host, environmental, or social changes. The first gammaretrovirus recently reported in humans (the Xenotropic Murine Leukaemia Virus-related virus or XMRV), is suspected to be derived from a non-human gammaretrovirus as it shares more than 90% nucleotide identity with the murine virus, MuLVs. It is currently one of the most surveyed emerging agent since its raises many questions with regard to its role in prostate cancer [16]and in patients suffering from chronic fatigue syndrome [17], its mode of transmission [18] and its geographical distribution.

Several spatial and temporal components, frequently working together, have been identified as promoting emergences, including traffic from animals, ongoing viral genetic evolution, host factors, environmental and social changes, or travels.

Environmental change (often caused by human interventions as deforestation which led animals like rodents to move to human living areas, or as dam and irrigation system construction promoting malaria and other mosquito borne diseases) is a major source, but also changes in living conditions. Urbanization, particularly in the developing world, can lead to very crowded conditions with limited hygiene. Social disruption and wars have also been associated with numerous outbreaks. The spread of an emerging agent may also result from the importation of an animal host (for example, the introduction of monkeypox into the US), a vector such as a mosquito, or even a food. Mobile reservoirs (e.g. birds) can transport pathogens from one region to another over long distances (WNV in 1999 in the US or H5N1 influenza A virus). The climate and weather can also be mentioned (e.g. diseases caused by zoonotic vectors such as West Nile Disease which are moving further from the tropics as the climate warms); changes in human susceptibility (e.g. immunocompromisation with AIDS), economic development (e.g. use of antibiotics to increase meat yield of farmed cows leads to antibiotic resistance, the nCJD caused by the transmission to human of meat coming from cattle, who are normally herbivores, being fed the remains of other cattle in the form of meat and bone meal); breakdown of public health; poverty and social inequality (e.g. tuberculosis in low-income areas); bioterrorism (Anthrax attacks).

EIDs: a challenge to human public health

EIDs are a crucial challenge to the organization of human public health policies, especially in transfusion medicine. The public health impact of an emerging infection, related to its frequency and the severity of the outcomes, the risk

of secondary transmissions and the public perception of the risk, often disproportionate to the severity of the infection, leads to take measures to prevent and control EIDs.

The prevention is the one of the most efficient measure to avoid such infections but unfortunately such an approach is not easy to set-up when the agent is unknown. Nevertheless, some unspecific measures, as the conservation of an intact ecosystems and their endemic biodiversity contribute generally reduce the prevalence of infectious diseases. Other relevant tools to prevent and control infections in humans can be mentioned as the control of the burden of mosquitoes during epizootic outbreaks, or as the survey of animals used as sentinels when involved in an EID. Furthermore, unexplained disease symptoms or clinical situations that may suggest the emergence of an infectious disease must be investigated. The next challenge is to detect, investigate and monitor emerging pathogens and the factors influencing their emergence. In this matter, the objective is to implement a continuum of complementary measures from the discovery to the control of the EID, including several stages: the recognition of the EID, adapted epidemiological investigations, etiologic investigations, diagnostic developments, focused research, technology transfer, training, control, and finally eradication of the pathogen. An applied research programme integrating laboratory technologies and optimized surveillance epidemiological tools must be developed to efficiently respond to the potential threat.

More specifically regarding the impact on transfusion medicine, two factors have to be considered: the transmission by blood of an emergent agent and the challenge to maintain blood supply during a pandemic affecting blood donor population as well as the transfusion staff. Any infection with an asymptomatic blood-borne phase has the potential for transmission by transfusion, when the infectious phase is prolonged (hepatitis B virus, hepatitis C virus or HIV infections), or short, (West Nile virus, hepatitis A virus Parvovirus B19 infections). The persistence of the infectious agent in collected blood or components, and its ability to cause infection by the intravenous route are also necessary characteristics for transmission by transfusion. Moreover, the transfusion transmission is of major concern when the agent causes identifiable and/or severe disease in the recipient. The characteristics of the agent and the genetic and immunologic status of the recipient also determine the frequency and severity of the disease resulting from the infection.

The history of HIV infection, which was the first emerging infection with a major effect on blood safety, prompts us to be vigilant facing new emerging threats. However, the decisions taken to reduce the potential transfusion risk of EID are not always based on documented scientific and epidemiologic criteria because most often these data are lacking when the infection appears. Thus, the precautionary principle is often invoked to justify proactive measures. To contribute to appropriate decision making, several surveillance systems have been implemented in some countries to detect 'signals' that may predict whether and how an emerging agent is able to spread and to assess the potential public health threat. More specifically, in transfusion medicine, efforts have been made to classify EIDs into a priority list (AABB's TTD committee [19]) to help clinicians and transfusion experts in the management of such infections. Different factors are analyzed to classify EIDs including the potential risk to humans, the plausible transmission by transfusion (presence in blood during an asymptomatic phase), the possibility for the agent to be present in the blood supply during an epidemic etc.… All these initiatives which provide a set of reliable tools to assess the risk should be implemented and adapted to the local emerging situation. However, a possible transmission by blood has to put in balance with another potential risk of transmission. Over the course of the outbreak of Chikungunya in Réunion Island in 2005–2007, the mean transfusion risk was estimated at 132 per 100 000 donations with a peak at 1500 per 100 000 donations at the height of the outbreak in February 2006 (accounting for a total of 47 blood donations) whereas, in the same period of time, the risk to be infected by mosquito-borne transmission was estimated at 312 500 of 757 000 inhabitants [8].

Conclusion

Infectious agents are well-equipped to invade and adapt to new ecological niches or hosts, change their virulence or modes of transmission, and develop resistance to drugs. On the basis of their high potential of replication, they have an evolutionary advantage. The delicate balance between humans and infectious agents has been conditioned over generations of contact, exposure to immune systems and human behaviour.

This equilibrium depends on changes in human demographics and behaviour, economic development and land use, international travel and commerce, changing climate and ecosystems, poverty, conflict, and famine. Thus, the prevention of dramatic pandemics partly depends on us. In case of emergence of an infectious disease, the exponential progresses made to develop molecular techniques used for the identification and diagnosis of infectious diseases and the coordination at the world level, have proven their efficiency on the control of such threats.

Disclosures

The author declares that there are no potential conflicts of interest.

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