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REVIEW

Novel swine-origin influenza A virus in humans: another pandemic knocking at the door

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Abstract Influenza A viruses represent a continuous pandemic threat. In April 2009, a novel influenza A virus, the so-called swine-origin influenza A (H1N1) virus (S-OIV), was identified in Mexico. Although S-OIV originates from triple-reassortant swine influenza A (H1) that has been circulating in North American pig herds since the end of the 1990s, S-OIV is readily transmitted between humans but is not epidemic in pigs. After its discovery, S-OIV rapidly spread throughout the world within few weeks. In this review, we sum up the current situation and put it into the context of the current state of knowledge of influenza and influenza pandemics. Some indications suggest that a pandemic may be mild but even "mild" pandemics can result in millions of deaths. However, no reasonable forecasts how this pandemic may develop can be made at this time. Despite stockpiling by many countries and WHO, antiviral drugs will be limited in case of pandemic and resistances may emerge. Effective vaccines are regarded to be crucial for the control of influenza pandemics. However, production capacities are restricted and development/production of a S-OIV vaccine will interfere with manufacturing of seasonal influenza vaccines. The authors are convinced that S-OIV should be taken seriously as pandemic threat and underestimation of the menace by S-OIV to be by far more dangerous than its overestimation.

Keywords Swine influenza · H1N1 · Swine-origin influenza A (H1N1) virus · Pandemic

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Introduction

Influenza viruses are divided into three serologically different types (A, B, and C) according to the antigenicity of conserved inner virus structures, i.e., the nucleoprotein (NP) and matrix proteins (M1 and M2) of the envelope. While influenza virus types B and C are usually human-specific, influenza A virus is preferentially endemic in water birds like ducks, geese, and shore birds (gulls), which usually do not fall ill from this infection. Depending on the antigenicity of two envelope spikes, which first mediate virus adsorption to target cells in vivo or erythrocytes in vitro (hemagglutinin, H) and second the release of viral progeny from the infected cells (neuraminidase, N), influenza A viruses are divided into 16 H (H1–H16) and 9 N (N1–N9) groups resulting in theoretically 16 × 9 serologic subtypes. Up to date, 105 influenza A virus subtypes have been discovered, all endemic in water birds. However, some subtypes have adapted to other birds (chickens) and mammalians (pig, horse, humans) in species-specific strains [1].

An influenza pandemic is an epidemic of an influenza virus that spreads on a worldwide scale and infects a large proportion of the human population. Influenza pandemics may occur when a new influenza virus strain is transmitted to humans from another animal species. Species that are thought to be important in the emergence of new human strains are pigs, chickens, and ducks. The World Health Organisation (WHO) warns that there is a substantial risk of an influenza pandemic within the next few years. Among the strongest candidates are a highly pathogenic variation of the H5N1 subtype of influenza A virus as well as other avian influenza A viruses including H7N3, H7N7, and H9N2 [2–5]. The impact of a pandemic caused by influenza viruses is difficult to predict: it depends on virulence of the virus, existing immunity among people, cross protection by

Table 1 Influenza pandemics since the 20th century

Year	Virus subtype	Deaths (estimated)	Reassortment
1918/1919 "Spanish flu"	H1N1	50 million	All segments of avian origin
1957–1963 "Asian flu"	H2N2	2–4 million	Five segments of H1N1 + PB1, HA, NA of avian origin
1968–1970 "Hong Kong flu"	H3N2	1–2 million	Six segments of H2N2 + PB1, HA of avian origin
1977–1979 "Russian flu"	H1N1	0.7 million	Identical with "Spanish flu" virus
2009–? Swine-origin influenza A virus	H1N1	?	Three segments of classis swine North America, two segments avian North America, one segment H3N2, two segments Eurasian swine lineage

antibodies acquired from seasonal influenza infection, and host factors [1].

In humans, three subtypes of influenza A virus (H1N1, H2N2, H3N2) verifiably caused pandemics of high morbidity and mortality (Table 1) [6]. Retrospective serological analysis has indicated that H2N2 is likely to have been responsible for a pandemic which began in 1889, and that a mild pandemic in 1900 may have been caused by H3N8. The 1918/1919 influenza pandemic infected 25% of the world's population and caused worldwide at least 50 million deaths. The most recent influenza pandemics including Asian influenza (H2N2, 1957–1963, about 2–4 million killed) and Hong Kong influenza (H3N2, 1968–1970, about 1–2 million killed) were less aggressive. Based on the assumption that a pandemic may occur every 30–50 years, virologists and public health officials have advised increased preparedness and improvement of governmental plans.

At present, both H1N1 and H3N2 influenza viruses continue to be present in the human population representing lower pathogenic variants, nevertheless causing overmortality among elder people in each winter epidemic wave. Influenza surveillance data show that in recent history (1970 onward), H3N2 infections have caused almost 14 times more influenza-related deaths than H1N1 infections. Moreover, H3N2 viruses are associated with a higher epidemic severity index, as measured by the rate of pneumonia and influenza mortality [7, 8]. Worldwide, the annual seasonal human influenza A virus epidemics result in about 3–5 million cases of severe illness, and about 250,000 to 500,000 deaths (http://www.who.int/mediacentre/factsheets/fs211/en/index.html).

Swine influenza

Swine influenza refers to influenza caused by those influenza strains that usually infect pigs. Swine influenza viruses are most commonly of the H1N1 subtype, but other subtypes can also circulate in pigs including H1N2, H3N1, and H3N2 [9, 10]. The H1N1 form of swine influenza is one of the descendants of the strain that caused the 1918 influenza pandemic [11]. Pigs can be infected by swine, avian, and human seasonal influenza A viruses. The human H3N2 virus is thought to originate from pigs. Swine influenza is common in pigs in the Midwestern United States (and occasionally in other states), Mexico, Canada, South America, Europe (including the UK, Sweden, and Italy), Kenya, Mainland China, Taiwan, Japan, and other parts of eastern Asia. Morbidity tends to be high and mortality low (1–4%) [9]. The virus spreads among pigs by aerosol, direct and indirect contact, and asymptomatic carrier pigs. Outbreaks in pigs occur year-round, with an increased incidence in the autumn and winter in temperate zones. Many countries routinely vaccinate swine populations against swine influenza [12]. Although swine influenza viruses are normally species-specific and only infect pigs, they do sometimes cross the species barrier and infect humans [13]. When transmitted, the virus does not always cause human influenza disease. Often, the only sign of infection is detection of antibodies in the blood by laboratory tests. People who are in contact with pigs are at risk of swine influenza infection, especially after intense exposure. However, only about 50 such transmissions have been recorded since the mid-twentieth century when identification of influenza subtypes became possible. Swine influenza strains are rarely transmitted human to human. In humans, the symptoms of swine influenza are similar to those of seasonal human influenza and influenza-like illnesses in general, namely chills, fever, sore throat, muscle pain, severe headache, coughing, weakness, and general discomfort. Reported clinical presentations range from asymptomatic infection to severe pneumonia resulting in death [9].

A prominent human outbreak of swine influenza in humans was described in 1976 [14]. A swine H1N1 influenza

virus infected soldiers at Fort Dix, New Jersey, resulting in death of one soldier. Based on concerns that this might be the elicitor of a new pandemic, a vaccine was developed and a nationwide vaccination program was started. After vaccination of more than 40 million people, it became obvious that vaccination was associated with Guillain-Barré syndrome in about 1 out of 100,000 vaccinees indicating a five to tenfold higher incidence than usually observed. Since the virus disappeared, the vaccination program was stopped. Antibodies that cross-react against peripheral nerve antigen have been suspected to be responsible for the high rate of Gillain-Barré syndromes [14–17].

2009 swine-origin influenza A (H1N1) virus (S-OIV) outbreak in humans

There is current concern that the spread of a new strain of swine influenza A/H1N1 virus (designated as swine origin-influenza A (H1N1) virus (S-OIV)) might develop into a pandemic [18]. Currently, the WHO level of pandemic alert is defined to be 5 (out of 6 possible levels) indicating that a pandemic is considered to be imminent (current information about the status can be found at http://www.who.int/csr/disease/swineflu/en/index.html). First information about the emergence of S-OIV dates from 24 April 2009, coming from the US Centers for Disease Control and Prevention (CDC), WHO, and the Government of Mexico (http://www.who.int/csr/disease/swineflu/en/index.html; http://www.cdc.gov/h1n1flu). The time and location of the outbreak is still unknown, but the virus was first identified in Mexico in mid-March (http://www.washingtonpost.com/wp-dyn/content/article/2009/05/02/AR2009050202353.html?hpid=topnews). It was identified when Mexican authorities sent samples from a flu patient that it could not subtype to the Canadian Public Healthy Agency [19]. Within days, hundreds of more suspected cases were identified in Mexico, with cases also showing up in the USA. The first death from S-OIV occurred on 13 April 2009, when a diabetic woman from Oaxaca in Mexico died from respiratory complications (http://www.webcitation.org/5gNf8rqeS). By 13 May 2009, 33 countries had officially reported 5,728 cases of S-OIV infection resulting in 61 deaths. Mexico had reported 2,059 laboratory confirmed human cases of infection, including 56 deaths. The Unites States had reported 3,009 laboratory-confirmed human cases, including three deaths. Two further deaths were reported from Canada (358 cases) and Costa Rica (8 cases) (http://www.who.int/csr/don/2009_05_13/en/index.html).

Despite the origin, the current virus strain is able to sustain relatively high human-to-human transmission requiring no contact with swine. There are several parameters to measure transmission of influenza A viruses in humans. Although these parameters vary considerably among studies and outbreaks, they may help to asses a pandemic threat [20, 21]. These parameters include secondary attack rate, reproduction number (R_0), and generation time (Table 2). An assessment of the secondary attack rate in families in the United States suggests that S-OIV cases infected 25–30% of family members comparing with 5–20% of family members afflicted with seasonal influenza (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm58d0421a1.htm). This is in contrast to disease transmission during the last severe human outbreak of influenza A, the avian H5N1 influenza that resulted almost entirely from direct contact between humans and birds [1]. Epidemiological estimates place the R_0 at 1.4–1.6 persons infected per case [22]. A genetic analysis predicts R_0 of 1.2 (http://www.nature.com/news/2009/090505/full/459014a.html?s=news_rss). The generation time is probably at the low end of a range between 3 and 5 days [22]. At this point, S-OIV does not seem as transmissible as the 1918 pandemic H1N1 strain but appears substantially more transmissible than seasonal influenza. However, transmission data for S-OIV are still poor.

It has been also observed that S-OIV retains its ability to move between species. On 2 May 2009, it was announced that a Canadian farm worker who had traveled to Mexico had transmitted the disease to a herd of pigs (http://news.bbc.co.uk/2/hi/americas/8031309.stm). Noteworthy, S-OIV is spread by humans but is not epidemic in pigs. Therefore, preventive measures like culling all pigs in Egypt are not justified.

In Mexico, May usually marks the end of dry season which is advantageous for spread of influenza A viruses. It may be speculated that the high humidity of summer and the increased exposure to ultraviolet light will lead to the slowing of S-OIV spread in Mexico (http://news.nationalgeographic.com/news/2009/04/090430-swine-flu-summer.html).

Table 2 Basic transmission characteristics for the assessment of virus spread

Characteristic	Definition
Secondary attack	Proportion of a (relatively) defined cohort (e.g., household or school) that falls ill after contact with an infected person
Reproductive number (R_0)	The average number of secondary cases infected by each primary case at a defined time
Generation time	The time period between infection and becoming infective for others

On the other hand, the outbreak comes at the beginning of the influenza season of the Southern Hemisphere countries such as New Zealand, South Africa, and parts of South America.

Generation of S-OIV (swine origin influenza A (H1N1) virus)

Influenza viruses harbor a negative-sense RNA genome, which is transcribed by its own polymerase. RNA transcription is associated with many point mutations persistently producing many changes in virus proteins including the surface proteins H and N [23, 24]. The mutations in surface proteins result in antigen drift which helps the virus to escape the immunity of its host. Since the influenza virus genome is segmented into eight parts, two or more different virus variants infecting the same cell can produce progeny virus with a mixed genome, which supports the variability of viral structures. It may result in an antigenic shift, if two different subtypes of influenza A virus reassort their genomic segments. The emergence of H2N2 and H3N2 in mankind has been traced to such genomic reassortment [6]. The 1957 Asian influenza virus (H2N2) acquired avian polymerase basic protein 1 (PB1), H and N genes, and the 1968 Hong Kong influenza virus (H3N2) acquired avian H and PB1 genes.

The cell receptor for influenza viruses is membrane-based sialic acid (SiA = *N*-acetylic neuraminic acid). Similar to a key in a lock, this SiA fits into a pocket-like structure at the top of the viral H protein, which serves as anti-receptor. The membrane of avian or mammalian cells expresses slightly different configurations of SiA, depending on how the galactose residue of SiA is linked to membrane oligosaccharides. On avian cells, the galactose of SiA is linked via α 2, 3 C atoms (α2,3 SiA) and on mammalian cells via α 2, 6 C atoms (α2,6 SiA). During evolution avian and human influenza viruses acquired H adapted to those species-specific receptor modifications [1]. In the pig trachea, epithelial cells contain both α2,3 SiA and α2,6 SiA, explaining why pigs are highly susceptible to both human and avian viruses and are thought to be a "mixing vessel" for avian and human viruses, reassortment of which might give rise to pandemic strain [1].

Swine-origin influenza A (H1N1) virus emerged from a triple-reassortant swine influenza A (H1N1) virus [18, 25]. Triple-reassortant swine influenza A viruses, containing genes from avian, human, and swine influenza viruses, emerged and became enzootic in pigs in North America at the end of the 1990s. Spread to humans was detected sporadically, but all patients recovered. Severe illnesses of the lower respiratory tract and unusual influenza symptoms like diarrhea were reported [25]. S-OIV is a reassortant of triple-reassortant swine influenza A (H1N1) virus that contains classic swine RNA-segments from the North America lineage [H, NP, non-structural proteins (NS)], avian influenza RNA segments from the North America lineage [polymerase basic protein 2 (PB2), polymerase acidic protein (PA)], and PB1 of human seasonal H3N2 viruses [18, 25]. Moreover, the N and M segments, that are of classic North America lineage swine origin in triple-reassortant swine

Table 3 RNA segments of swine-origin influenza A (H1N1) virus (S-OIV)

RNA segment	Encodes for	Derived from
H	H (hemagglutinin, surface glycoprotein, receptor binding, fusion activity)	Classic swine, North American lineage
N	N (neuraminidase, surface glycoprotein)	Eurasian swine lineage
M	M1 (matrix protein, interaction with vRNPs and surface glycoproteins, nuclear export, budding);	Eurasian swine lineage
	M2 (membrane protein, proton channel)	
PB2	PB2 (polymerase basic protein 2, component of RNA polymerase, cap recognition)	Avian, North American lineage
PB1	PB1 (polymerase basic protein 1, component of RNA polymerase, endonuclease activity, elongation);	Human seasonal H3N2
	PB1-F2 (proapoptotic activity)	
PA	PA (polymerase acidic protein, component of RNA polymerase, protease)	Avian, North American lineage
NP	NP (nucleoprotein, RNA binding, RNA synthesis, RNA nuclear export)	Classic swine, North American lineage
NS	NS1 (non-structural protein 1, multifunctional protein, viral interferon antagonist);	Classic swine, North American lineage
	NS2/NEP (non-structural protein 2, nuclear export of vRNPs)	

influenza A (H1N1) viruses, were exchanged by N and M from the Eurasian influenza A (H1N1) swine lineage (Table 3) [18, 25].

Virulence and pathogenesis

The outcome of influenza virus infection is influenced by the host's immune status and the virulence of the influenza strain [1]. In an immunologically naïve host, virulence is mostly determined by the virus. Protective immune responses are mostly directed against the influenza virus major surface glycoproteins H and N. The novel genetics of S-OIV reduce the probability of a substantial immunity in humans although some protection of humans that had been infected naturally with H1N1 viruses cannot be excluded. Antibodies to the matrix M2 protein, which is conserved within A-type influenza viruses, are cross-protective between different subtype-virus infections, although the level of protection is limited. Moreover, peptides generated from influenza endogenous antigens such as NP which are targets for cytotoxic lymphocytes (CTLs) may elicit immune responses that show cross-reactivity in their recognition of the different subtypes of human influenza A viruses [5, 26].

Many viral genes can determine virulence and contribute to pathogenicity of influenza A viruses. H proteins, which have to be cleaved by cellular proteases before initiation of infection through fusion between viral envelope and endosomale membrane, possess a single arginine at the cleavage site in low-pathogenic viruses. Cleavage of the H of low-pathogenic viruses is, therefore, limited to trypsin-like proteases and occurs only in few organs, resulting in mild or asymptomatic infection. H proteins of highly pathogenic viruses have multiple basic amino acids at the cleavage site enabling H cleavage by multiple proteases in different organs [2, 6, 27]. Moreover, the polymerase complex (including the PB1, PB2 and PA proteins) is also implicated in virulence [2, 6, 28]. Some mutations that can enhance the activity of polymerase and increase virulence in mice have been found in H5N1 highly pathogenic avian influenza virus strains [29]. Notably, H5N1 viruses that are virulent in mice encode lysine at position 627 in PB2, whereas H5N1 viruses that are not virulent in mice, as well as other avian influenza A virus strains, encode glutamic acid at this position [30]. The substitution of aspartic acid to asparagine at position 701 in PB2 has been also shown to play a crucial role in the replication and lethality of H5N1 viruses in mice [31]. The viral PB1 segment is of particular interest as virulence factor, since, in addition to the glycoprotein genes, the PB1 gene was the only other segment that was exchanged in the pandemic viruses of 1957 and 1968. Reconstruction of prototypic 1918 pandemic virus by reverse genetics demonstrated that all eight virus segments originated from an avian host [32]. Therefore, three pandemic viruses had avian-like PB1 genes. Recent identification and characterization of a novel influenza virus protein PB1-F2 encoded by the PB1 gene introduced a further potential virulence factor that may explain the selection of PB1 in pandemic influenza viruses [33, 34].

A preliminary analysis of S-OIV proteins involved in virus virulence and pathogenicity revealed that they are most similar to strains that cause mild symptoms in humans. In concordance, there is low mortality (5 cases until 13 May 2009) outside of Mexico and the virus is unlikely to cause severe infections similar to those caused by the 1918 pandemic influenza or the H5N1 influenza. However, there is a concern of further mutations of the virus which may change its virulence and pathogenicity dramatically (http://www.nature.com/news/2009/090505/full/459014a.html?s=news_rss). It is not also clear why the case symptoms outside Mexico were primarily mild [18] while the Mexican cases had led to multiple deaths. The Mexican fatalities are alleged to be mainly young adults of 25–45, a common trait of pandemic influenza (http://www.newscientist.com/article/dn17025-deadly-new-flu-virus-in-us-and-mexico-may-go-pandemic.html). In contrast, seasonal influenza strains produce the worst symptoms in young children, the elderly, and others with weaker immune systems. However, reliable data are still lacking in Mexico and the number of cases in other countries remains too small statistically to assess mortality rate.

The incubation time appears to range between 2 and 7 days for S-OIV [18]. Although this can only be regarded as rough and preliminary estimate, this may be longer than that of seasonal influenza A viruses that has been calculated to be about 1.4 days [35]. Based on seasonal influenza data, viral shedding might be expected from 1 day prior to disease onset until 5–7 days after first symptoms or until symptoms resolve. In certain patient groups including immunocompromised individuals, severely ill patients, and young children virus shedding time may be prolonged [36].

There seems to be no genetic explanation for the greater severity of Mexican S-OIV cases since samples from Mexico, Nova Scotia, and Ontario have the same sequence (http://www.canada.com/Health/Canadian+completes+sequencing+virus/1569084/story.html; http://www.theglobeandmail.com/servlet/story/RTGAM.20090506.wcanflu0506/BNStory/National/home?cid=al_gam_mostview). Research on previous pandemic strains suggested that mortality can vary widely between different countries, with mortality being concentrated in the developing world [37]. Nutritional status of the host can influence not only the host response to the pathogen, but can also influence the genetic make-up of the viral genome [38]. Moreover, bacterial co-infections are also being considered as possible cause for differences in

outcome of influenza infection in different locations. It has been suggested that the majority of deaths in 1918–1919 influenza pandemic likely resulted directly from secondary bacterial pneumonia caused by common upper respiratory-tract bacteria (largely streptococcal or pneumoccocal bronchopneumonias) rather than from "primary" viral pneumonia (i.e., with little or no bacterial growth) [39]. In the current S-OIV outbreak, the cause of first deaths was diagnosed as atypical pneumonia, a pneumonia which, helped by the influenza, becomes more dangerous. Such situation requires early and aggressive treatment, including antibiotic and intensive care which may be less available in some areas resulting in increased morbidity and mortality. This also suggests that antibiotic treatment should be included in any preparedness strategy. Notably, choice of adequate antibiotic therapy may be crucial. Some antibiotics may even heighten morbidity and mortality [40]. Other antibiotics like some macrolide antibiotics were shown to inhibit replication of influenza A viruses in vitro [41] and exert inhibitory effects on influenza infection in vivo in animal models [42].

Prevention and treatment

Influenza A viruses including S-OIV are transmitted from infected individuals through air by coughs or sneezes, creating aerosols containing the virus [43, 44]. Influenza can also be transmitted by saliva, nasal secretions, feces, and blood. Infections occur through contact with these body fluids or with contaminated surfaces. Based on data showing that 25% of S-OIV patients had diarrhea [18], the potential for fecal viral shedding and fecal-oral transmission should be considered and investigated.

Influenza viruses can remain infectious for about 1 week at human body temperature, over 30 days at 0°C, and indefinitely at very low temperatures (such as lakes in northeast Siberia). However, most influenza strains can be inactivated easily by disinfectants and detergents [45]. Moreover, influenza A viruses are relatively sensitive to higher temperatures. Importantly, swine influenza virus are killed by cooking temperatures of 70°C, corresponding to the general guidance for the preparation of pork and other meat. In fact, swine influenza has not been shown to be transmitted to people through properly handled and prepared pig meat or other products derived from pigs [46].

The standard recommendations that can help to prevent the spread of seasonal influenza are also effective for prevention of S-OIV (see http://www.who.int/csr/disease/swineflu/en/index.html; http://www.cdc.gov/h1n1flu/). CDC and WHO recommendations involve not touching the mouth, nose or eyes, as these are primary modes of transmission. Coughing into a tissue, disposal of the tissue, and immediate hand washing is recommended. Generally, hands should be washed often with soap and water, especially after being in the company of the public. Alcohol-based hand cleaners are also effective. However, there is so far little data available on the risk of airborne transmission of S-OIV virus. Mexican authorities are distributing surgical masks to the general public. The authorities of some other countries consider facial masks unnecessary for the general public. Many authorities recommend the use of respirators by health-care workers in the vicinity of pandemic influenza patients, in particular during aerosol generating procedures.

It is not known whether current human seasonal influenza vaccines can provide any protection to S-OIV. The development of a vaccine protecting from S-OIV infection may be crucial if pandemic proceeds and is under consideration. Therefore, WHO needs to access as many viruses as possible in order to select the most appropriate candidate virus. Current development, large-scale manufacturing, distribution, and delivery of a new vaccines may take several months. The WHO announced that production of the unchanged seasonal vaccine should continue for now, and that the WHO would assist the development process an effective vaccine (http://www.who.int/mediacentre/news/statements/2009/h1n1_20090427/en/index.html). Following WHO, two separate immunisations might be required for seasonal influenza and S-OIV. A decision on whether to begin producing a S-OIV vaccine is pending.

Most of the previously reported swine influenza cases recovered fully from disease without requiring medical attention and without antiviral medicine [18, 25]. However, there are two approved classes of antiviral drugs used against influenza, including N inhibitors such as oseltamivir (Tamiflu) and zanamivir (Relenza), and M2 protein inhibitors (adamantane derivatives such as amantadine and rimantadine) [4]. N inhibitors are currently being preferred for influenza virus infections since they are less toxic and more effective [1, 4]. Antiviral treatment should be started soon after influenza onset (within 2 days), but treatment with antiviral drugs should be still considered after 48 h of symptom onset, particularly for hospitalised patients or people at high risk for influenza-related complications [4]. Prophylactic treatment may be considered for persons who are not ill, but who have been in (suspected) contact with influenza-infected individuals. When used to prevent influenza disease, antiviral drugs are about 70–90% effective. The duration of prophylactic treatment has to be adjusted depending on the individual situation.

Currently, oseltamivir is generally regarded as the N inhibitor of choice due its more convenient administration route (oral) compared to zanamivir (inhalation). Initially, N inhibitors were assumed to be less prone to select resistant influenza viruses than M2 protein inhibitors. However, treatment of H3N2 influenza led to resistance in 0.4% of

adult cases and 5.5% of children [4]. Moreover, the CDC released data showing a high level of oseltamivir resistance among nearly all seasonal influenza A/H1N1 isolates on 12 December 2008 [47]. Notably, all of these H1N1 isolates were susceptible to adamantanes, whereas all H3N2 isolates were resistant against adamantanes. Of major concern is the fact that these oseltamivir-resistant viruses appear fit and readily transmissible from human-to-human [48, 49]. In this context, zanamivir is an attractive antiviral drug because of non-overlapping resistance patterns with oseltamivir [4]. In fact, the oseltamivir-resistant H1N1 isolates retained susceptibility to zanamivir [48, 49]. At the moment, data on the clinical effectiveness of anti-influenza drugs against S-OIV is lacking. Genetic and penotypic analysis indicated S-OIV to be sensitive to oseltamivir and zanamivir, but resistant to adamantanes [50].

The use of combination therapy has been suggested in order to decrease the emergence of resistant virus strains [51]. Simulations reveal that using a second effective antiviral such as zanamivir to treat even 1% of cases would delay the spread of resistant strains. Even a drug such as amantadine (Symmetrel) for which resistance frequently emerges may be useful in combination therapy. However, since S-OIV have been suspected to be adamantane-resistant [50] it remains questionable if this drug class may have a role in the case of S-OIV pandemic.

As of 5 May 2009, the CDC suggested that therapy with neuraminidase inhibitors should be given with priority to hopitalised patients and and individuals of high risk for complications for seasonal influenza. (http://www.cdc.gov/h1n1flu/antiviral.htm). The WHO states that the information is insufficient to make recommendations on the use of the antivirals in prevention and treatment of swine influenza virus infection [46]. Clinicians should make decisions based on the clinical and epidemiological assessment and harms and benefits of the prophylaxis/treatment of the patients.

Although many nations and the WHO have stockpiled oseltamivir, shortages may arise in the case of pandemic. Pharmacokinetic investigations revealed that co-administration of oseltamivir with probenecid (a substance registered for treatment of gout) results in decreased elimination of oseltamivir carboxylate (the anti-influenza effective metabolite of oseltamivir) and, therefore, in increased oseltamivir carboxylate levels [51, 52]. Therefore, combination of oseltamivir with probenicid may enable delivery of oseltamivir treatment to more influenza patients.

Besides registered anti-influenza drugs, ribavirin and interferons, antiviral substances approved for other indications than influenza, were shown to inhibit influenza A virus replication and may, therefore, serve as additional treatment options [4]. Moreover, non-antiviral drugs not normally employed in the treatment of viral pneumonia (e.g., statins, macrolide antibiotics, gemfibrozil, acetylsalicylic acid) or natural products (flavonoids, flavones, polyphenols) have been suggested for the control of influenza virus replication and/or respiratory inflammation that accompanies severe influenza A virus infections [1].

Conclusions

There is considerable concern that the current S-OIV outbreak in humans may become a pandemic due to its geographical spread of multiple community outbreaks, suspected little to no immunity, and (initial) information about somewhat unusual age groups affected. The lack of data about crucial factors such as virulence, transmission rates and patterns, effectiveness of current treatments as well as innate propensity of influenza virus to develop in pandemic strains preclude a reliable prediction. Although virulence and pathogenicity seem so far mild more aggressive viruses may arise. In fact, the pandemic of 1918, which also seemed mild in its early phases, finally killed at least 50 million people worldwide. Moreover, even the “mild” pandemics of 1957 and 1968 killed many people. In contrast to previous pandemics, antiviral agents, antibiotics to treat bacterial co-infections, and improved supportive care may help to manage influenza disease in infected persons. Nevertheless, the only way to avoid an influenza pandemic (wave) is an effective vaccination program. Therefore, it is important to increase and coordinate preventive activities at a global level to slow virus transmission to provide enough time for the preparation and distribution of a well-matched vaccine.

References

1. Michaelis M, Doerr HW, Cinatl J Jr (2009) Of chickens and men: avian influenza in humans. Curr Mol Med 9:131–151. doi:10.2174/156652409787581565
2. Cinatl J Jr, Michaelis M, Doerr HW (2007) The threat of avian influenza A (H5N1). Part I: epidemiologic concerns and virulence determinants. Med Microbiol Immunol (Berl) 196:181–190. doi:10.1007/s00430-007-0042-5
3. Cinatl J Jr, Michaelis M, Doerr HW (2007) The threat of avian influenza a (H5N1): part II: clues to pathogenicity and pathology. Med Microbiol Immunol (Berl) 196:191–201. doi:10.1007/s00430-007-0045-2
4. Cinatl J Jr, Michaelis M, Doerr HW (2007) The threat of avian influenza A (H5N1). Part III: antiviral therapy. Med Microbiol Immunol (Berl) 196:203–212. doi:10.1007/s00430-007-0048-z
5. Cinatl J Jr, Michaelis M, Doerr HW (2007) The threat of avian influenza A (H5N1). Part IV: development of vaccines. Med Microbiol Immunol (Berl) 196:213–225. doi:10.1007/s00430-007-0052-3
6. Horimoto T, Kawaoka Y (2005) Influenza: lessons from past pandemics, warnings from current incidents. Nat Rev Microbiol 3:591–600. doi:10.1038/nrmicro1208

7. Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH, Schonberger LB (1997) The impact of influenza epidemics on mortality: introducing a severity index. Am J Public Health 87:1944–1950. doi:10.2105/AJPH.87.12.1944
8. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, Fukuda K (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 289:179–186. doi:10.1001/jama.289.2.179
9. Kothalawala H, Toussaint MJ, Gruys E (2006) An overview of swine influenza. Vet Q 28:46–53
10. Ducatez MF, Webster RG, Webby RJ (2008) Animal influenza epidemiology. Vaccine 26:D67–D69. doi:10.1016/j.vaccine.2008.07.064
11. Taubenberger JK, Morens DM (2006) 1918 Influenza: the mother of all pandemics. Emerg Infect Dis 12:15–22
12. Thacker E, Janke B (2008) Swine influenza virus: zoonotic potential and vaccination strategies for the control of avian and swine influenzas. J Infect Dis 197:S19–S24. doi:10.1086/524988
13. Myers KP, Olsen CW, Gray GC (2007) Cases of swine influenza in humans: a review of the literature. Clin Infect Dis 44:1084–1088. doi:10.1086/512813
14. Sencer DJ, Millar JD (2006) Reflections on the 1976 swine flu vaccination program. Emerg Infect Dis 12:29–33
15. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, Eddins DL, Bryan JA (1979) Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. Am J Epidemiol 110:105–123
16. Marks JS, Halpin TJ (1980) Guillain-Barré syndrome in recipients of A/New Jersey influenza vaccine. JAMA 243:2490–2494. doi:10.1001/jama.243.24.2490
17. Nachamkin I, Shadomy SV, Moran AP, Cox N, Fitzgerald C, Ung H, Corcoran AT, Iskander JK, Schonberger LB, Chen RT (2008) Anti-ganglioside antibody induction by swine (A/NJ/1976/H1N1) and other influenza vaccines: insights into vaccine-associated Guillain-Barré syndrome. J Infect Dis 198:226–233. doi:10.1086/589624
18. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team (2009) Emergence of a Novel Swine-Origin Influenza A (H1N1) Virus in Humans. N Engl J Med [Epub ahead of print]
19. Butler D (2009) Swine flu goes global. Nature 458:1082–1083. doi:10.1038/4581082a
20. Andreasen V, Viboud C, Simonsen L (2008) Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implications for pandemic control strategies. J Infect Dis 197(2):270–278. doi:10.1086/524065
21. Viboud C, Bjørnstad ON, Smith DL, Simonsen L, Miller MA, Grenfell BT (2006) Synchrony, waves, and spatial hierarchies in the spread of influenza. Science 312:447–451. doi:10.1126/science.1125237
22. Fraser C, Donnelly CA, Cauchemez S, Hanage WP, Van Kerkhove MD, Hollingsworth TD, Griffin J, Baggaley RF, Jenkins HE, Lyons EJ, Jombart T, Hinsley WR, Grassly NC, Balloux F, Ghani AC, Ferguson NM, Rambaut A, Pybus OG, Lopez-Gatell H, Apluche-Aranda CM, Chapela IB, Zavala EP, Guevara DM, Checchi F, Garcia E, Hugonnet S, Roth C (2009) The WHO rapid pandemic assessment collaboration. Pandemic potential of a strain of influenza A (H1N1): early findings. Science [Epub ahead of print]
23. Ghedin E, Sengamalay NA, Shumway M, Zaborsky J, Feldblyum T, Subbu V, Spiro DJ, Sitz J, Koo H, Bolotov P, Dernovoy D, Tatusova T, Bao Y, St George K, Taylor J, Lipman DJ, Fraser CM, Taubenberger JK, Salzberg SL (2005) Large-scale sequencing of human influenza reveals the dynamic nature of viral genome evolution. Nature 437:1162–1166. doi:10.1038/nature04239
24. Neumann G, Kawaoka Y (2006) Host range restriction and pathogenicity in the context of influenza pandemic. Emerg Infect Dis 12:881–886
25. Shinde V, Bridges CB, Uyeki TM, Shu B, Balish A, Xu X, Lindstrom S, Gubareva LV, Deyde V, Garten RJ, Harris M, Gerber S, Vagoski S, Smith F, Pascoe N, Martin K, Dufficy D, Ritger K, Conover C, Quinlisk P, Klimov A, Bresee JS, Finelli L (2009) Triple-reassortant swine influenza A (H1) in humans in the United States, 2005–2009. N Engl J Med [Epub ahead of print]
26. Allwinn R, Preiser W, Rabenau H, Buxbaum S, Stürmer M, Doerr HW (2002) Laboratory diagnosis of influenza—virology or serology? Med Microbiol Immunol (Berl) 191:157–160. doi:10.1007/s00430-002-0137-y
27. Stieneke-Grober A, Vey M, Angliker H, Shaw E, Thomas G, Roberts C, Klenk HD, Garten W (1992) Influenza virus hemagglutinin with multibasic cleavage site is activated by furin, a subtilisin-like endoprotease. EMBO J 11:2407–2414
28. Salomon R, Webster RG (2009) The influenza virus enigma. Cell 136(3):402–410. doi:10.1016/j.cell.2009.01.029
29. Gabriel G, Dauber B, Wolff T, Planz O, Klenk HD, Stech J (2005) The viral polymerase mediates adaptation of an avian influenza virus to a mammalian host. Proc Natl Acad Sci USA 102:18590–18595. doi:10.1073/pnas.0507415102
30. Hatta M, Gao P, Halfmann P, Kawaoka Y (2001) Molecular basis for high virulence of Hong Kong H5N1 influenza A viruses. Science 293:1840–1842. doi:10.1126/science.1062882
31. Li Z, Chen H, Jiao P, Deng G, Tian G, Li Y, Hoffmann E, Webster RG, Matsuoka Y, Yu K (2005) Molecular basis of replication of duck H5N1 influenza viruses in a mammalian mouse model. J Virol 79:12058–12064. doi:10.1128/JVI.79.18.12058-12064.2005
32. Tumpey TM, Basler CF, Aguilar PV, Zeng H, Solorzano A, Swayne DE, Cox NJ, Katz JM, Taubenberger JK, Palese P, Garcia-Sastre A (2005) Characterization of the reconstructed 1918 Spanish influenza pandemic virus. Science 310:77–80. doi:10.1126/science.1119392
33. Zamarin D, Garcia-Sastre A, Xiao X, Wang R, Palese P (2005) Influenza virus PB1-F2 protein induces cell death through mitochondrial ANT3 and VDAC1. PLoS Pathog 1:e4. doi:10.1371/journal.ppat.0010004
34. Coleman JR (2007) The PB1-F2 protein of Influenza A virus: increasing pathogenicity by disrupting alveolar macrophages. Virol J 4:9. doi:10.1186/1743-422X-4-9
35. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA (2009) Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis 9:291–300. doi:10.1016/S1473-3099(09)70069-6
36. Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Leach S, Valleron AJ (2008) Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am J Epidemiol 167:775–785. doi:10.1093/aje/kwm375
37. Murray CJ, Lopez AD, Chin B, Feehan D, Hill KH (2006) Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–1920 pandemic: a quantitative analysis. Lancet 368:2211–2218. doi:10.1016/S0140-6736(06)69895-4
38. Beck MA, Handy J, Levander OA (2004) Host nutritional status: the neglected virulence factor. Trends Microbiol 12:417–423. doi:10.1016/j.tim.2004.07.007
39. Morens DM, Taubenberger JK, Fauci AS (2008) Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis 198:962–970. doi:10.1086/591708
40. Hussell T, Wissinger E, Goulding J (2009) Bacterial complications during pandemic influenza infection. Future Microbiol 4:269–272. doi:10.2217/fmb.09.3
41. Miyamoto D, Hasegawa S, Sriwilaijaroen N, Yingsakmongkon S, Hiramatsu H, Takahashi T, Hidari K, Guo CT, Sakano Y, Suzuki

T, Suzuki Y (2008) Clarithromycin inhibits progeny virus production from human influenza virus-infected host cells. Biol Pharm Bull 31:217–222. doi:10.1248/bpb.31.217
42. Tsurita M, Kurokawa M, Imakita M, Fukuda Y, Watanabe Y, Shiraki K (2001) Early augmentation of interleukin (IL)-12 level in the airway of mice administered orally with clarithromycin or intranasally with IL-12 results in alleviation of influenza infection. J Pharmacol Exp Ther 298:362–368
43. Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M (2007) Transmission of influenza A in human beings. Lancet Infect Dis 7:257–265. doi:10.1016/S1473-3099(07)70029-4
44. Tellier R (2006) Review of aerosol transmission of influenza A virus. Emerg Infect Dis 12:1657–1662
45. Suarez DL, Spackman E, Senne DA, Bulaga L, Welsch AC, Froberg K (2003) The effect of various disinfectants on detection of avian influenza virus by real time RT-PCR. Avian Dis 47:1091–1095. doi:10.1637/0005-2086-47.s3.1091
46. WHO (2009) Swine influenza: frequently asked questions. Wkly Epidemiol Rec 84:149–151
47. Centers for Disease Control, Prevention (CDC) (2008) Update: influenza activity-United States, September 28–November 29, 2008. MMWR Morb Mortal Wkly Rep 57:1329–1332
48. Moscona A (2008) Global transmission of oseltamivir-resistant influenza. N Engl J Med 360:953–956. doi:10.1056/NEJMp0900648
49. Poland GA, Jacobson RM, Ovsyannikova IG (2009) Influenza virus resistance to antiviral agents: a plea for rational use. Clin Infect Dis 48:1254–1256. doi:10.1086/598989
50. Centers for Disease Control, Prevention (CDC) (2009) Update: drug susceptibility of swine-origin influenza A (H1N1) viruses, April 2009. MMWR Morb Mortal Wkly Rep 58:433–435
51. Wattanagoon Y, Stepniewska K, Lindegårdh N, Pukrittayakamee S, Silachamroon U, Piyaphanee W, Singtoroj T, Hanpithakpong W, Davies G, Tarning J, Pongtavornpinyo W, Fukuda C, Singhasivanon P, Day NP, White NJ (2009) Pharmacokinetics of high-dose oseltamivir in healthy volunteers. Antimicrob Agents Chemother 53:945–952. doi:10.1128/AAC.00588-08
52. Holodniy M, Penzak SR, Straight TM, Davey RT, Lee KK, Goetz MB, Raisch DW, Cunningham F, Lin ET, Olivo N, Deyton LR (2008) Pharmacokinetics and tolerability of oseltamivir combined with probenecid. Antimicrob Agents Chemother 52:3013–3021. doi:10.1128/AAC.00047-08