Chapter 12
History of Influenza Pandemics

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Abstract Influenza pandemics have been amongst the largest and the deadliest epidemics in the history of man, and were observed already in ancient times. For example, records from the fifth century B.C. suggest that influenza pandemics were observed in ancient Greece. In Europe, during the Middle Ages and the Renaissance, numerous concordant reports from different countries describe epidemics of respiratory infections that resemble influenza pandemics. However, it is not possible to be certain that these epidemics were due to influenza. In the twentieth century, three influenza pandemics have occurred, including the deadly Spanish flu pandemic. Modern virology has unravelled the mechanisms of emergence of pandemic viruses, and considerable knowledge on influenza viruses has been accumulated. The picture is now clear: influenza A is a zoonotic virus whose reservoir is in wild birds. In rare cases, these avian viruses are introduced into man and, eventually, become pandemic viruses. Although these mechanisms are now understood, the time frame required for adaptation of the avian virus to its new host remains unknown. Maybe the next pandemic will show us how rapid this adaptation can be.

12.1 Introduction

The world has seen pandemics of influenza A for a very long time (Creighton 1965; Major 1945; Shope 1958). Nevertheless, even if records of past epidemics describe diseases with clinical presentation resembling influenza infections, it is difficult to be certain that these epidemics of the past were the consequence of emerging influenza viruses. Recent knowledge has revealed that pandemic viruses emerge from the avian reservoir (Scholtissek 1994). In some cases, the emerging influenza requires adaptation before its dissemination in man. This adaptation can be

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achieved in an intermediate host, e.g. pigs or possibly poultry (Russell and Webster 2005). The history of pandemics seems to have started very early in mankind; some assume that influenza viruses could have become zoonotic and subsequently adapted to man when poultry started to be raised for food.

In the Sixth Book of the Epidemics, Hypocratus describes a contagious upper respiratory tract infection whose symptoms suggest an influenza-like illness. Indeed, epidemic rheumy fever and influenza-like symptoms are reported throughout human history, suggesting very contagious pathogens and very high attack rates (Creighton 1965; Patterson 1986). This conjunction is highly suggestive of influenza pandemics, especially when the mortality rates described are quite high.

This chapter describes some of the information available from past centuries about widespread upper respiratory tract infections that could have been influenza pandemics.

12.2 Before 1500

Early information on putative pandemics is difficult to collect. The first report seems to be that of Hypocratus, who described, in the Book of the Epidemics, a highly contagious disease observed in northern Greece (ca. 410 B.C.). The symptoms described very much resemble those of influenza. The second convincing report comes from England in 664 A.D. Monks reported that an epidemic swept through Britain, supposedly facilitated by clerics travelling from a synod held at Whitby Abbey (Creighton 1965).

Later reports from different parts of Europe suggest that a pandemic was observed in England, France and Italy in 1173–1174. At this time, the word "plague" was used for every epidemic responsible for significant mortality (Major 1945). A French chronicle reported that: "In May, an inflammatory plague spread all over the Occident, and all eyes swept following a cruel rhinorhea". Similar reports were provided by the churchmen of Melrose Abbey, who described "an eveil and unheard-of-cough". This might well have been an influenza pandemic, this assumption being supported by the emergence of obviously similar diseases, with very high attack rates, even mortality, at a time when the average lifespan was not longer than 30 years (Creighton 1965).

In 1357, an epidemic was described in Florence in Italy, for which the word "influenza" was used for the first time (for "influenza di freddo" or cold influence). Again, in the fourteenth century, in the South of France, a doctor from Montpellier reported an epidemic of upper respiratory tract infection that was "so important that only one out of ten of the population could escape the disease". Elderly people died in huge numbers during this epidemic, although the word "elderly" should be understood within the criteria of the times (Major 1945).

In 1414, French chroniclers described a very large epidemic that started in February. According to their writings, this epidemic was brought by a "smelly and

cold wind" (in French, "vent puant et tout plein de froidure"). They reported that everyone, including clericals, nobles, and ordinary people, became infected. In Paris, up to 100,000 people were so ill that they "lost the eating and drinking. They could do nothing else than resting, they had a very high fever with shivering and cough…". This cough was so severe that the chroniclers reported numerous inguinal hernias.

During this period, different names were given to these epidemics. The 1414 epidemic was called either "tac" suggesting rapid onset, or "horizon".

Another epidemic reported in 1427 was called "dando" (sounds like "in the back" in French), and later on "coqueluche" (from cucullus meaning capuchon or small cap). This name was given to describe patients who wore coats and a cap while infected. Reports of this epidemic are available in France and England, and this epidemic is currently accepted as a true influenza pandemic. Again, clerics from St. Albans Abbey described the disease thoroughly. According to their notes, it started in February and "it invaded the whole people, and so infected the aged along with the younger that it conducted a great number to the grave." The death toll at that time was also very high in Paris. However, no records of the number of deaths are available (Creighton 1965).

12.3 Between 1500 and 1888

After 1500, descriptions of epidemics are very consistent. The first well described epidemic was reported in 1580 (Neustadt and Fineburg 1983). It clearly came from Asia during the summer, spread to Africa and then to Europe. European countries were infected northwards over a period of 6 months. Eventually, the epidemic was observed in the Americas. Numerous deaths were reported from Spanish, Italian and French cities although no figures are available. The name Influenza has been used since then to describe these massive epidemics.

The following epidemics observed in Europe are thought to have moved westwards, some crossing the Atlantic Ocean. Reports from European countries suggest that massive influenza epidemics occurred in 1658, 1679, 1708, and 1729. The latter started in Russia and had three waves, the third of which being the most severe (Patterson 1986). King Louis the XVth was infected and he called this infection a disease that spread like a foolish little girl ("follette" in French).

In 1768, Voltaire, who was in Saint Petersburg, described in a letter a disease (called "grippe" in French) that during his trip around the world passed through Siberia and infected his old body. The word "grippe" is thought to have come from a German word "grippen" that means "to catch". The word influenza, which originated in Florence, was widely used, and is seen in British reports of influenza-like diseases since 1743. At that time, it was suggested that astronomy, i.e. the conjunctions of stars and planets, could influence health status (influenza di stelle), together with cold (influenza di freddo). In 1767, in a letter to his son, Lord

Chesterfield described an epidemic in London that was very likely a seasonal epidemic. He described the disease as "a little fever that kills nobody but elderly people that is now called by a beautiful name: influenza".

In 1775, reports from a French doctor called Bachaumont describe the dissemination in France of an "epidemic common cold" that started in London. According to his writings, "…this disease is causing serious concerns to the people of Britain. Numerous are coming into southern France to escape from the disease. Since then, this plague has spread to southern France, causing numerous deaths in Toulon, Marseille and Paris". The infection rate was very high but only elderly people died. During this epidemic, up to 12 deaths of elderly people were registered per day in Paris (De Lacey 1993; Patterson 1986).

A pandemic was also certainly observed in 1781. This pandemic reached the whole world. It originated in China, spread to Russia and was subsequently disseminated westwards across Europe. It reached the east coast of Northern America in the spring of 1781 and moved westwards. This worldwide pandemic was responsible for the deaths of many young people. In Saint Petersburg, up to 30,000 cases were recorded on the same day. Similarly, it was described that half the population of Rome was infected. It is not thought to have been a pandemic with a high death rate.

Less than a decade later, in the winter of 1789–1790, influenza was widespread throughout Europe and northern America, George Washington being seriously ill (Patterson 1986).

In 1803, a large and severe epidemic was reported in France, being responsible for numerous deaths amongst the "vigorous people". Johann Freidriech Reichardt, a German ambassador in France at that time, reported that a large epidemic was observed. He described cases that could be observed from numerous places, including a large number of young people.

Other epidemics are reported in the nineteenth century (1817, 1830 and 1837), the latest of which being responsible for a very large number of cases. In 1837, a French chronicler reporter that "… half of the population of Paris was in bed, this epidemic was transforming Paris into a giant Hospital where half of the inhabitants were infected by influenza and the other half was taking care of the cases". This is a very good description of what could have been an influenza pandemic.

In 1889, a new epidemic emerged from Russia. It is said that approximately 40% of the world's population was infected, and that the influenza disease was really very severe. This pandemic has been well documented (Enserink 2006). Based on serological testing, some assume that the virus was an H2N2 subtype; however, it remains difficult to be sure of the subtype. Already at this time, some bacteriologists detected bacteria in the sputum of patients (Patterson 1986). Dr. Pfeiffer reported that unknown bacteria could be detected from the sickest of his patients. He called this bacteria Pfeiffer's bacillus (*Haemophilus influenza*) and, for a very long time, numerous microbiologists were convinced that this bacterium was the causative agent of influenza.

In 1900, a medium-sized epidemic was observed. Again, according to serological data, it is possible that this was a pandemic due to the emergence of an H3N8 strain, which was responsible for a "mild" pandemic. However, the viral subtype for both the 1889 and 1900 supposed pandemics cannot be identified with certainty. We should consider this as speculation, even if some archeoserological data support these as possible pandemics (Enserink 2006).

12.4 Virologically Confirmed Pandemics of the Twentieth Century

It is very difficult to be sure of the influenza subtypes responsible for pandemics before 1918 because there is a critical lack of specimens that can be tested for the presence of RNA that would provide consistent information regarding viral subtypes.

The first influenza viruses to be cultivated *in vitro* were isolated in 1931 from swine and in 1933 from a human specimen (Shope 1931; Smith 1935). One of these early historical strains [A/Puerto Rico/8/1934 (H1N1)] is still used for vaccine production. This virus was the circulating strain of 1934, being a variant of the H1N1 pandemic virus that emerged 16 years earlier.

The recent development of new technologies like reverse-transcription-polymerase chain reaction (RT-PCR) and reverse genetics has allowed several research teams to amplify and subsequently reconstruct viruses from pathological specimens from cases that died from influenza during the 1918 pandemic (Taubenberger et al. 1997; Taubenberger 2003). With the help of these techniques we have now identified the "original" viruses of the three pandemics of the twentieth century, and much has been learned about the mechanisms of emergence of these viruses.

12.4.1 The Spanish Flu of 1918 (A H1N1)

The so-called "Spanish Flu" has been the most devastating disease of modern times. The global death toll is estimated at 40–50 million, while 500 million to 1 billion people (representing approximately 30–50% of the world's population) are thought to have been infected (Niall et al. 2002). The history of this pandemic is well described as numerous reports are available, especially in military archives. However, the beginning of the pandemic remains obscure as yet (Reid and Taubenberger 2003). It is clear that the emergence and subsequent adaptation of the deadly A H1N1 virus took several months or even years before the start of the outbreak. This virus hit the whole world very badly within a very short time. In the early stages of the pandemic, in 1916, a French report describes a small-scale epidemic with a very high infection rate in a medium-sized city in the south of

France, with very few fatalities. Similar cases were observed in the troops of both sides during the first World War (WWI), but due to the embargo on news because of the war, there was no dissemination of this information.

Two places are suspected of being the site of emergence of the actual pandemic virus. The first hypothesis involves the province of Canton in China. The hypothesis is that this virus originated from China and subsequently travelled to the United States due to the massive immigration of Chinese people into North America (Reid and Taubenberger 2003). The virus then swept through the United States before spreading to the rest of the world (Iezzoni 1999). The second possibility is that the virus originated from the United States directly. The first cases were recorded in March 1918, and the first epidemic clusters described were located in a military camp in Furston (now called Fort Riley in Kansas), in Detroit, and in a prison in South Carolina (Soper 1918). Subsequently, the virus spread over a large part of the United States. Meanwhile, military troops sent to Europe landed in France in Brest and Bordeaux. These boats were loaded with infected soldiers. In some cases, numerous deaths were recorded during the journey across the Atlantic Ocean. The virus was introduced into Europe and cases were subsequently recorded in the French and British armies. The virus then spread to Spain, Italy, Germany and Russia. North Africa was hit in June 1918, and cases were also recorded in India, Asia and New Zealand. Until June, the pandemic was significant but no worse than previous pandemics (Niall et al. 2002). A limited number of fatal cases were recorded, mainly amongst young children and the elderly. This was only the first wave.

The second wave began at the end of August in Europe and North America. In Europe, it began in Brest, France, and in the United States in Boston. In Boston, a camp (Camp Deven) was opened to prepare the troops for war. Up to 45,000 troops were in the camp. The first case observed in this camp was recorded on the 7th of September. The following day, dozens of cases were recorded and by the 18th of September, 6,600 cases of influenza infection were recognised (Wooley 1919). At the peak of the epidemic in this camp, up to 1,176 cases were admitted to hospital in a single day. The epidemic was described as being a consequence of the dissemination of a bacterium described by Pfeiffer in 1889.

In Brest, the mortality rate was enormous, ten-fold higher than that observed during the first wave, the difference being that cases and deaths were now observed in young people (15–35 years old).

The exact spread of the epidemic remains unclear. Some suggest that the second wave originated in France and was sent back to northern America via naval ships. In North America, the major port of embarkation of the troops was Philadelphia. This city was at the origin of viral spread for the second wave in North America. The epidemic originated from the navy camp in the harbour, disseminated to the civilian population, first slowly and then rapidly, and subsequently moved westwards (Soper 1918). In North America, the second wave ended by December 1918 (Iezzoni 1999).

In Europe, dissemination of the virus was observed simultaneously. Despite the news embargo, the troops knew that a disease was responsible for a large epidemic and some tried to escape from the battlefields by describing the infection. This led to massive gatherings of infected and non-infected troops, thus boosting the epidemic.

Spain was also hit by the pandemic. This country was not at war and information was freely available. The Spanish newspapers openly described the epidemic. The name “Spanish flu” is a result of this. Moreover, the King of Spain and his court were severely hit by the virus.

During this second wave, the disease was really very severe. Although mortality was due not only to viral infections (50% was supposed to be due to bacterial super-infections), numerous cases of fulminant flu were reported. As an example, the French poet Guillaume Apollinaire fell ill on the 8th of November and died on the 9th. This rapid and deadly evolution of flu was observed also for Edmond Rostand, Gustav Klimt and Egon Schiele.

In October 1918, the number of cases in troops on both sides was so large that war was no longer possible. On the battleground, up to 37,000 United States troops and 25,000 French soldiers were ill. Historians assume that the pandemic was certainly responsible for the premature end of WWI (Crosby 1976; Patterson 1986).

At the same time, in France, the Ministry of Interior Affairs decided to close all public places, and collections of garbage were organised. Similarly, disinfectants were sprayed in places with high incidence.

The pandemic was devastating the world over. As an example, in Spitzberg, several villages were completely destroyed and the entire population died. The pandemic first hit the young. These young people died and subsequently there was nobody to hunt and look for food. As a consequence, the remaining inhabitants starved to death.

In January 1919, the third wave hit the planet. This last wave of the Spanish Flu was of lesser magnitude and ended in the spring of 1919. The impact of this last wave was very important in Australia. As an island, the Australians had decided to stop all contact with the rest of the world in an attempt to escape the epidemic. However, the virus entered Australia in 1919 with devastating results; the mortality rate was even higher than in countries that had experienced the two previous waves.

Overall, the lethality was estimated at 3.5% and the estimated number of deaths ranges from 40 million to up to 100 million (Frost et al. 1930; Niall et al. 2002).

How did this virus emerge and why was it so lethal? To the first question, there is no answer as yet. According to data collected from several teams, including that of J. Taubenberger, the A H1N1 virus that has been reconstructed shows similarities with avian viruses (Taubenberger 2003). These similarities are observed at the level of the viral nucleic acid sequences. However, analysis of the proteins shows that this virus has signatures of mammalian influenza. It is still not clear if this virus was transmitted directly from birds to man of if an intermediate host was involved. There is no record of any epidemic in poultry prior to the human pandemic. One of the differences between avian and human viruses is that they bind to different receptors (Gamblin et al. 2004; Glaser et al. 2005). Hence, a key element of the adaptation of an influenza virus to its new host is the acquisition of mutations that allow binding to the human cellular receptor. Sequences of the A H1N1 virus detected in material collected from cases that died of influenza in 1918 show a receptor binding site intermediate between avian and human, as if the virus was

developing mutations to adapt to its new host (Gamblin et al. 2004). However, we do not know if the virus emerged directly from birds.

12.4.2 The Asian Flu of 1957 (A H2N2)

The second pandemic of the twentieth century was observed 40 years after the Spanish Flu. Again, this virus was thought to have emerged from China, in the province of Kweichow (Bull Org Mond Santé 1959). First reported in February 1957, this virus spread to Yunan province and moved rapidly through China. Up to 500,000 Chinese people were infected at this time. In March 1957, Mongolia and Hong Kong were hit, followed by Singapore in April. All Asia was infected by mid-May, and up to 2,000 cases were reported daily in Manilla for example. As a result of this local dissemination, the influenza strain subsequently called A2 by virologists was nicknamed "Asian flu" by the public (Bull Org Mond Santé 1959). The World Health Organisation (WHO) and virologists rapidly identified this virus as being a new strain, significantly different from the previously circulating virus known as A1 (Bull Org Mond Santé 1959). The modern classification of strains, using both surface glycoproteins for virus classification, was implemented in 1970. However, in 1957, there was knowledge that influenza viruses could be in birds, and that different serotypes could be identified. Again, there was no indication of an ongoing epizootic at the onset or before the pandemic.

The spread of this virus out of Asia was helped by aircraft and ships. As an example, an American aircraft landed in Yokosuka in Japan in April 1957. It came from Hong Kong. Upon arrival in Japan, the crew was ill. Specimens were collected from the crew and A2 viruses were detected in culture. In June, the crews of United States Navy vessels coming from Asia were heavily infected and helped introduce the virus to North America. Numerous gatherings were responsible for further dissemination of the virus (conventions, boy scout jamborees, etc.; Podosin and Felton 1958). The geographic dissemination of the A H2N2 virus has been described (Bull Org Mond Santé 1959; Cox and Subbaro 2000). Within 9 months, the virus had spread to the whole planet. The impact was much lower as compared to the 1918 pandemic. The overall estimation of the number of deaths is approximately 2 million.

Again, the emergence of the virus has been only partly deciphered. We know that this virus emerged from the animal reservoir in a more complex fashion than the A H1N1 strain in 1918. The mechanism of emergence is called genetic reassortment, a mechanism linked to the structure of the influenza A genome. This virus has a segmented genome (eight gene segments). It can infect birds (avian viruses), man (human viruses) but also other hosts including pigs (Scholtissek 1994). Pigs are interesting animals in the biology of influenza viruses since they can be infected by human viruses as well as viruses of avian origin. In birds, influenza viruses can be endemic, and numerous subtypes can circulate in wild and domestic birds (Ferguson et al. 2003; Munster et al. 2007; Scholtissek 1994).

In remote villages in Asia, families usually raise domestic birds and swine in their homes. This close proximity between animals and man can favour genetic exchange between viruses of different origin. It is assumed that the A H2N2 pandemic virus resulted from a genetic exchange between a human and an avian virus, and that this genetic exchange or reassortment occurred in pigs (Scholtissek 1994). In 1984, Scholtissek suggested that a pig had been co-infected by the human A H1N1 virus and an avian A H2N2 virus. During this co-infection, several cells of the host were co-infected and the gene segments coding for the two surface proteins (H2 and N2) were substituted with the respective gene segments of the human virus, together with a third gene segment, PB1 (coding for one of the three proteins of the polymerase complex). This reassortment resulted in a new virus with a human genetic background (five gene segments coming from the H1N1 virus) and new surface glycoproteins. This virus was adapted for dissemination in man and resulted in a new pandemic virus.

Again, the delay required for this adaptation is unknown. There was no report of any epidemic in poultry, and no A H2N2 virus was detected before the emergence of the pandemic virus. Is reassortment rapid or not? We have no indication of the time frame necessary for such genetic evolution, or if it resulted from a single event, or three successive events.

As a result of the emergence of the A H2N2 virus, the A H1N1 virus disappeared; once a new virus has been introduced into a geographic area, the previously circulating virus disappears. The mechanism for this drastic change remains unknown. We can assume a very high attack rate for an emerging virus for which nobody yet has neutralising antibodies, and it can thus spread very efficiently. Virus spread can be expressed by the reproducibility factor, R_0, which is the mean value of the number of secondary cases per index case. The R_0 value varies according to the transmissibility of the virus: a highly transmissible virus will have a high R_0. To initiate an epidemic, a virus must have an $R_0 > 1$. This value is used to construct theoretical models for the putative next pandemic (Longini et al. 2005). It was determined that the R_0 value of seasonal flu is approximately 1.4. On the other hand, the R_0 value of an emerging pandemic virus like the 1918 virus was >2 or 3. Thus, such a highly transmissible virus can block any diffusion of a previously circulating subtype (Longini et al. 2005).

In 1957, vaccine production was implemented very rapidly; the WHO initiated vaccination campaigns that started a short time after the beginning of the pandemic. This certainly reduced the impact of this pandemic as compared to that of Spanish Flu. A peculiar observation was made during the H2N2 pandemic. The impact in the elderly was lower than would have been expected, especially for those older than 80. A tentative explanation is that this age-group of patients had already encountered H2N2 viruses during the Russian flu of 1889 and could recruit neutralising antibodies from their immune memory developed during the primary infection with the A H2N2 virus that emerged at the end of the previous century. This remains speculative however.

12.4.3 The Hong Kong Flu of 1968 (A H3N2)

The last real pandemic was called the Hong Kong Flu. It emerged in July 1968 in Hong Kong and, like the Asian flu, spread to the rest of the world within several months (Bull Org Mond Santé 1969). It was disseminated from Hong Kong to the rest of Asia, then to Russia, Europe and the Americas. Europe and North America were hit in January 1969, and the WHO identified this virus as a new subtype quite rapidly, although not immediately. This virus was called A3 and its genetic evolution was rapidly understood.

The mechanism of emergence of this virus was very similar to that of the A H2N2 virus. It resulted from a genetic reassortment between a human and an avian virus (Scholtissek 1994). The gene segments introduced were those coding for haemagglutinin (H3) and the polymerase protein PB1. Hence, one of the surface glycoprotein (named N2) was conserved. This might explain, in part, the relatively low impact of this virus in terms of mortality (estimations of mortality are approximately 0.8 million). However, infection rates were very high, and this pandemic showed two clear waves. Again, vaccines were rapidly available.

As in 1957, the mechanism of emergence is understood, but the timeframe required for such genetic exchanges between human and avian viruses remains unknown. Again, this pandemic showed similar features as compared to the A H2N2 pandemic. Firstly, the emerging virus led to the complete extinction of the previously circulating lineage. Secondly, the impact in the elderly population was unexpectedly low. This could also be a consequence of the possible A H3N8 pandemic of 1900. In vitro studies showed that patients older than 70 had neutralising antibodies against A H3N2. These antibodies were directed against H3. Again, exposure many years previously as the explanation for pre-existing antibodies in old patients remains speculative.

12.4.4 The Russian Pseudo-Pandemic of 1977

In virology, one of the major differences between the first and the second parts of the twentieth century is that laboratories able to detect, cultivate and store viruses were developed during the latter. As observed after the severe acute respiratory syndrome (SARS) CoV epidemic, the risk of re-emergence of this virus resides both in a possible new introduction from its animal reservoir, or its re-introduction from laboratories holding viral stocks. This is also true for influenza viruses from previous pandemics. In 1968, the emergence of A H3N2 led to the disappearance of A H2N2, the latter in turn having being responsible for the disappearance of A H1N1. In 1969, the only human virus in circulation was A H3N2.

In 1977, in the Saint Petersburg region of Russia, many young children were infected with an A H1N1 virus. This virus was infectious only in children, who had not encountered the A H1N1 virus before its disappearance in 1957. Analysis of

this emerging virus revealed that it was genetically identical to a strain that had been circulating in 1954 (Kilbourne 2006).

There are two putative explanations for the re-emergence of this subtype. First, it came out of a virology laboratory. Second, the virus survived in the permafrost or in the arctic waters of Russia and has been infecting people visiting regions where this virus remained infectious for two decades. Although this latter possibility cannot be excluded (Zhang et al. 2006), the former is the most likely. This shows that when a virus is adapted to man, its emergence even in remote places in the world can lead to its worldwide dissemination.

12.5 Putative Emerging Pandemics: 1976 A swH1N1, 1997 A H5N1, 2003 A H7N7, A H5N1 and Other Alerts

We now know that the animal reservoir for influenza viruses is enormous. There are 16 different Ha and 9 different Na subtypes, thus making a very large number of putative pandemic viruses for humanity (Munster et al. 2007).

Several cases of human infection with viruses coming from the animal reservoir have been observed. In none of these cases was the virus maintained in the human population. Such introductions must be taken very seriously. In 1976, at Fort Dix, New Jersey (USA) a soldier felt ill with flu. He died very rapidly after a training march exercise. This case was investigated and an A H1N1 virus was isolated. At that time, only the A H3N2 virus was present in man. The United States authorities feared the re-emergence of a deadly H1N1 virus and initiated a very large vaccination program. The vaccine was produced and administered to 48 million United States citizens. The vaccination program was stopped because of adverse side effects, and the lack of further cases of infection with this virus. Characterisation of the virus showed that it was a swine virus, different from the previously circulating human H1N1. No additional cases have since been reported (Neustadt and Fineburg 1983).

In May 1997, a 3-year-old boy died of influenza in Hong Kong. The virus was detected but could not be identified using the regular identification process (H1 and H3 Ha typing). After several days of analysis, the virus was identified as an H5N1 strain similar to that responsible for an epidemic in domestic birds. Between May and December 1997, 18 cases were recorded in Hong Kong, of which 6 were fatal. No human-to-human transmission was observed, all cases having been exposed to infected poultry. The authorities decided to cull domestic birds and, following culling, no further human cases were seen by the end of December (Claas et al. 1998).

In February 2003, a very large epizootic was observed in domestic birds in the Netherlands. Between March and May 2003, 85 human cases infected with A H7N7 were recorded, 1 of which was fatal (Fouchier et al. 2004). A single chain of transmission was observed (Fouchier et al. 2004). Again, control of this nascent pandemic was achieved by the massive culling of birds. Overall, 30 million birds were destroyed and the situation subsequently controlled.

The A H5N1 virus emerged again in December 2003, this time with a different genetic background as compared to the 1997 strains (Li et al. 2004). Since then, the virus has been responsible for 329 cases including 201 deaths (2 October 2007). Despite massive culling, there is no control of the epizootic and viruses have been detected in several countries in Asia, Africa and Europe. This virus is a clear pandemic threat.

This history of influenza pandemics illustrates that these events are observed rarely, but regularly. Their impact is often so great that humanity remembers these deadly outbreaks. These pandemics are not a consequence of the modern world; they simply demonstrate that influenza viruses are zoonotic viruses that can be introduced into man.

Most virologists are certain that there will be pandemics in the future. However, nobody can say when these will occur. In 2007, the best candidate for a pandemic is A H5N1, but others, such as A H9N2, may also emerge (Perdue and Swayne 2005).

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