Emerging viral diseases and infectious disease risks

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Summary. New pathogens and antimicrobial-resistant forms of older pathogens continue to emerge, some with the potential for rapid, global spread and high morbidity and mortality. Pathogens can emerge either through introduction into a new population or when the interaction with the vector changes; emergence is also influenced by microbiological adaptation and change, global travel patterns, domestic and wild animal contact and other variants in human ecology and behaviour. Quick, decisive action to detect and control novel pathogens, and thereby contain outbreaks and prevent further transmission, is frequently hampered by incomplete or inadequate data about a new or re-emerging pathogen. Three examples of pathogens that are current causes for human health concern are avian influenza, West Nile virus (WNV) and the severe acute respiratory syndrome (SARS) coronavirus. Pathogens directly or indirectly transmitted by aerosolized droplets, such as avian influenza and SARS, pose considerable

containment challenges. Rapid screening tests for other newly described pathogens such as WNV require time for development and may be <100% reliable. The importance of vigilance in the detection and control of newly recognized infectious threats cannot be overstressed. The presence of infectious agents in the blood supply could again have a significant impact on the safe use of both blood and blood-derived products in the care of patients with haemophilia, as did the human immunodeficiency virus in the 1980s. Emerging pathogens will continue to be a reality requiring the collaborative efforts of public health and individual healthcare providers worldwide to contain outbreaks and prevent transmission.

Keywords: avian influenza, haemophilia, human immunodeficiency virus, pathogens, severe acute respiratory syndrome, West Nile virus

Introduction

The emergence of new infectious pathogens and the recurrence of older pathogens in unique settings have become common topics in the medical literature and lay media, indicating an increasing concern among healthcare providers and the general public alike. The presence of infectious agents in the blood supply, for example, has had – and could again have – a profound influence on the safe use of both blood and blood-derived products in the care of patients with haemophilia. This article provides an overview of emerging infectious diseases in general and discusses some examples of viral pathogens that are currently cause for concern, including West Nile virus (WNV), severe acute respiratory syndrome (SARS) and avian

influenza. It also lays the foundation for discussions about the implications of emerging infectious diseases for the safety of the blood supply and for the care of patients who depend on the safety of the blood supply, such as those with haemophilia.

Infectious disease outbreaks of the last decade

In the last decade there have been a number of major global infectious disease outbreaks that have had the potential to be major health threats. Many of these rapidly spreading viruses, including SARS and avian influenza, appear to have originated as zoonoses in Asia [1]. These viruses have also demonstrated an extraordinary capacity to move quickly (and often surreptitiously) between animal and human populations and across continents.

Definition of an emerging infectious disease

Defining an emerging infectious disease is not necessarily straightforward. Morbidity and mortality from

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emerging infectious diseases are understood to be a continual threat, yet the exact nature of that threat is not well defined. One widely accepted definition was proposed in 1992 by the Institute of Medicine (IOM) in the USA, which defined an emerging infectious disease as a new, re-emerging, or drug-resistant infection whose incidence in humans has increased within the past two decades or whose incidence has threatened to increase within the near future [2]. Based on this definition, a spectrum of potential infectious diseases becomes apparent.

Potential infectious disease threats

A continuum exists in types of pathogens that emerge and infect new populations. The continuum includes infectious diseases such as SARS that appear to be newly introduced to humans from animals as well as bioengineered organisms that produce disease in unforeseen ways, such as the transmission of anthrax by contaminated mail in the USA in 2001. Outbreaks of disease once thought to be well controlled may be associated with a breakdown in core public health measures such as treatment of established infection (e.g. tuberculosis) or routine childhood immunizations (poliomyelitis). The continuum of potential disease threats also includes new antimicrobial-resistant forms of established pathogens, such as methicillin-resistant *Staphylococcus aureus*. In addition, scientists continue to recognize previously unidentified infectious origins of some chronic diseases, such as Lyme borreliosis [3].

Factors contributing to emerging infections

In 1992 the IOM identified numerous factors that contribute to emerging infectious diseases, all of which may impact the safety of the blood supply [2]. These factors include:

- 1 human demographics and behaviour;
- 2 technology and industry;
- 3 economic development and land use;
- 4 international travel and commerce;
- 5 microbiological adaptation and change;
- 6 breakdown of core public health measures.

In 2003, the IOM published an update to the 1992 report in which additional contributing factors were identified [3]:

- 1 human susceptibility to infection;
- 2 climate and weather;
- 3 changing ecosystems;
- 4 poverty and social inequality;

- 5 war and famine;
- 6 lack of political will;
- 7 intent to harm.

Many of these factors are interdependent. International travel and commerce and human demographics and behaviour, for example, are closely related and have undergone considerable change in the last century. Over the last 150 years as the global population has increased dramatically, the length of time required to circumnavigate the globe has decreased dramatically (Fig. 1) [4]. International travel and commerce have affected the size and mobility of human populations, bringing some environments, humans and other animal species into contact with each other for the first time. These changing human demographics may enable an infectious agent to become adapted to and disseminated within a new host population, often resulting in an expansion of the agent's geographic range [5]. The combination of these factors has accelerated the global spread of infectious agents.

Route of transmission of emerging infectious disease

Emergence of an infectious disease can occur either through its introduction into a new population or when the interaction with the vector of a disease changes. The latter scenario is the likely manner in which viruses such as WNV and Lyme borreliosis have spread [5]. The WNV strain found in the USA, for example, is believed to have spread from the Middle East and be a variant of the virus first isolated in 1937 in the West Nile District of Uganda in Africa. It is uncertain how WNV spread to the USA. It has been hypothesized that the strain in the USA was

Fig. 1. Speed of global travel in relation to world population growth [4].

transported in an infected bird illegally imported from the Middle East or Central Europe where the disease had previously been endemic. Mosquito transmission subsequently resulted in transmission to birds, horses and humans in the USA. After its initial appearance in New York City in 1999, WNV spread to the lower 48 states in the US in <2 years [6].

Recent infectious disease concerns

New, emerging infectious diseases and disease agents continue to be discovered and described. While incomplete, the list in Table 1 provides an indication of the variety and quantity of pathogens that confront public health officials and present potential threats to human health [3].

West Nile virus

In 1999, the first cases of WNV infection were recognized in New York City. Over the next several

Table 1. Partial list of emerging infectious diseases and disease-causing agents*.

HIV/AIDS
Tuberculosis
Dengue
Malaria (resistant <i>Plasmodium falciparum</i>)
Severe acute respiratory syndrome
Cholera
Meningococcal meningitis
Cryptosporidiosis
Filoviruses (Ebola/Marburg)
<i>Legionella pneumophila</i>
Lyme disease
Poliomyelitis
Toxin producing streptococci and <i>Staphylococcus aureus</i>
Human Herpesvirus-8
Parvovirus B19
Hepatitis C
Arenaviruses (Lassa)
<i>Cyclospora cayentanensis</i>
Hantavirus (Sin Nombre)
New variant CJD (BSE)
Bunyaviruses (Rift Valley)
Rotavirus
<i>Escherichia coli</i> 0157:H7
<i>Bartonella henselae</i> (cat scratch disease)
Community acquired MRSA
Avian influenza (H5N1)
West Nile virus
<i>Salmonella enteritidis</i>

AIDS, acquired immunodeficiency syndrome; BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus*.

*Data adapted from Smolinski *et al.* [3].

years, the virus spread throughout the northeastern part of the country and subsequently spread west to the Mississippi River and south into Florida. By 2002, cases were being reported across most of the Midwest, and by 2005 every state in the continental USA had reported cases of WNV in humans, birds, mammals or mosquitoes [7].

Since 2002, following reports of transfusion-associated WNV infections, the US blood supply has been screened for the virus. As of 15, November 2005, 382 presumptively viremic blood donors had been identified and reported to the US Centers for Disease Control and Prevention (CDC). These donors were generally asymptomatic for WNV infection at the time of blood donation but tested seropositive when pooled samples were screened using nucleic amplification technology (NAT). Some of these individuals subsequently developed clinical symptoms [8].

Severe acute respiratory syndrome

At the outset of the SARS epidemic in Asia, a number of small mammals commonly maintained in open food markets in Canton were found to be infected with the SARS coronavirus. More recent data have suggested that certain species of bats native to China may be the definitive host of the virus in nature [9].

Severe acute respiratory syndrome was first recognized in Hanoi, Vietnam in February 2003, although it is now believed to have originated in the Guangdong Province in southeast China in November 2002 [10]. In late February 2003, the first case of SARS in Hong Kong was reported in a physician from the Guangdong Province, who travelled to Hong Kong for a wedding. While staying overnight in a local hotel, it appears he transmitted the virus to 12 people on his floor. Subsequent generations of infection from the physician (who died in a Hong Kong hospital 2 days after arriving at the hotel), his relatives and others staying in the hotel involved more than 95 healthcare workers and 100 close contacts in the city of Hong Kong [11].

The global spread was rapid. Other infected hotel guests subsequently travelled to Vietnam, where 37 healthcare workers and 21 close contacts became infected, and to Singapore, where 34 healthcare workers and 37 close contacts were infected [11]. Another returned to Canada, where a cluster of infections commenced in a local hospital, involving family members, healthcare workers and other patients. Ultimately, over 200 people in Canada were infected, approximately one-third of whom died [12].

Avian influenza

Avian influenza is a major potential threat to the populations of the world and may be the source of the next flu pandemic [13]. There were three major flu pandemics in the last century: the so-called 'Spanish flu' in 1918–1919, potentially responsible for up to 50 million deaths worldwide; the Asian flu in 1957–1958, responsible for approximately 70 000 deaths in the USA; and the Hong Kong flu in 1968–1969, responsible for 34 000 deaths nationwide. Many epidemiologists believe that the human population is overdue for a pandemic [14]. Figure 2 illustrates a timeline of the emergence of several strains of the influenza virus.

Since 1918 there have been a number of shifts in the influenza virus's haemagglutinin and neuraminidase components, its key antigens. Fifteen types of haemagglutinin (H1–H15) and nine types of neuraminidase (N1–N9) have been recognized. Combinations involving subtypes H1–H3 and N1–N2 have been responsible for both seasonal and epidemic outbreaks in humans. The definitive hosts of influenza in nature are non-domesticated birds, particularly ducks that carry H1–H15 type viruses. Direct bird-to-human (and to date, rare instances of human-to-human) transmission of avian influenza has been reported [15] with increasing frequency in the last two and a half years.

Mechanism of influenza antigenic shift

Influenza viruses undergo constant subtle evolution and mutation of their principal proteins, a process referred to as antigenic drift. In addition to this naturally occurring and random process, influenza strains from different host species can periodically recombine. Swine may serve as hosts for both human and duck influenza strains and hence can function as ideal mixing vessels for major antigenic recombina-

tion and the emergence of novel influenza strains. When such shifts or recombinations occur and result in a virus with the capacity to maintain ongoing transmission between humans, a major pandemic may occur [16].

In 1997 in Hong Kong, the first evidence emerged that avian viruses could directly infect humans without going through this interim mixing step [15,16]. In 1997, there was an outbreak of influenza associated with an avian (H5N1) strain in humans that was preceded by an outbreak of the same strain in poultry [17]. With six deaths among 18 hospitalizations, H5N1 exhibited unusual lethality and was considered by some public health officials and epidemiologists as a pandemic warning call.

By December 2003, confirmed cases of avian influenza among humans were reported in Vietnam and Thailand, and since January 2004, human cases have been reported in Vietnam, Thailand, Cambodia, Indonesia and the People's Republic of China. The total number of cases as of 17, November 2005 was 130, with 67 deaths [18]. Sustained outbreaks among domestic poultry flocks in Asia preceded these human cases.

While the major outbreaks of avian influenza have occurred among domestic poultry flocks, evidence of avian influenza viral infection in migrating birds throughout Asia (and more recently in Europe) has also been demonstrated. It has been suggested that migratory birds may be responsible for the widespread introduction of avian influenza into other bird populations, both domestic and wild [19].

Conclusion

New pathogens continue to emerge, some with the potential for rapid, global spread and high morbidity and mortality. Laboratory tests for viral detection can be developed once a virus is identified, but their development takes time and their reliability may be <100%.

Pathogens spread by aerosolized droplets, such as avian influenza and SARS, pose considerable containment challenges, although neither pathogen appears to clearly impact the safety of the blood supply. In the case of SARS, patients can be screened, but the exact mode of human-to-human transmission remains uncertain. In contrast, reasonably (although not universally) effective screening exists for some newly described blood-borne pathogens such as WNV. Nonetheless, the hard-learned lesson from the human immunodeficiency virus (HIV) experience in the 1980s is that the importance of vigilance in the

Fig. 2. Timeline of emergence of influenza viruses in humans. (Figure courtesy of the Centers for Disease Control and Prevention.)

detection and elimination of newly recognized threats to blood safety cannot be overstressed. For these reasons, emerging pathogens will continue to be a reality requiring the best efforts of both public health officials and individual healthcare providers worldwide to identify emerging pathogens in a timely fashion, contain outbreaks and prevent transmission.

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