

The epidemiology of influenza

I. Stephenson* and M. Zambon†

*Specialist Registrar in Infectious Diseases, Leicester Royal Infirmary, Leicester LE1 5WW; and †Respiratory Virus Reference Unit, Central Public Health Laboratory, 61 Colindale Avenue, London NW19 8HT, UK

Influenza remains a globally important cause of febrile respiratory illness. Influenza virus activity in the community results in significant mortality, morbidity and economic disruption, particularly in those at high risk of developing complications, such as the elderly and those with underlying chronic medical conditions, including pulmonary disease and diabetes mellitus. The occurrence in Hong Kong in 1997 of avian influenza H5N1 in man, which resulted in six deaths, served to remind us of the importance of continuing surveillance and preparation for the next pandemic.

Key words: Antigenic shift; health care burden; influenza; morbidity; mortality; pandemic; surveillance.

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Introduction

Few infections exert such a huge toll of absenteeism, medical consultations, hospitalization, death, societal disruption and economic loss as influenza. When symptomatic, influenza infection typically results in an acute febrile and generally debilitating illness characterized by coryza, cough and myalgia. Patients at high risk of complications and mortality include the elderly, the very young and those with pre-existing cardiorespiratory disease. General practice and virological surveillance collates important information that can be used to assess impact on mortality, morbidity and health care providers. During influenza outbreaks, primary care consultations and hospital admissions rise, as well as mortality from all causes.

Structure and classification

Influenza viruses are enveloped RNA viruses with a segmented genome belonging to the family Orthomyxoviridae. Influenza A and B possess two surface glycoproteins embedded in the membrane, neuraminidase (NA) and haemagglutinin (HA), which are both capable of stimulating immune responses in humans [1]. NA facilitates cleavage of viral progeny from infected cells, prevents viral aggregation and aids movement of the virus

through the mucosal respiratory tract epithelium. HA is involved with receptor binding and membrane fusion. Another transmembrane structure, the M2 ion channel, is important in the regulation of internal pH needed to allow ribonucleoprotein uncoating and virus replication.

Influenza viruses are classified on the basis of their core proteins into three distinct types: A, B and C. Strains are classified according to host species of origin, geographical site, year of isolation and serial number, and for influenza A, by serological properties of subtypes of HA and NA. A total of 15 HA (H1–H15) and nine NA (N1–N9) subtypes have been identified for influenza A within its natural host reservoir of aquatic birds. However, only three HAs (H1, H2 and H3) have established stable lineages in man, implying host specificity. Influenza A is usually responsible for pandemics and annual outbreaks, while influenza B is more stable, causing outbreaks every 2–4 years. Influenza C is poorly understood, and usually associated with sporadic and subclinical infection.

Antigenic shift and drift

Replication of the influenza genome requires RNA polymerase activity. This enzyme lacks proof-reading ability and has limited potential to correct mistakes during RNA transcription, resulting in a high frequency of mutations in any newly replicated virus population. These new strains accumulate random point mutations that may result in amino acid substitutions in surface glycoproteins that allow new variants to evade immunity. Viruses that

Correspondence to: I. Stephenson, Specialist Registrar in Infectious Diseases, Leicester Royal Infirmary, Leicester LE1 5WW, UK. e-mail: istephens@globalnet.co.uk.

Table 1. Recently identified sporadic cases of animal-to-human transmission of influenza A subtypes

<i>Reference</i>	<i>Year</i>	<i>Subtype</i>	<i>Source of infection</i>	<i>No. infected</i>	<i>Symptoms</i>
2	1976	H1N1	Swine to human	230 (1 death)	Respiratory
3	1977	H7N7	Seal to human	4	Conjunctivitis
4	1993	H1N1	Swine to human?	2	Mild respiratory
5	1995	H7N7	Avian to human	1	Conjunctivitis
6	1997	H5N1	Avian to human	18 (6 deaths)	Respiratory
7	1999	H9N2	Avian to human	2	Mild respiratory

Table 2. Comparison of pandemic and inter-pandemic influenza

<i>Influenza type</i>	<i>Cause</i>	<i>Population immunity</i>	<i>Outcome</i>
Pandemic influenza A	Emergence of novel or re-emerging subtype of influenza A (antigenic shift)	Little or no background immunity (except partial immunity in elderly if re-emerging virus)	High attack rates globally, excess mortality and morbidity
Inter-pandemic influenza	Antigenic drift of existing influenza (A or B)	Little immunity in infants. Background immunity in adults by cross-reacting antibody to related strains	Variable outbreaks or epidemics with variable morbidity and mortality

have undergone antigenic changes or 'antigenic drift' to evade humoral immunity are capable of reinfection and cause inter-pandemic outbreaks.

The segmented nature of the genome allows the possibility of reassortment of virus segments. Simultaneous infection of a cell by two viruses may allow recombination of RNA segments and result in the emergence of a new virus with novel surface and internal proteins. Pandemic influenza occurs as the result of 'antigenic shift' when a virus subtype with a new HA emerges to which there is no or little background immunity in the population. Influenza viruses have been isolated from many animal species, and evidence suggests that antigenic shift results from genetic reassortment between human and animal reservoirs (Table 1) [8]. This process is facilitated by agricultural practices, particularly in South East Asia, which allow close proximity between humans, ducks, poultry and pigs. Comparisons of pandemic and inter-pandemic influenza are shown in Table 2.

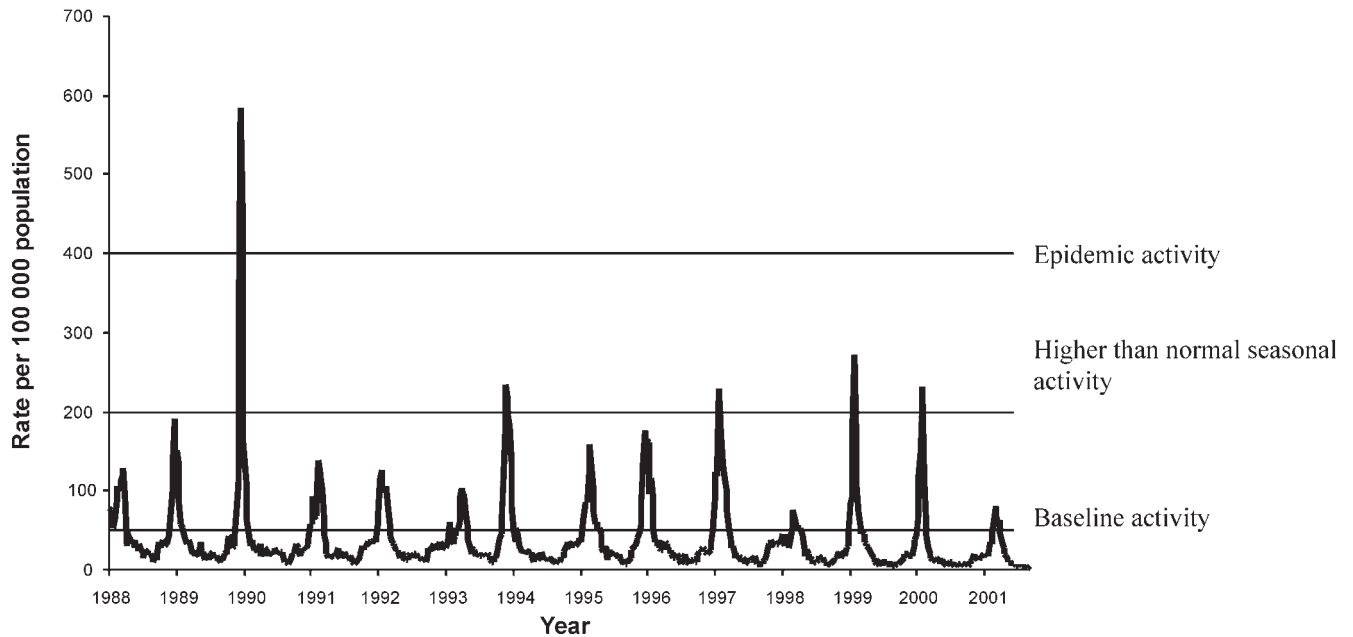
Surveillance

Influenza surveillance aims to monitor morbidity and mortality, identify onset of activity, and characterize viral isolates to decide future vaccine composition. Worldwide monitoring of important global infections is essential for accurate and timely information. In the case of influenza, this is organized by the World Health Organization (WHO). The WHO international network comprises four reference collaborating centres and ~110 national influ-

enza centres, where viral isolates are identified and typed. There is some evidence that a herald wave of one season's virus strain occurs in the latter part of the preceding season, before re-emerging as an epidemic the following season [9]. Isolates obtained from these herald waves provide useful information in deciding vaccine composition for the next year.

As most respiratory viral infections are treated in general practice, many countries are developing surveillance networks based around primary care sentinel practices similar to those already well established in the European Union. Some countries operate schemes that link virological and epidemiological surveillance. For example, in England and Wales, the Royal College of General Practitioners operates a scheme where representative practices submit weekly returns for consultation rates for influenza-like illness (ILI), and in a proportion of cases, nose-and-throat swabs [10]. ILI consultation rates are an indirect assessment of circulating influenza [10–12]. Baseline typical winter weekly rates are 30–70 consultations per 100 000 population (Figure 1). These figures rise markedly during epidemic periods; for example, the rate reached 800/100 000 in 1975–1976, when it was estimated that ~5% of the population of England and Wales consulted their general practitioner [12]. A consultation rate of 400 per 100 000 population is considered to be of epidemic level. US surveillance primary care data from Texas and Michigan have found that 17–52% of upper respiratory illness attributed to influenza results in medical visits, with >600 consultations per 100 000 in

Figure 1. Royal College of General Practitioners consultation rates for influenza-like illnesses 1988–2001 in England (baseline activity: 50 consultations per 100 000 population; normal seasonal activity: 50–200 consultations per 100 000; epidemic activity: 400 consultations per 100 000).



peak years [13,14]. These data have been used to demonstrate strong association between the incidence of acute respiratory illness and death registrations in the UK [14–16]. Regression analysis finds a strong correlation between deaths and influenza activity, with estimated excess mortality associated with influenza even during years without major epidemics [17].

Seasonality

Usually, influenza emerges abruptly and peaks rapidly over several weeks, before gradually disappearing over several months [18,19]. In temperate areas of both the northern and southern hemispheres, influenza is seasonally limited to the colder winter months; and in tropical zones, it is restricted to the wet seasons. Factors such as reduced ventilation, crowding indoors and improved survival of aerosolized viruses in the conditions of low temperature and high humidity found in the winter have been suggested [20,21].

Transmission

Virus-laden respiratory secretions are expelled from an infected person during coughing and sneezing, spreading infection to susceptible individuals. The short incubation period, typically of 2–3 days, high viral titre and duration of shedding in nasopharyngeal secretions contribute to the explosive nature and rapid spread of outbreaks.

Burden of influenza on the community

Households

Longitudinal community-based family studies using self-reported illness, virus isolation and serological monitoring initially investigated influenza infections over several years in the USA. More recently, studies using surrogate markers of circulating influenza activity, such as consultation rates for ILI in general practice, have been used to assess the impact of outbreaks. The spread of influenza within age groups and communities varies with each epidemic, depending on herd immunity to the prevalent strain and on prevailing weather conditions. For H3N2, pre-existing immunity is often limited because of frequent changes in the major surface antigens, giving potential for the greatest clinical impact. Influenza H1N1 and B are more antigenically stable with less variability, resulting in higher herd immunity. During influenza outbreaks, the typical pattern observed is of highest attack rates in school-age children and lower rates in adults. Households with children have the highest occurrence of influenza [22–24]. Overall, the prevalence, burden and outbreak intensity of influenza A are greater than those of influenza B, although in some individual seasons, influenza B may be the predominant or only strain [11,19,25–27]. Influenza B generally causes greatest impact in children and less apparent disease in adults, although it may produce more indolent outbreaks in communities with persisting antibody titres following previous exposure. Surveillance data covering 1987–1996

from sentinel practices in England, Wales and The Netherlands found that H3N2 epidemics were associated with the highest consultation rates, especially in the age groups 0–4 and >65 years. During H3N2 epidemics, an estimated excess of 2–3% of the practice population, mostly young children, is seen over a 4 week period [11]. Table 3 shows some epidemiological features of influenza A.

In Tecumseh, MI, between 1966 and 1971, estimates of influenza A and B annual attack rates were 17 and 8%, respectively, and in Seattle, WA, between 1965 and 1969, attack rates of 19 and 20% for influenza A and B were demonstrated, respectively [25,26]. During surveillance from 1975 to 1979, attack rates of H3N2 were 18–24 and 0.4–6% in epidemic and non-epidemic years, respectively. For influenza B, attack rates in epidemic periods approached 17%, and in other years were 2–3% [27].

The risk of re-infection and illness is probably related to serum haemagglutination-inhibition titres, and these are considered to be a correlate of protection [22]. Infection with H1N1 during its re-emergence in 1977 rarely produced symptoms in those who had lived through the previous H1N1 period ending in 1957. Although most positive H1N1 cultures were in those with symptomatic illnesses born after 1956, there were significant infection rates, as detected by seroconversion, for those born before 1956. However, the peak of hospitalizations of older people was associated with the peak of H1N1 activity, suggesting that immunity is incomplete and that re-infection does occur [13,28,29].

Costs

Among school children, absenteeism is a useful measure of influenza activity. School absenteeism has been shown to correlate to the epidemic curve, and may rise up to one-third higher than its base levels. Up to 37% of all enrolled school children suffered absence during the 1976–1977 epidemics [18,30]. The high incidence of influenza in children is not only an important health care issue; it impacts upon family and community economics by usually requiring loss of work by one of the parents.

The major impact of influenza on individual healthy adults is probably the associated debility. Cost-of-illness studies suggest annual US direct costs of influenza are US\$1–3 billion, but indirect costs including loss of earnings amount to \$10–15 billion [31]. In 1989, the cost of influenza activity in France was estimated to total €2.1 billion. On the basis of 1997 German Sickness Funds, costs of influenza (mainly direct medical and indirect cost attributed to loss of productivity and absenteeism) were €1 billion [32].

Elderly

Limited physiological reserves, partially waning immune

Table 3. Some important epidemiological features of influenza A

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- Antigenic drift and interpandemic outbreaks
 - Antigenic shift and pandemics
 - Seasonality with low transmission rates out of season
 - Global appearance, spread and disappearance of new strains and subtypes
 - Explosive onset and rapid termination of outbreaks
 - Children and teenagers important in spread within community
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responses and underlying chronic conditions with advancing age contribute to increased mortality and morbidity from influenza. As ~30% of elderly people suffer from at least one acute respiratory illness per winter, even low rates of morbidity and mortality have significant impact. Studies from England and the USA suggest that the peak influenza activity in the elderly coincides with peak hospitalization and primary care consultation rates. Between 23 and 47% of community-acquired respiratory illnesses in elderly people result in a medical visit, of which approximately one-third receive antibiotics [14,33]. In the Houston surveillance studies, there were 12.8 consultations per 100 people >55 years old in winter months, contrasting with 4.2 in summer [14].

There are numerous reports of influenza outbreaks in care homes, with high attack rates and fatality rates even exceeding 50% as a result of severe pneumonia [34,35]. Analysis of certified influenza deaths during the 1989–1990 epidemic in England and Wales identified that 50% of deaths and 15% of hospital admissions attributed to influenza and pneumonia lived in residential homes. Clearly, this group of people is at greatest risk of complications and death [36,37].

Mortality and burden in the elderly

Although the minority of influenza hospital admissions occur in those aged >65 years, 75% of influenza deaths and 90% of excess influenza winter deaths occur in this age group [38–40]. Mortality in people aged >65 years is 20- to 30-fold greater in the presence of underlying chronic medical conditions [41]. Significant decreases in functional abilities following influenza in the elderly require increased convalescence support [42].

During influenza outbreaks, hospital admission rates for all respiratory illnesses increase, as does mortality from all causes [43,44]. Some 50% of respiratory illnesses occurring in nursing homes require medical consultation, and 90% of these result in a prescription for antibiotics [34]. Increases in attendance at emergency rooms and general practitioner (GP) referral rates during influenza epidemics place hospital services under pressure. In England and Wales, an average 422 000 extra GP consultations and 9077 excess respiratory hospital admissions

in those aged >65 years occurred during each epidemic period from 1989 to 1998. These excess figures were greatest during H3N2 epidemics [45,46].

Influenza in chronic illnesses

Of patients presenting in England and Wales in general practice with ILI, those with chronic respiratory conditions were almost twice as likely to develop complications [47]. Acute respiratory infections are a leading cause of hospitalization in those with underlying chronic medical conditions, and mortality in nursing homes is associated with the number of underlying chronic illnesses [36,48]. Influenza causes exacerbations of chronic obstructive airways disease (COAD) and may contribute to deterioration in pulmonary function in those infected [44,45,48]. In the USA, COAD patients with respiratory tract infection increase per capita expenditures by 10%, and in-patient hospital costs are >2.5 times higher than for those without COAD [49]. Those suffering from congestive cardiac failure also have excess mortality approaching that seen with chronic pulmonary disease during periods of influenza activity [44,48]. Between 11 and 28% of acute cardiopulmonary admissions to US hospitals were attributed to H3N2 during outbreaks [50]. Patients with diabetes are more likely to develop complications and die from influenza than the general population. Excess mortality from diabetes increased by 5–15 and 30% during influenza epidemics in the periods 1957–1966 in the USA and 1989–1990 in England and Wales, respectively [43,51,52]. Fourfold increases in deaths from influenza and pneumonia were found in those with cardiac disease and diabetes compared with those only with cardiac disease [41].

Pandemic influenza

Only three HAs (H1, H2, H3) and two NAs (N1, N2) in the last century have been implicated in extensive human outbreaks (Table 4). In 1918 (Spanish flu: A/H1N1), 1957 (Asian influenza: A/H2N2), 1968 (Hong Kong influenza: A/H3N2) and 1977 (A/H1N1), strains emerged to cause pandemic influenza. The reasons for the decline of the dominant subtypes and the emergence of the new strains remain unclear, although it seems likely that, during interpandemic intervals, population immunity broadens, reaching a point where the strain loses its capacity for further drift capable of eluding host defences. However, since 1977, H3N2 and H1N1 have been co-circulating, indicating the uncertainty over the time period for such herd immunity to emerge.

Pandemic mortality

During pandemic influenza, patterns of mortality and morbidity change as the proportion of total deaths shifts

Table 4. Recent global pandemics of influenza

Year	Influenza A subtype
1918–1919	H1N1
1957	H2N2
1968	H3N2
1977	H1N1

in the age distribution to younger groups. This is probably due to the partial immunity of older subjects who may have been exposed to antigenically similar strains many years previously. The most striking example of this occurred in 1918, when an almost complete reversal of patterns of influenza mortality occurred. Seventy per cent of all influenza deaths in England in 1918–1919 occurred in the female population under 35 years of age, in contrast to the 7–11% of all deaths between 1890 and 1917 [53]. Subsequent pandemics have also been associated with similar, if less dramatic, increases in the proportion of younger people affected, although the proportion has fallen with each successive pandemic, probably owing to improved medical facilities [54].

Concluding remarks

Influenza is capable of exerting significant mortality, morbidity and economic disruption. Vaccine production is complicated by the antigenic diversity created by 'shift' and interpandemic 'drift'. It is likely that another pandemic will occur in the future. In 1997, an outbreak of highly pathogenic H5N1 influenza in chickens occurred in Hong Kong. Around this period, cases of influenza due to avian H5N1 occurred in humans, causing six deaths among 18 hospital admissions [6]. However, H5N1 was inefficiently transmitted from person to person, and the immediate threat was reduced by the mass slaughter of poultry. Influenza H9N2 is widespread in poultry in Asia and has caused mild self-limiting respiratory infection in children [7]. Furthermore, other sporadic cases of animal-to-human transmissions of unusual influenza A subtypes have been identified over the last few years (Table 1). These experiences highlight the clear potential for pandemic spread, and the need for continued surveillance and vigilance.

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