to involve the microcirculation and mitochondrial metabolism. Mechanisms may include the release of cytokines into the circulation [44].

Central nervous system disease

An important complication of influenza A virus infection is central nervous system (CNS) dysfunction, that can take a number of forms [45], including influenza-associated acute encephalopathy (IAAE). This is an uncommon neurological syndrome generally of children and adolescents that typically presents during the early phase of influenza virus infection [45].

There are several hypotheses regarding pathogenesis of IAAE. The most straightforward one is that it is caused by viral infection of the CNS. In support of this hypothesis, influenza virus has been detected occasionally by virus isolation or nested RT-PCR in CSF of patients [46–50] and in brain tissue from fatal cases [39;51]. Virus has been detected in neuropil and ependyma of the brain by direct immunofluorescence [39] and in Purkinje cells of the cerebellum and neurons of pontine nuclei by immunohistochemistry [40]. However, the frequent failure to detect virus in CSF and brain of affected patients despite thorough attempts, as well as the lack of inflammation in brain tissue of fatal cases, suggest that virus infection is, at most, only one of the possible pathogeneses. A second hypothesis for the pathogenesis of IAAE is hypercytokinemia, which does not require extra-respiratory virus infection. The severity of CNS dysfunction is correlated with the concentration of pro-inflammatory cytokines in blood and cerebrospinal fluid [45]. However, some patients with severe influenza-associated acute encephalopathy do not have elevated cytokine levels [47]. A third hypothesis that has been proposed is renal and hepatic dysfunction from influenza virus infection, although it is unclear how this occurs [49].

Grossly, the brain in patients with IAAE shows diffuse swelling, which may be severe [28]. Histologically, this corresponds with severe diffuse cerebral congestion and edema, with the notable absence of inflammatory cell infiltrate [28;39;48]. Vascular changes such as hyalinization of the blood vessel wall and thrombosis may be present [50]. The clinical consequences of these lesions include altered consciousness and convulsions. The outcome is highly variable but may result in persistent neurological sequelae or death [45].

Other rare CNS complications of influenza include post-influenza encephalopathy, Reye's syndrome, Klein-Levin syndrome, post-encephalitic Parkinson's disease, and encephalitis lethargica [45;52;53]. These are not further discussed here.

Myocarditis

Myocarditis has been observed in association with fatal influenza in each of the three pandemics of the previous century (e.g., [28;54;55]), and in interpandemic periods (e.g., [56;57]) but its pathogenesis is poorly understood. The advent of endomyocardial biopsies at the time of acute disease together with sensitive (*in situ*) RT-PCR techniques have made it possible to detect the presence of influenza viral RNA in inflamed myocardial tissue in some cases [41;58] but not in others [59;60;60]. It is not clear what the target cells of influenza virus in human heart tissue are: Cioc and Nuovo [41] detected influenza viral RNA in lymphocytes and macrophages within the myocardium of a person who died suddenly and unexpectedly with marked diffuse myocarditis and marked cardiomyocyte necrosis. Ray et al. [56] detected influenza viral antigen throughout the myocardium (cell types showing antigen expression not stated) of a patient with massive myocardial necrosis and associated lymphocytic and mononuclear infiltrates. The necrosis and inflammatory process in the myocardium could be explained by a combination of direct cytolytic effect of viral infection and the host immune response.

The myocarditis consists of cardiomyocyte necrosis associated with variable infiltration of predominantly mononuclear inflammatory cells. There may be interstitial hemorrhage and edema [28;41;54;61;62]. The clinical outcome differs dependent on the duration of the myocardial disease. If the patient dies acutely of fulminant influenza, the main lesion is in the lungs. If the patient dies later, it may be from heart failure. If the patient survives, the resulting myocardial fibrosis may result in heart block due to problems with electrical conduction [60; 63].

Myositis or myopathy

Myositis or myopathy is sporadically reported as a complication of both influenza A virus and influenza B virus infections [64]. Myopathy is a better term than myositis, because the majority of muscle biopsies from such cases do not show infiltration by inflammatory cells [64]. The pathogenesis of influenza-associated myopathy is poorly understood. The first hypothesis is direct viral invasion of the muscle. This is supported by the isolation of influenza A virus from muscle biopsies of two patients with influenza A virus infection. However, they were unusual cases. One was a 4-year-old boy with Reye's syndrome [65], the other was a 72-year-old man with muscle weakness [66]. Also, direct infection of myocytes has not been proven by immunohistochemistry. The second hypothesis is an immune-mediated process. However, the absence of inflammatory cell infiltrates in the majority of muscle biopsies argue against this [64].

Histologic examination of affected muscle biopsies shows muscle degeneration, necrosis, and regeneration, in some cases associated with inflammatory cells [65–69]. The main clinical symptom of influenza-associated myopathy is transient muscle pain in the lower extremities. Most cases resolve completely. Rarely, severe muscle damage develops that results in myoglobinuria and acute renal failure [64].

Differences between pandemic and interpandemic influenza

Influenza pandemics cause higher morbidity and mortality rates than seasonal epidemics during interpandemic periods. This is mainly due the lack of specific immunity to the new virus, so that infection is more likely to result in complicated disease, in particular pneumonia [1]. This raises the question whether the character of the lesions caused by a pandemic virus are qualitatively different from those caused by an interpandemic virus. Unfortunately, it is difficult to compare the pathology of pandemic and interpandemic influenza, because the vast majority of pathological reports are from pandemic periods, and because pathological reports typically describe the late stage of disease and may be complicated by the effects of therapeutic intervention, so that subtle differences may be masked.

Taubenberger and Morens [25] reviewed the pathology of influenza viral pneumonia in interpandemic periods. The observed lesions were similar to those found during pandemic periods. An interesting observation comes from two studies during an interpandemic period comprising a total of 55 fatal influenza virus infection [70;71]. In these studies, influenza viral antigen was detected in tracheal, bronchial, and bronchiolar epithelial cells, but not in alveolar epithelial cells or alveolar macrophages, even in cases showing diffuse alveolar damage. This contrasts with the findings from the 1957 pandemic [22;23], where viral antigen was detected in alveolar epithelial cells (probably both type I and type II pneumocytes) and alveolar macrophages.

Extra-respiratory complications of influenza described during pandemics, including encephalopathy (reviewed in [52] and [45]), myocarditis (e.g., [56]), and myopathy (reviewed in [64]) also have been reported in interpandemic periods. Based on the available information, the character of these complications does not appear to differ in pandemic and interpandemic

periods. Together, these studies indicate that, although the proportion of infected people who develop complicated influenza is lower during interpandemic periods, the same types of complications occur and are similar in character to those in pandemic periods.

Special features of human infection with avian influenza viruses

Until 1997, direct human infection with avian influenza viruses was considered to be rare and of little consequence to human health. Highly pathogenic avian influenza (HPAI) virus had been isolated from the blood of a man with clinical symptoms of infectious hepatitis ([72;73], and there had been rare reports of transient conjunctivitis from avian influenza virus infection [74;75]. In 1997, this changed when infection with HPAI virus of the subtype H5N1 was diagnosed in people in Hong Kong, resulting in 6 deaths out of 18 confirmed infections despite intensive care [76–78]. Subsequently, one person died of HPAI virus infection of the subtype H7N7 [79], and a low pathogenic avian influenza (LPAI) virus of the subtype H9N2 was identified as the cause of respiratory disease—albeit mild—in humans [80]. Furthermore, sequencing and phylogenetic analysis of the reconstructed influenza virus of the subtype H1N1 that caused the 1918 pandemic indicates that its genes were derived from avian-like influenza strains [81]. Together, these findings indicate that transmission of avian influenza virus from birds to humans might be rare, but is by no means impossible and has potential severe disease consequences, both for the individual infected and, if the virus is able to adapt to its new host, for the whole population.

H5N1 virus

HPAI H5N1 virus continues to circulate among poultry in many countries of Asia, Africa, and Europe and occasionally spreads to humans with often fatal consequences. Understanding of the pathology of H5N1 virus infection in humans is critically hampered by the few autopsies performed on people who have died of the infection. A recent review identified only nine full autopsies, including one of a fetus, out of 216 laboratory-confirmed fatal cases at the time of publication [82].

Based on clinical evaluation of infected people, the primary disease is centred on the lungs [83]. However, the pattern of attachment of H5N1 virus differs markedly from that for human influenza virus, with important consequences for subsequent disease [5]. In the tracheo-bronchial tree, attachment of human influenza virus is strongest in the trachea and progressively decreases lower down in the tracheo-bronchial tree. In contrast, H5N1 virus shows the strongest attachment in the distal part of the tracheo-bronchial tree—the bronchioles—with progressively less attachment towards the trachea (Fig. 1). The pattern of viral attachment also is distinct within the alveoli. Whereas human influenza virus has a preference for type I pneumocytes, H5N1 virus preferentially attaches to type II pneumocytes and alveolar macrophages (Fig. 1). It has been hypothesized that infection of these cell types might explain the high pathogenicity of H5N1 virus: type II pneumocytes are important for surfactant production, fluid transport out of the alveolar lumen, and re-epithelialization after damage, while alveolar macrophages are important for phagocytosis of pathogens and regulation of the inflammatory response in the alveoli [5;84]. The preference of H5N1 virus for attachment to type II pneumocytes is corroborated by studies that show that these cells have avian-type receptors for influenza virus and can be infected by H5N1 virus *in vitro* [4] and *in vivo* [82]. This pattern of viral attachment may also explain why the rare autopsies have shown lesions centred on the alveoli and bronchioles, without reported lesions in trachea or bronchi [82].

The respiratory tract lesions of H5N1 avian influenza in humans are consistent with exudative and proliferative phases of diffuse alveolar damage [82] and thus resemble the lesions of pneumonia from human influenza virus infection. Characteristic features include type II pneumocyte hyperplasia, interstitial infiltration of lymphocytes and in some cases neutrophils,

and predominance of macrophages— some showing hemophagocytosis—in alveolar lumina. Additional histologic features include desquamation of epithelial cells into alveolar lumina, hemorrhage, and bronchiolitis. By immunohistochemistry and *in situ* hybridisation, viral antigens and RNA have been found in type II pneumocytes, as well as ciliated and non-ciliated tracheal epithelial cells [82].

The isolation of the virus from the blood of two patients [85;86] and the detection of H5N1 viral RNA by RT-PCR in 9 of 16 patients [87] suggests that viremia can occur at reasonably high levels and for prolonged periods in people with symptomatic H5N1 virus infection [30]. Such viremia would allow H5N1 virus to spread to extra-respiratory tissues. Indeed, pathological investigations provide evidence for the presence of H5N1 virus in multiple extra-respiratory tissues by immunohistochemistry, *in situ* hybridisation, or both, often in association with lesions. The brain, where H5N1 virus has been found in neurons, is edematous without significant histologic lesions, or with demyelination, necrosis, and accumulation of reactive histiocytes. The intestine, where H5N1 virus has been found in intestinal epithelial cells and in mononuclear cells in the mucosa, has no abnormalities except lymphocytic apoptosis. The liver, where H5N1 virus has been found in Kupffer cells, shows hepatic necrosis, hepatic lipidosis, cholestasis, and Kupffer cell activation. Lymph nodes, where H5N1 virus has been found in lymphocytes, have reactive histiocytes with hemophagocytotic activity. Such evidence of hemophagocytosis also is present in spleen, bone marrow, lungs, and liver. The placenta, where H5N1 virus has been found in Hofbauer cells (fetal macrophages) and cytotrophoblasts, has syncytiocytotrophoblast necrosis, necrotizing deciduitis, and diffuse villitis. The fetus, where H5N1 virus has been found in lung tissue, shows no specific histologic lesions except edema and scant neutrophil infiltration in the lung. The kidney has acute tubular necrosis in absence of the presence of H5N1 virus [82].

The clinical consequences of these lesions typically manifest as severe pneumonia that often progresses rapidly to acute respiratory distress syndrome. Clinical features outside the respiratory tract include vomiting, diarrhea, myalgia, and—rarely— seizures. Nonspecific clinical presentation or atypical presentation (e.g., encephalopathy and gastroenteritis) often result in initial misdiagnosis of subsequently confirmed cases [83;88].

Together, these studies indicate that the primary lesion in fatal cases of both H5N1 virus infection and human influenza virus infection is the same, namely diffuse alveolar damage. The main difference in respiratory disease is the absence of reports of uncomplicated tracheo-bronchitis in H5N1 virus infection, which is the most common manifestation of human influenza virus infection. This may be due to differences in the attachment preferences—upper respiratory tract for human influenza virus, lower respiratory tract for H5N1 virus—or due to incomplete reporting of less severe H5N1 virus infections.

The level and duration of viremia and the extent of extra-respiratory spread appear to be greater for infections with H5N1 virus than with human influenza virus. It is not clear whether this difference is real or an artifact of more detailed pathologic examination with more up-to-date methods of the few H5N1 influenza cases studied.

Other avian influenza viruses (H7N7, H7N3, H7N2, and H9N2)

Between 1959 and 1996, infections with either high or low pathogenic forms of avian influenza virus (H7N7) infection were reported in six people ([72;74;75;89]. The presumed routes of infection were direct exposure to highly pathogenic avian influenza in poultry [72], accidental laboratory infection [89], pre-and post-mortem examination of infected seals [74], and a piece of straw entering the eye while cleaning out a duck house [75]. In five of six cases, a conjunctivitis developed at 1 to 3 days after inoculation and resolved after 4 days to 2 weeks [74;75;89]. Additionally, one person developed an asymptomatic intraepithelial keratitis one

week after inoculation that resolved over the next three weeks [89]. In one of six cases, the virus was isolated from the blood of the patient one month after presumed exposure. The patient had clinical symptoms of an infectious hepatitis, including yellow sclera, dark urine, and loss of appetite. The relationship between these symptoms and isolation of the virus were not clear [72].

In 2003, an outbreak of HPAI H7N7 virus infection in poultry occurred in the Netherlands, and the virus was detected in 86 people who handled affected poultry and three of their family members. The majority of these people (78/89, 88%) presented with conjunctivitis alone, while a smaller proportion had conjunctivitis and influenza-like illness (5/89, 6%) or influenza-like illness alone (2/89, 2%). Six of seven cases of influenza-like illness were mild. However, one patient developed severe pneumonia and died from acute respiratory distress syndrome and related complications. On autopsy, significant pathological changes were limited to the respiratory tract. Grossly, the lungs were edematous, emphysematous, firm, and about three times the normal weight. Histologically, there was severe diffuse alveolar damage, characterized by flooding of the alveolar lumina with serosanguineous fluid mixed with fibrin and neutrophils (Fig. 4). Although the virus was isolated from postmortem lung samples, viral antigen could not be detected in lung tissue by immunohistochemistry [79;90].

In 2004, an outbreak of HPAI H7N3 virus infection in poultry occurred in Canada. Two people who had direct conjunctival exposure to infected poultry were infected and developed conjunctivitis and mild influenza-like illness. Disease developed one to 3 days after inoculation and resolved fully [91]. In 2006, one person who was exposed to infected poultry from a U.K. farm with a LPAI H7N3 virus outbreak became infected and developed conjunctivitis [92].

Between 1999 and 2003, at least four separate human cases of LPAI H9N2 virus infection have been confirmed in China [80;93]. One of these cases had a history of probable contact with live chickens before illness; the others had no history of contact with animals. All four were children between 1 and 5 years of age and presented with influenza-like illness. In two children, symptoms included fever, anorexia, inflamed pharynx, and vomiting. In the other two, they included fever and cough. Three of four children recovered after two to six days, the outcome for the last child was not stated.

Influenza hemagglutinin receptor binding preferences for either alpha-2,3 or alpha-2,6 receptors clearly play a role in host-virus interaction but changes in receptor specificity alone are not adequate to account for host adaptation and transmissibility [4;94–96]. Infections with avian influenza viruses of H7 subtype have been associated predominantly with conjunctivitis, even though most H7 and H5 viruses share a predominant alpha-2,3 receptor specificity. Thus, other factors must account for the conjunctival tropism of H7 influenza viruses. Some of the human infections with H9N2 viruses were associated with increased specificity for alpha-2,6 receptors prevalent in human upper respiratory tract [4;97].

Perspectives

Influenza remains a major public health concern, both for its pandemic potential and for the impact of seasonal influenza. Furthermore, direct bird-to-human transmission of avian influenza viruses, particularly of the H5 and H7 subtypes, have caused human disease and mortality. There are many gaps in our knowledge of the pathogenesis and pathology of influenza in humans, despite published pathology studies of influenza virus infection going back at least to 1889 [25]. Because the majority of these studies by necessity took place at the time of pandemics, the last of which occurred in 1968, they lacked the benefit of advanced immunological and molecular biological techniques at our disposal today. This precluded accuracy in both localization of virus in tissues and identification of cell types involved.

Therefore, directed pathology studies, based both on biopsies of influenza patients and autopsies of fatal cases, need to be performed to fill in these gaps. These studies ideally should cover the broad scale of presentation of both human and avian influenza virus infections in humans, from uncomplicated disease to pneumonia and extra-respiratory complications. Also, these pathology studies need to be integrated with virological, immunological, and clinical aspects of influenza virus infection. The knowledge gained can be used to compare and contrast human and avian influenza virus infections in humans. It can also supplement knowledge from laboratory, clinical, and population studies to gain a better overall picture of influenza in humans, in order to guide strategies to combat this many-faceted disease.

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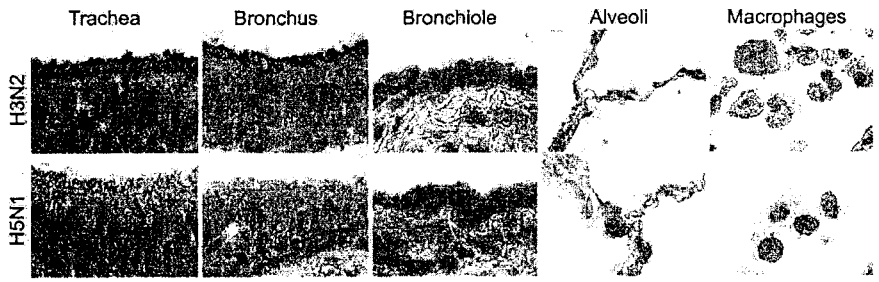

Figure 1.
Attachment of human H3N2 influenza virus (top row) and highly pathogenic avian H5N1 virus (bottom row) in human trachea, lower respiratory tract (bronchus, bronchiole, and alveoli), and alveolar macrophages [5].

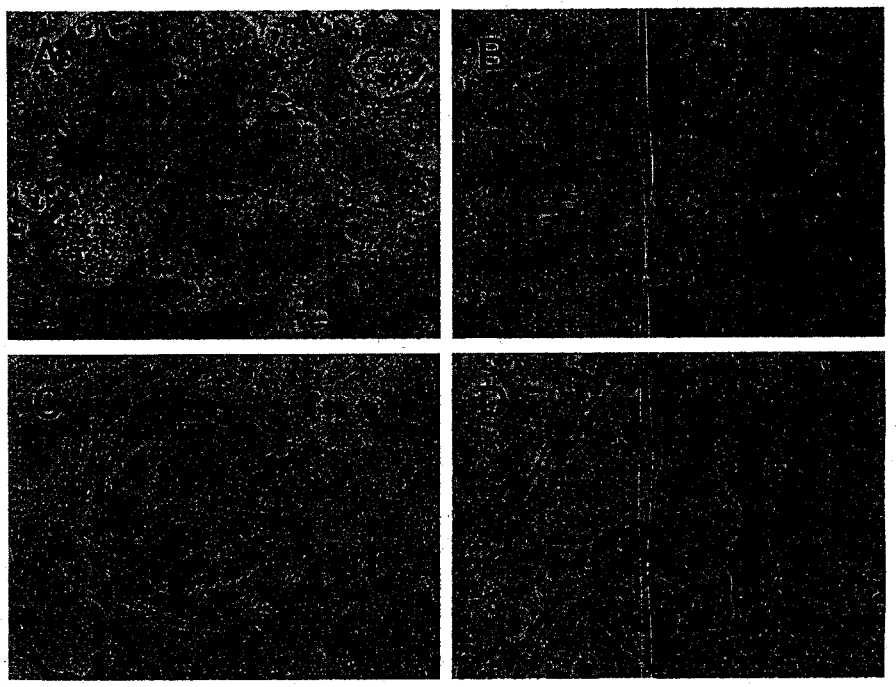

Figure 2.
Charastic lesions of human influenza virus infection in the lung. (A) Acute massive alveolar edema and congestion (1957 pandemic autopsy case, original magnification 200X). (B) Acute massive alveolar edema with hyaline membrane formation and interstitial inflammation (1918 pandemic autopsy case, original magnification 200X). (C) Thrombus in a small pulmonary vessel (1918 pandemic autopsy case (original magnification 40X). (D) Regeneration as evidenced by alveolar type II pneumocyte hyperplasia and interstitial fibrosis (1918 pandemic autopsy case, original magnification 200X).

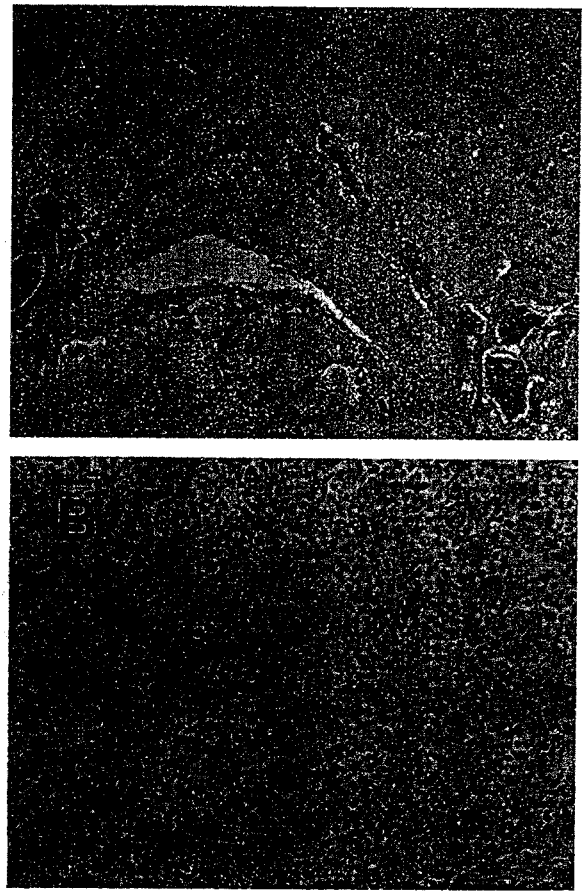

Figure 3.
Lesions of secondary bacterial infection in fatal human influenza cases. (A) Secondary bacterial bronchopneumonia with neutrophils in the lumen of a bronchiole with transmural infiltration of wall and into surrounding lung tissue (1918 pandemic autopsy case, original magnification 40X). (B) Secondary bacterial bronchopneumonia with neutrophils filling the lumen of an alveolus (1918 pandemic autopsy case, original magnification 40X).

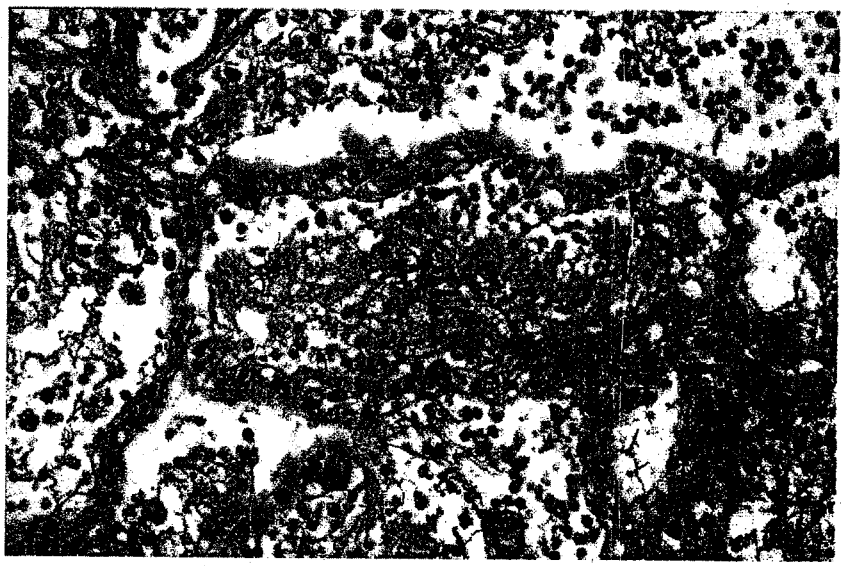

Figure 4.
Lesions of highly pathogenic avian influenza H7N7 virus infection in the lung [79]. There is diffuse alveolar damage, with serosanguineous fluid mixed with fibrin and neutrophils in alveolar lumina.

(13)

パンデミック(H1N1)2009 ウイルスに対する
献血適合性、血液製剤の安全性、血液供給の維持の評価のためのガイダンス案

2009 年 11 月 ガイダンス草案(この文書は意見聴取のみを目的としたものである。)

1 導入

●この文書は、パンデミック(H1N1)2009 ウイルスに対して、献血適合性と血液製剤の安全性を評価し、また、血液と血液製剤の供給量を維持するために、勧告を行うものである。

2 背景

●2009H1N1インフルエンザウイルスによるウイルス血症については、限られた情報しか得られていないが、米国その他の地域において、輸血により季節性インフルエンザに感染した事例は報告されておらず、同様に輸血により2009H1N1インフルエンザに感染した事例は報告されていない。

●現時点において、2009H1N1インフルエンザに感染した無症候状態の者の血液や血清から2009H1N1インフルエンザウイルスは分離されていないが、研究は継続中である。

●輸血による2009H1N1インフルエンザ感染の可能性は不明のままである。

3 勧告

献血の延期

● 現時点で利用可能なデータに基づけば、2009H1N1インフルエンザに感染した者、又は感染の疑いのある者、若しくはインフルエンザ様症状を呈している者と接触した者に対して献血を制限する理由はない。

● 2009H1N1インフルエンザに感染した者又は感染の疑いのある者は、献血の日に健康状態が良好であることを確保するため、解熱剤なしで熱が下がり、症状がなくなってから、少なくとも24時間経過するまでは献血を制限すべきである。

●更に、現時点で利用可能なデータに基づけば、2009H1N1インフルエンザワクチン(生ワクチン又は不活化ワクチン)を接種した者やオセルタミビル(商品名タミフル)及びザナミビル(商品名リレンザ)の予防投与を受けた者について、献血を制限する理由はない。

製品管理

● 献血後48時間以内に供血者が2009H1N1インフルエンザに感染、又は感染の疑いがある、若しくはインフルエンザ様症状を呈したという情報が寄せられた場合、メディカル・ディレクターは、既存の標準作業手引書(SOP)に基づいて、当該献血血液の安全性について評価しなければならない。

(12)

Guidance for Industry

Recommendations for the Assessment of Blood Donor Suitability, Blood Product Safety, and Preservation of the Blood Supply in Response to Pandemic (H1N1) 2009 Virus

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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