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A history of influenza

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1. SUMMARY

From the history of influenza epidemics and pandemics, which can be traced back with some accuracy for the past three hundred years, and with less certainty before this time, it is apparent that outbreaks occur somewhere in the world in most years. Annual epidemics are due to antigenic drift; and pandemics, occurring at 10 to 50 years intervals, are due to new virus subtypes resulting from virus reassortment. Nothing has been introduced during the past 100 years to affect the recurrent pattern of epidemics and pandemics; and our future in the new century is clearly indicated by our past. This past experience is reviewed in the present paper.

2. INTRODUCTION

Since 1932, when the influenza virus was first isolated in the laboratory, the history of this infection can be recorded and confirmed by laboratory diagnosis. In the two centuries before this time, infections can be identified by the known signs and symptoms of disease and the explosive nature of outbreaks. Thus, although sharing many symptoms with other respiratory infections, influenza presents in addition as a sudden onset of three-day fever, with muscle pain and a degree of prostration out of all proportion with the severity of other symptoms. Secondly, epidemics usually occur suddenly without warning, infecting a large percentage of people, and disappear after a few weeks or months; these epidemics are commonly heralded by an increase in hospital admissions of elderly patients with bronchopneumonia, particularly associated with *Staphylococcus aureus*, and an excess of deaths, mainly in the elderly and those suffering from chronic heart and lung disease. From these observations outbreaks can be identified in the historical record without difficulty, although this identification becomes less secure as one goes back further in time; and reference to influenza can be found in both scientific and lay publications since 1650. More dramatically, pandemics of influenza occur: these appear suddenly in a specific geographical area, spread throughout the world infecting millions and cause a large numbers of deaths. Evidence of pandemics is also present in the historical record which include 10 probable and three possible pandemics since AD 1590 (Potter 1998); and allusion to earlier possible pandemics is suggested throughout history.

With the above in mind, it is not surprising that influenza remained the most studied of viruses and virus diseases, until the advent of HIV two decades ago. It has focused the interests of researchers, epidemiologists, physicians and the pharmaceutical industry, whose studies are reported in a vast literature. Despite this, little has been done in the past century to change the pattern of influenza infections; and our future is clearly indicated by the past.

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3. INFLUENZA EPIDEMICS

3.1. History

Epidemics of influenza occur in most countries in some years, and in some countries in most years: for many they

are common annual events, unpredictable in time and severity. However, history indicates certain features which make influenza epidemics more likely. Firstly, epidemics tend to occur in winter months when cold, crowding of people and higher humidities are a feature: indeed, in areas where continuous high humidity is a characteristic, infections may occur throughout the year. Secondly, in more recent times epidemics are often first seen in Eastern or Southern Hemisphere countries, and later spread to Europe and North America in the winter months of these areas: seeding of infection may occur prior to epidemics, to be followed by epidemics when conditions are optimal. Thirdly, epidemics are more likely to occur when a variant virus appears which shows antigenic changes from previous strains, and cross-reacting antibody, acquired by previous infection, is low in both percentage positive and titre. The influenza virus has radiating from the surface multiple copies of two glycoproteins termed haemagglutinin (HA) and neuraminidase (NA): it is antibody to these proteins which equates with immunity, and it is accumulating mutations in these glycoproteins, particularly the haemagglutinin, which constitutes the virus variation termed antigenic drift. The monitoring of antigenic variation in the influenza virus is a key factor in anticipating epidemics, and in vaccine design where for any year the prevalent virus strain(s) must be incorporated into the current vaccines. The responsibility for monitoring virus variation rests with the World Health Organization who have commissioned over a hundred research laboratories in various parts of the world to monitor antigenic changes in the infecting viruses and the incidence and spread of infection.

The pattern of influenza epidemics is shown diagrammatically in Fig. 1. In a seven-year period, which can be any seven-year period during the past 50 years, epidemics of influenza have been recorded in all countries where monitoring of infection has been studied. The diagram shows that during the winter months there is an excess of deaths in the years when influenza is not recorded. In epidemic years, 10% or more of a population may be infected; 50% of infected persons will develop symptoms, and an excess number of deaths will occur (Christie 1987). The number of deaths is proportional to the number of people infected, usually about 0·1%, and influenza has been described as an invariable disease caused by a variable virus. Most of the deaths occur among the elderly, such as those with chronic heart and lung disease or metabolic disorders. Although vaccine against the prevalent virus strains is produced each year, the use of this has not been wide: only a proportion of the 'at risk' group receive vaccine, and although shown to protect 60–90% of the individuals against infection, and a higher percentage against hospitalization, immunization has never made an impact on the course of an epidemic.

3.2. Antigenic drift

The influenza virus is subject to rapid mutation, particular to the HA and NA glycoproteins against which immunity is directed, and serum antibody to the virus HA is the most important factor in immunity (Potter and Oxford 1979). The different influenza viruses, marked A to E in Fig. 1, occur in different years and represent the progressive accumulation of mutations with time in the virus HA,

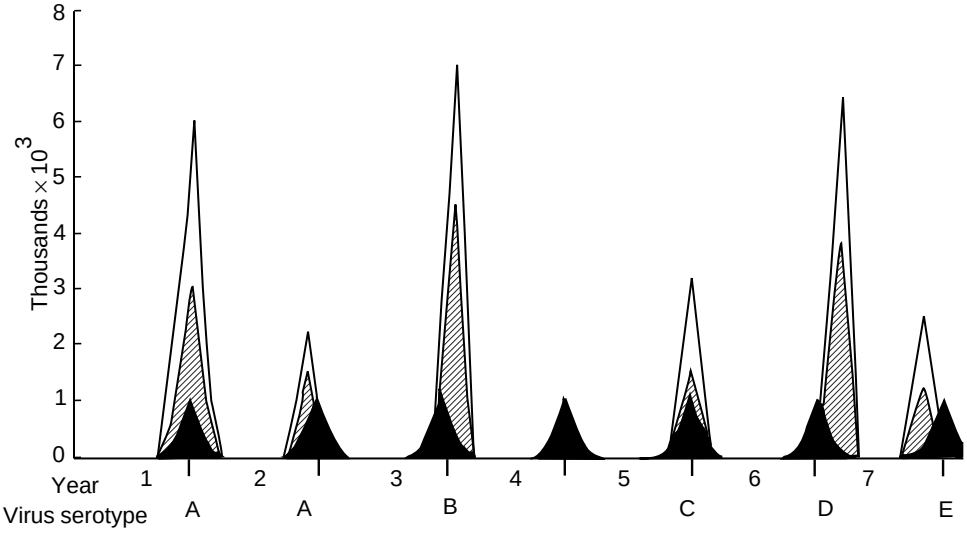

Fig. 1 Diagram of influenza epidemics over a 7-year period. ◆, Excess winter deaths in a non-influenza year; ◇, number of influenza cases; ▨, number of excess deaths from influenza; A–D; different virus variants

termed antigenic drift, and this correlates with a step-wise decline in antibody acquired in earlier years to protect against drifting virus. Thus, for the five epidemic influenza viruses A–E occurring in the 7-year period shown in Fig. 1, virus B exhibits the least and virus E the greatest number of mutations compared to the original virus A. Antisera against homologous virus HA reacts strongly in Haemagglutination Inhibition (HI) tests, less strongly with virus bearing a few mutational differences, and not at all where there are numerous mutational differences (Table 1). The meaning of this is that HI antibody acquired by previous infection is less efficient in protecting against mutated virus, and, as mutations accumulate, tends towards no protection. This pattern explains the repetition of influenza epidemics, and the pattern has been repeatedly observed since laboratory tests were available to record it: nothing has happened in the last century to alter this pattern, and all the indications are that it will continue into the new century.

4. INFLUENZA PANDEMICS

4.1. History

Two conditions must be satisfied for an outbreak of influenza to be classed as a pandemic. Firstly, the outbreak of infection, arising in a specific geographical area, spreads throughout the world; a high percentage of individuals are infected resulting in increased mortality rates. Secondly, a pandemic is caused by a new influenza virus A subtype, the HA of which is not related to that of influenza viruses circulating immediately before the outbreak, and could not have arisen from those viruses by mutation (Webster and Laver 1972). Each influenza A virus possesses one of 15 distinct HA molecules, designated H1, H2, H3, and so on, which do not cross-react in serological tests: as stated above, immunity to influenza is principally related to antibody to the HA (Hobson *et al.* 1972), and the appearance of a new virus subtype with a different HA means that immunity acquired from past influenza infection confers no protection against the new virus subtype, and the spread of infection by the latter is unchecked. This is a totally different phenomenon to antigenic drift, and is termed antigenic shift.

Table 1 Antigenic drift in epidemic influenza viruses

Epidemic influenza virus	Post-infection ferret sera to influenza virus				
	A	B	C	D	E
A	320*	–	–	–	–
B	80	320	40	–	–
C	–	160	1280	320	160
D	–	–	–	320	80
E	–	–	80	320	640

*Serum Haemagglutination Inhibition Antibody Titre; – = a negative reaction (<20).

Despite the reservations that must be imposed on the reports of pandemic influenza in the older literature, numerous commentators have attempted to identify pandemics throughout the entire historic period: hence, reports of possible influenza can be found in early Greek writings of 412 BC to the more precise records of the present time (Potter 1998). The first report of an influenza epidemic, where symptoms were probably influenza, occurred in 1173–4 (Hirsch 1883); several reports are from the 14th and 15th century, and the first convincing report was by Molineux (1694). Numerous references of influenza epidemics were made for the 17th century in America and Europe. From the beginning of the 18th century, the quality and quantity of data increased and medical historians were drawn to comment on the number of infected persons, whether they were considering an epidemic or a pandemic, the countries involved and the possible origins of the virus strains involved. Comprehensive accounts of influenza in the 18th and 19th century period are contained in four accounts (Hirsch 1883; Thompson 1890; Creighton 1894; Finkler 1899) which have been extensively reviewed (Beveridge 1977; Pyle 1986; Patterson 1987). Since the pandemic of 1889–92, data have been more reliable and more thoroughly reviewed, and since 1957, when the causal viruses were available for analysis, the status of pandemics is not questioned.

4.2. Pandemics before 1700

The outbreak of influenza reported in 1173 (Hirsch 1883) is not considered to be a pandemic, and other reports to 1500 are too meagre to allow comment. In contrast, the outbreak of 1510 was probably a pandemic reported with spreading from Africa to engulf Europe. The outbreak of 1557 was possibly a pandemic; but the first influenza pandemic agreed by all authors occurred in 1580. This pandemic originated in Asia during the summer of that year, spread to Africa, and then to Europe along two corridors from Asia Minor and North-West Africa (Pyle 1986). The whole of Europe was infected from south to north in a 6-month period, and infection subsequently spread to America (Pyle 1986; Beveridge 1991). Illness rates were high; 8000 deaths were reported from Rome, and some Spanish cities were decimated (Beveridge 1991).

4.3. Pandemics from 1700 to 1830

Data from 1700 is more informative of pandemics that those of previous years, and Fig. 2 gives a diagrammatic record of pandemics from that date to the present time. The first

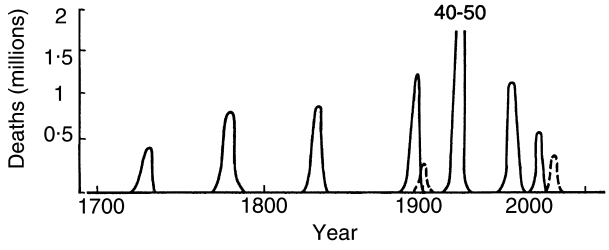

Fig. 2 History of influenza pandemics 1700–2000. Not to exact scale

agreed influenza pandemic of the 18th century began in AD 1729 (Hirsch 1883; Finkler 1899; Pyle 1986; Patterson 1987): the outbreak started in Russia in the spring months, spread westwards in expanding waves to embrace all Europe within a 6-month period (Pyle 1986), and encompassed the whole known world over a 3-year period with high death rates. Distinct waves of infection were recorded; the later were more severe than the first (Brown 1932; Beveridge 1977; Patterson 1987).

The next pandemic occurred after a gap of some 40 years between 1781–2 (Finkler 1899; Pyle 1986). Most authors agree that the outbreak began in China in the autumn, spread to Russia and from there westwards in widening circles to encompass the whole of Europe in a period of 8 months (Pyle and Patterson 1984). There is evidence of extensive seeding in both Russia and North America in the early months of the pandemic, followed by extensive outbreaks. The attack rate was reported to be high, particularly among young adults (Thompson 1890): at the peak of the pandemic, 30 000 fell ill each day in St. Petersburg; two-thirds of the population of Rome became ill; and the outbreak is reported to have raged through Britain during the summer of 1782.

The pandemic of 1830–3 ranks in terms of severity with the pandemic of 1918–20 (Beveridge 1977; Pyle 1986; Patterson 1987). The pandemic began in the winter of 1830 in China, from where it spread southwards by sea to reach the Philippines, India and Indonesia, and across Russia into Europe. The contagion spread into North America to cause outbreaks in 1831–2, recurred in Europe at the same time and recurred again in Europe in 1832–3 (Pyle and Patterson 1984). All authors comment on the high attack rate of 20–25% of the population, but the mortality rate was not exceptionally high (Patterson 1987).

4.4. Pandemics since 1830–33

Pandemic influenza was recorded in 1830–3, 1898–1900, and four times in the 20th century (Fig. 2). It is not appropriate to detail these events in the present text, but full accounts for the latter half of the 19th century can be found in the literature (Jordan 1927; Burnet and Clark 1942; Pyle 1986; Patterson 1987). However, it is appropriate to record two pandemics of the 20th century, since much of our current fears and knowledge are embodied in this history.

4.4.1. Pandemic of 1918–20. The influenza pandemic of 1918–20 is one of the most dramatic events of medical history: statements include, 'the greatest medical holocaust in history' (Waring 1971); 'the pandemic ranks with the plague of Justinian and the Black Death as one of the three most destructive human epidemics' and 'deaths in the hospital exceeded 25% per night during the peak' (Starr 1976). The pandemic has been extensively chronicled (Crosby 1976; Beveridge 1977). The impact on North America (Jordan 1927; Pyle 1986; Crosby 1989), India (Gill 1928), Africa (Patterson and Pyle 1983), Australia (Burnet and Clark 1942) and Europe (MacNeal 1919; Crosby 1976) has been detailed; and a large literature describes the events in countries, towns and military camps and personal experiences (Walters 1978; Grist 1979). The origin of the pandemic is not known. Reviewers have commentated on a possible origin in China; however, the first outbreaks occurred at approximately the same time in North America at Detroit, South Carolina and San Quentin Prison in March 1918, and reviewers accept that this evidence supports a theory for the origin of the pandemic in the USA (Crosby 1989). From here the pandemic can be traced in place and time, and this is shown in Fig. 3.

From the above focal points, infection spread outwards and then eastwards as young Americans were drawn to the army and naval training establishments of the American Expeditionary Force (AEF), and to the war in Europe. Although large numbers of cases were recorded, the infection appeared to be no more virulent than had been seen in the past. All authors agree that infection was transmitted by ship by the AEF personnel to military depots at Bordeaux, France in April 1918. From here, infection spread to the British Expeditionary Force (BEF) and other forces involved in the war in April/May 1918, and in the same months reached Italy and Spain. This period also saw outbreaks in Germany, and the pandemic was clearly influencing the course of the war. In June, the disease arrived in Britain, and from there was transmitted by the BEF to Murmansk and Russia, where it spread with great rapidity (Fig. 3). Infection reached North Africa in May 1918 and circled Africa to affect Bombay and Calcutta and then China, New Zealand and the Philippines in June 1918. In each country infection spread quickly for a few weeks, and then sharply declined. The events of March–July 1918 outlined above were not viewed as exceptional; pandemics of influenza had occurred before, and the number of deaths recorded were comparable with past experience: in contrast, the events which were to follow remain unique to the history of influenza.

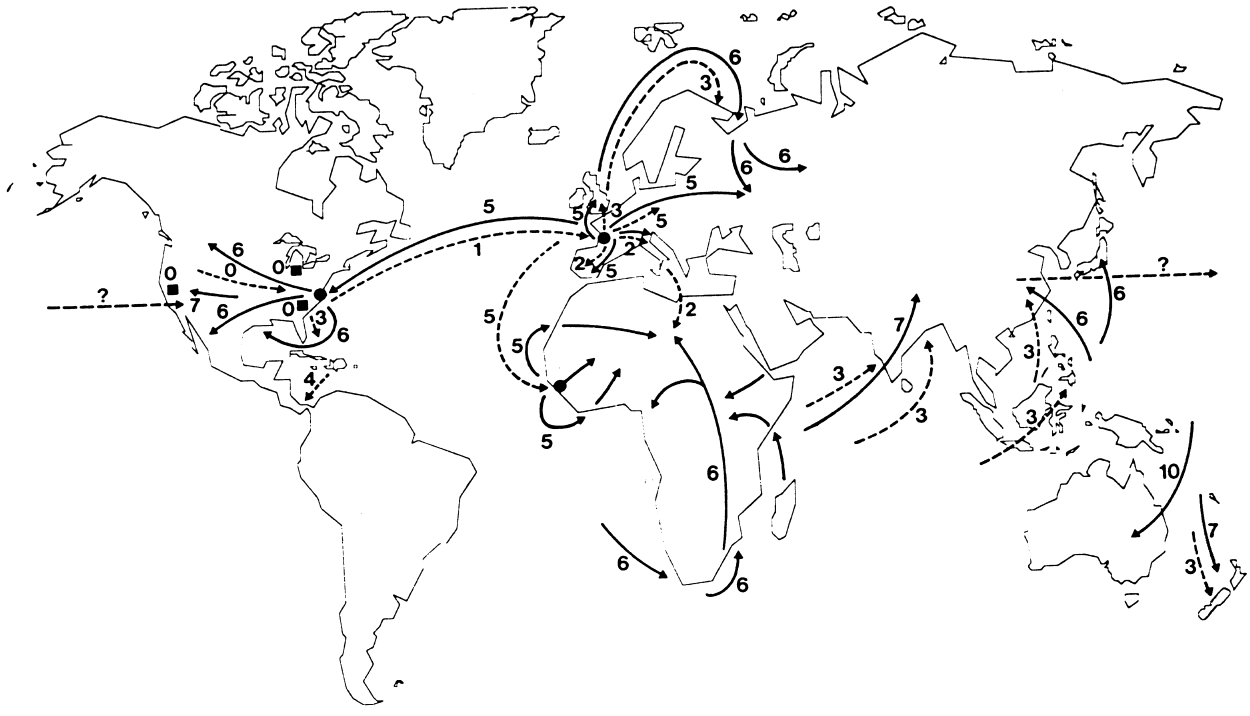

Fig. 3 The influenza pandemic of 1918–20. First outbreaks (■) March 1918; lines of spread of first wave (----➤), and lines of spread of second wave (→); numbers of month after March 1918 (0) when epidemic infection was recorded (number accompanies arrow); focal points of second wave (●). (From the records of Gill 1928; Crosby 1976; Beveridge 1977; Pyle and Patterson 1984; Pyle 1986; Patterson 1987.) Reprinted from Nicholson *et al.* (1998) *Textbook of Influenza*, with permission from the Publishers, Blackwell Science, Oxford

First, in August 1918, influenza broke out on a boat travelling from England to Freetown, Sierra Leone; on landing, the affected crew were taken to a local hospital and as a result influenza broke out amongst dock workers and later in other parts of the town. Within a few cycles of infection, it was apparent that the disease had become more virulent, with a 10-fold increase in the death rate amongst cases. Secondly, the influenza epidemic in Europe saw the emergence from Brest, one of the main ports of France serving the needs of the war, of a markedly more virulent form of influenza which rapidly spread to all of Europe. Finally, a ship arriving at Boston, USA from Europe unleashed on that city, and subsequently the whole country, the more lethal form of influenza (Fig. 3); however, with hindsight, it has been suggested that this may have arisen from earlier seeding infection (Glezen 1996). The pandemic reached Australia in January 1919; it spread through Africa from Freetown to other ports, and from there by lines of communication to cause in a few weeks 1·5–2·0 million deaths (Patterson and Pyle 1983). India was infected in October 1918 where the epidemic resulted in seven million deaths. The epidemic in North America caused approximately 600 000 deaths; in England and Wales the official deaths numbered 200 000 (Beveridge 1991) and a similar percentage of the populations of other European countries and Australia died, again within a few weeks. The death rate in Samoa and Alaska was 25% of the population (Beveridge 1991; Ghendon 1994). Unique to this pandemic, deaths occurred principally in the group of age 20–40 years. Many countries experienced second (1918–19) and third waves (1919–20) of the more virulent form of infection. No figures exist for many parts of the world, but the pandemic is estimated to have infected 50% of the world's population, 25% suffered a clinical infection and the total mortality was 40–50 million: the often quoted figure of 20 million deaths is palpably too low (Crosby 1976).

RNA fragments have been recovered from preserved lung tissue of victims of the influenza of AD 1918–20: when transcribed to DNA and sequenced, these showed close similarity to the influenza virus isolated by Shope (Taubenberger *et al.* 1997). Thus, the antibody studies of sera from persons who lived through the pandemic and the sequence data from the pandemic virus indicate that the 1918–20 pandemic was caused by an influenza A (H1) virus which is closely related to the virus later found in pigs (Shope 1931), and which remains an infection of this species to the present time.

4.4.2. Pandemic of 1957–8. The influenza virus which caused the AD 1957–8 pandemic originated in the Yunan Province of China in February 1957 (Pyle 1986); it caused extensive infection in China during March, reached Hong Kong in April, and then spread rapidly to Singapore, Taiwan and Japan (Fukumi 1959). At this point the WHO became aware of the outbreak caused by a new influenza virus subtype (Chu *et al.* 1957). A special meeting of authorities on influenza held in May 1957 accurately predicted subsequent events, apart from an early epidemic in Japan: the outbreak would spread quickly to the Southern Hemisphere causing severe epidemics during the winter, and would spread and seed itself in the Northern Hemisphere where latter epidemics would occur in the winter of that region. The spread of the pandemic is shown in Fig. 4. Infection spread to India, Australia and Indonesia in May; to Pakistan, Europe, North America and the Middle East in June; to South Africa, South America, New Zealand and the Pacific Islands in July; and to Central, West and East Africa, eastern Europe and the Caribbean in August (Dunn 1958; Payne 1958). Two major land routes of spread were firstly, across Russia to Scandinavia and Eastern Europe (Payne 1958; Langmuir 1961), and secondly, from a large conference held at Grinnel, Iowa involving 1800 young persons from 43 states and several foreign countries, which drew individuals from epidemic areas to initiate an outbreak of 200 cases during the conference and allowed much dissemination from infected individuals returning home (Fig. 4). Except for these two events, infection was transmitted mainly along sea lanes (Pyle 1986) and, within approximately 6 months, the pandemic had spanned the globe.

Most detailed studies of the pandemic come from North America and Europe where infection was seeded from June 1957, and where the first outbreaks started in September with the peak in October of that year; epidemics coincided with the opening of the winter school term (Payne 1958). A second wave of infection was observed early in 1958, which broke out in numerous regions including Europe, North America, the former USSR and Japan (Payne 1958); the two waves of infection were similar in severity in some countries (Dauer and Serfling 1961), but greater for the second wave in others (McDonald 1958): in total, the pandemic affected some 40–50% of people, of which 25–30% experienced clinical disease. The course of infection was clinically typical (Nicholson 1992), with most deaths due to secondary bacterial pneumonia. The mortality rate was estimated at approximately 1 in 4000; these occurred predominantly in the very young and very old. Deaths due to the pandemic were calculated at approximately 80 000 in the USA (Dauer and Serfling 1961), and a similar number, adjusted for population, occurred in many

Fig. 4 The influenza pandemic 1957–8. Point of origin (■) February 1957; lines of spread of pandemic (→); number of months after February 1957 (0) when epidemic infection was recorded (number accompanies corresponding arrow). (Adapted from Payne 1958.) Reprinted from Nicholson *et al.* (1998) *Textbook of Influenza*, with permission from the Publishers, Blackwell Science, Oxford

other countries; thus, the total death rate probably exceeded 1 million people.

4.5. Features of pandemic influenza

Although the study of influenza pandemics is of absorbing interest to epidemiologists and medical historians, it also serves to underline the importance of this disease in periodically causing great morbidity, significant mortality and to be socially and economically disruptive. In addition, the repeating pattern of pandemics, and our accepted inability to predict or contain them, indicates that pandemics will continue to occur. It is therefore important to analyse the past for information that might help in the future.

Of the 10 pandemics, agreed by all reviewers, that have occurred in the past 300 years, the point of origin is suggested as China/Russia/Asia for all where data is available. This analysis clearly indicates that the next pandemic will probably originate in this area, and this view is supported by most authorities.

Since the virus subtypes which cause pandemic influenza do not arise by mutation from existing strains (see above), the origin of these viruses has been a subject of considerable speculation and research. Of the many theories advanced, the most plausible suggests that pandemic viruses arise as reassortants of human and avian virus strains. Thus, an avian influenza virus, probably from ducks in which they are widely distributed and possessing distinct HA and NA molecules, and a human influenza virus initiate a dual infection in cells of the species in which both can multiply; the pig is the favoured species for this. The influenza A virus genome contains eight separate gene fragments, and providing all eight are represented in the virus progeny, it does not matter from which parent these gene fragments are drawn. The result may be a reassortment virus containing genetic material that determine both human infectivity and an avian HA glycoprotein to which the majority of the human population has never been exposed, and who have no immunity. It is in China, where one-quarter of the population of the earth live, and where ducks, pigs and humans live in the closest proximity and the highest density, that reassortment is most likely to occur; this correlates with the point of origin of pandemic viruses (see above), and the views of many authorities (Shortridge and Stuart-Harris 1982).

The interval of time between pandemics varies from a decade (1889–1900 and 1957–68) to some 50 years (1729/33–1781/2); the interval has not significantly increased or decreased with the passage of time, suggesting that increased population and travel are not determining factors. The interval between pandemics in the period from 1700 to 1889 is approximately 50–60 years and for the period since 1889 is 10–40 years; the interval may therefore be shortening. If more recent experience is to be a guide, the next pandemic will be within 40 years of the last, and will occur before 2008 counting from the 1968 pandemic, or 2017 if the pandemic of 1977 is accepted. This latter pandemic is unusual in many respects (Potter 1998), and its inclusion in the natural history of pandemics is debatable. It is unrewarding to attempt to seek a pattern for pandemics which will allow predictions; but it is self evident from the history of pandemics that each year that passes brings the next pandemic one year closer.

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