報道発表資料

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医薬食品局血液対策課
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ヒト胎盤エキス（プラセンタ）注射剤使用者の献血制限について

平成18年8月23日に開催された薬事・食品衛生審議会血液事業部会安全技術調査会において、ヒト胎盤エキス（プラセンタ）注射剤を使用した方の献血を制限する措置を日本赤十字社が実施することが了承された。

1．経緯等

(1) 変異型クロイツフェルトヤコブ病（vCJD）は、献血の際に血液から検査する方法が未だ実用化していないため、例えば、欧州滞在歴のある方などvCJD伝播のリスクが否定できない方について、問診により献血制限を行う暫定的な措置を講じてきているところである。

（※）暫定的な措置の内容
- 平成17年2月に国内でvCJD患者が確認され、英国滞在歴を有していたことを踏まえ、同年6月より、特定の期間に1日以上英国滞在歴のある方の献血を制限。
- 輸血及び臓器移植（ヒトの臓器に由来するもの）を受けた方からの献血を制限。

(2) ヒト胎盤エキス（プラセンタ）注射剤を使用した方の取扱いについても、安全技術調査会において平成16年10月から審議されてきたところであり、今般、以下の措置を講じることとしたものである。

2．新たな措置の内容

(1) 同注射剤によるvCJD感染事例は報告されていないが、輸血や臓器移植と同様にヒト由来の臓器から製造されていることから、vCJDの伝播の理論的なリスクが否定できないため、念のための措置として、その使用者について問診により献血を制限することとする。

（注）ヒト胎盤エキス（プラセンタ）注射剤については、国内では2製剤が薬事法の承認を受けている。
[1] メルスモン（注射薬）（メルスモン）
効能・効果　更年期障害・乳汁分泌不全
[2] ラエンネック（注射薬）（日本生物製剤）
効能・効果　慢性肝疾患における肝機能の改善
※　美容形成（シミ・シワ・ニキビ等）に一部使われていることも知られている。

(2) 日本赤十字社においては、1ヶ月後を目途に措置を実施する予定である。

→ 関連資料 … 薬事・食品衛生審議会　平成18年度第1回血液事業部会安全技術調査会

トップへ

報道発表資料　厚生労働省ホームページ

医薬品
医薬部外品　研究報告　調査報告書
化粧品

別紙 3-1

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2006 年 2 月 28 日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称			研究報告の公表状況	Emerging viral diseases and infectious disease risks Tapper, M.L. Haemophilia 12, (Suppl. 1), 3 - 7 (2006)	公表国 米国	
販売名（企業名）						

研究報告の概要	使用上の注意記載状況・その他参考事項等
西ナイルウイルス感染症，鳥インフルエンザ，重症急性呼吸器症候群(SARS)に特に重点をおいた「新規感染症」の概念，及びそれに関連すると思われる血液製剤とその使用患者の安全性について取り上げている。1992年以来，米国の医学研究所(IOM)は「新規感染症は，新型の，または再興する，または薬剤耐性の感染症であり，ヒトへの罹患率が過去20年以内に増加しているか，近い将来増加する恐れがある疾患」と定義している。海外旅行や国際商取引，人口統計学上及びそれに付随した行動の劇的な変化により感染因子は世界的に蔓延し，加速している。 2002年以来，輸血に関連する西ナイルウイルス感染症報告を受けて，米国においてウイルス検査を行った結果，多くの感染供血者(献血時には無症候であった)が特定された。その一方，SARSウイルスとトリインフルエンザウイルスでは，現時点で安全な血液供給に影響を及ぼす事態は生じていない。しかし，血液供給と血液由来製剤の安全性を脅かす新興病原体の検出と除去に対して厳重に警戒するよう提言している。	BYL-2006-0220-1

報告企業の意見	今後の対応
血漿分画製剤を介した西ナイルウイルス感染は現在までにまったく報告されていない。また，2003 年 5 月 1 日の FDA ガイドラインでは，血漿分画製剤に使用する血漿プールに対しては西ナイルウイルスの検査は必要ないとしている。さらに，弊社のウイルス不活化処理は血漿プールにおいて，西ナイルウイルスを不活化させるのに十分であることが証明されている。インフルエンザウイルス及びコロナウイルスに関しても同様に，弊社のウイルス不活化処理またはウイルス除去処理により安全性が確保されている。	現時点で新たな安全対策上の措置を講じる必要は無いと考える。引き続き関連情報の収集に努める。

Haemophilia (2006), 12, (Suppl. 1), 3–7

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.

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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

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

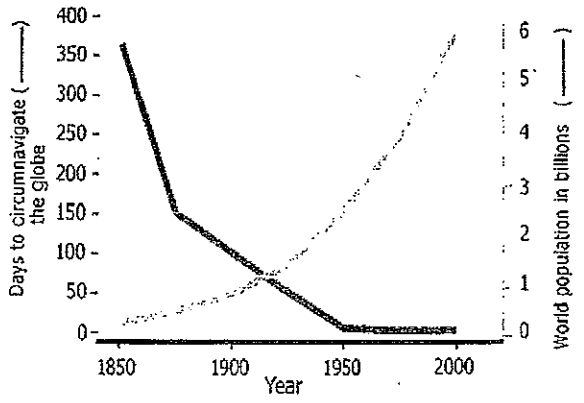

Fig. 1. Speed of global travel in relation to world population growth [4].

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 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].

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

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

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].

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 recombination 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].

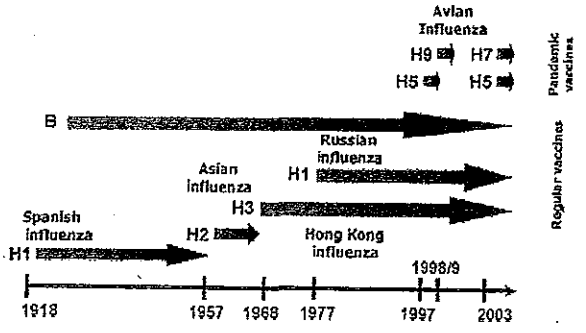

Fig. 2. Timeline of emergence of influenza viruses in humans. (Figure courtesy of the Centers for Disease Control and Prevention.)

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

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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