

Influenza: the changing scene

Douglas Fleming

Influenza is an unpleasant illness which can lead to death, mainly in the elderly. Douglas Fleming describes the current incidence of flu, some new methods of diagnosis and recent advances in treatment.

● What is influenza?

The word influenza is currently used to describe an infection caused by an influenza virus: it has been used for centuries, but the influenza virus was not identified until 1933. As a clinical entity, what doctors generally describe as influenza is better described as influenza-like illness since there are several viruses which can cause a febrile illness with sore throat, cough, headache and myalgia. Though there is a low level of influenza-like illness throughout the winter, there are clearly identifiable periods of increased incidence which in recent years have been consistently associated with increased isolation of influenza viruses.

The incidence of influenza-like illness reported to

general practitioners is highly variable, though some cases are seen in every year (Fig. 1). Many European countries have developed monitoring systems for influenza with clinical and virological components. In England and Wales the best known surveillance system is the Weekly Returns Service of the Royal College of General Practitioners which provides information on influenza-like illness and other respiratory diagnoses. Winter outbreaks usually last 8–10 weeks, but have varying impact by age. Those in which the weekly incidence of influenza-like illness exceeds 400 per 100,000 are described as epidemic. This level was exceeded in 1989 (580), though this was only half that reached in the pandemic of 1968 (1,180). Since 1990, there have been

four outbreaks in which the incidence peaked between 200 and 300 per 100,000. In the recent winter (1999/2000) incidence peaked at 231 per 100,000 (all ages) in week 2 of 2000 and there were particularly high rates in people aged 65 years and over. During influenza outbreaks there is also an increased incidence of acute bronchitis and acute otitis media. The reported incidence of acute bronchitis in the 65 years and over age group in week 1 of this year reached the highest level recorded in the last 20 years of the Weekly Returns Service.

The word pandemic is used to describe a worldwide epidemic of influenza attributable to a major change in the influenza virus, usually involving the nucleus and known as antigenic *shift*. Antigenic *drift* describes continuous change involving the haemagglutinin and neuraminidase processes of the outer shell of the virus. Identification of the molecular structure of neuraminidase has led to the development of the class of drugs known as neuraminidase inhibitors.

Influenza varies considerably in its impact on

Fig. 1. Incidence of influenza-like illness during winters 1993/1994 (+), 1994/1995 (■), 1995/1996 (△), 1996/1997 (×), 1997/1998 (*), 1998/1999 (○) and 1999/2000 (◇)

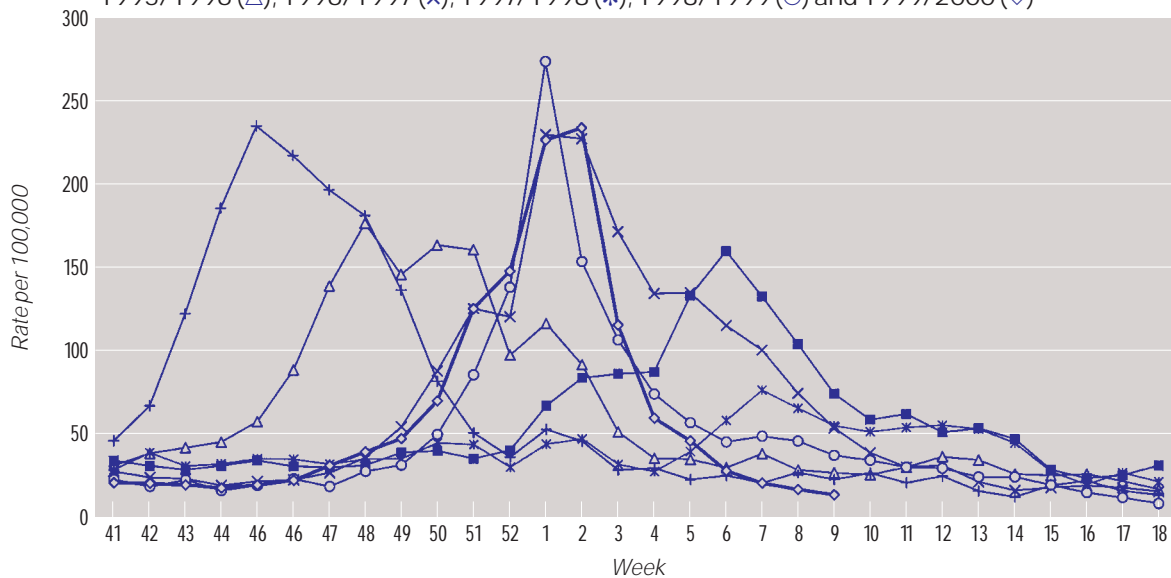
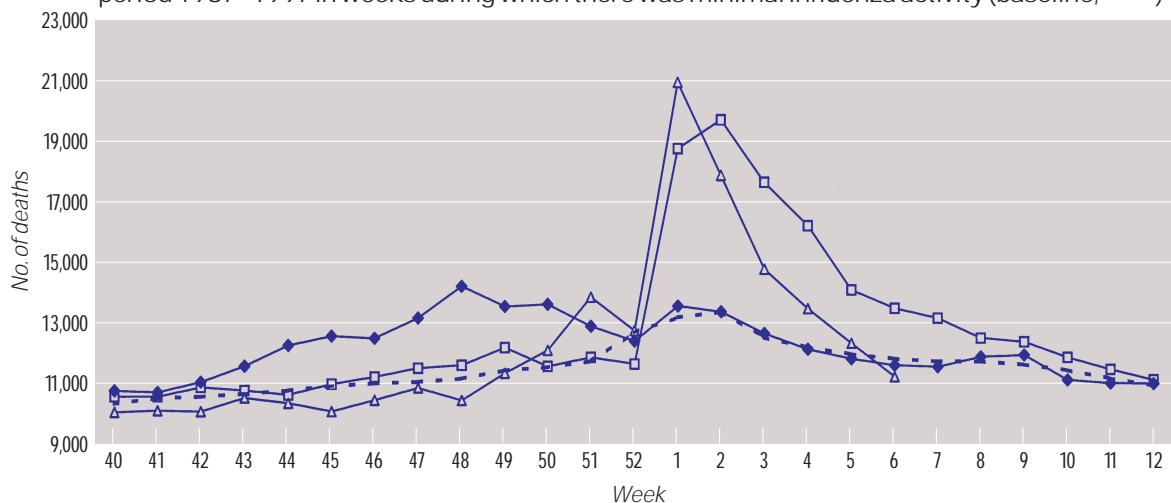
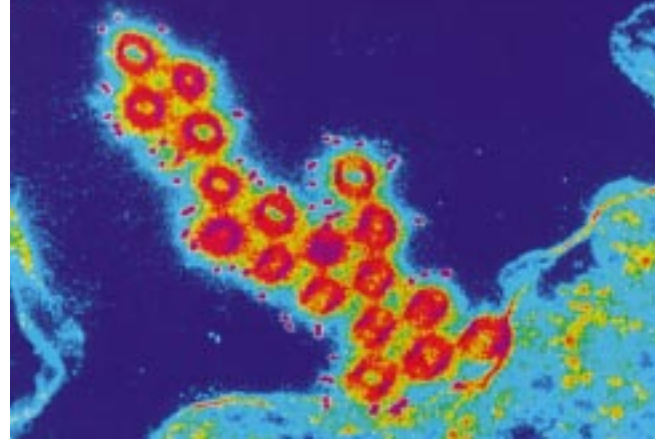


Fig. 2. Death notifications in England and Wales during winters 1993/1994 (◆), 1996/1997 (□) and 1999/2000 (△) compared with expected numbers of deaths derived from data from the period 1987–1997 in weeks during which there was minimal influenza activity (baseline, ---)





ABOVE:
Coloured electron micrograph of influenza virus-like particles.
PHOTO COURTESY P. GÓMEZ-PUERTAS AND A. PORTELA, CENTRO NACIONAL DE BIOLOGÍA FUNDAMENTAL, MADRID, SPAIN

individuals, ranging from sub-clinical infection, through trivial symptomatic illness and illness prompting consultation, to illness causing hospitalization and even death. In Fig. 2 weekly deaths in England and Wales observed in the influenza AH₃N₂ outbreak in 1993, the mixed AH₃N₂ and B outbreak in 1996/1997 and the AH₃N₂ outbreak in 1999/2000 are plotted against a baseline of deaths derived from mortality data over the period 1987–1997 and based on weeks when influenza viruses were not circulating. The excess mortality (observed over expected) in the three winters estimated by this method amounted to 16,000, 28,000 and 18,000 respectively. There is no period of apparently reduced mortality after the influenza period has passed, indicating that influenza-related deaths are not in people in the terminal phase of another illness. Influenza therefore can be a serious illness, though it is not serious for the majority of people who get it. Nevertheless, its epidemic character and high attack rate make it a serious public health problem.

● Diagnosis

Influenza cannot be diagnosed solely on clinical presentation. The likelihood of influenza as the cause of an acute respiratory infection involving rapid onset, fever and cough is considerably increased when influenza viruses are known to be circulating. Currently, such information is available through data from national systems of influenza surveillance, though this does not involve intensive local sampling. This, however, may not be necessary, since spread across a country the size of the UK is usually rapid. A new and effective near patient test capable of use in the consulting room may be imminent. It is unlikely that every person who might have influenza could be tested. Tests currently available take about 15 minutes to apply and cost more than £10 each. In addition, they have a limited shelf life. The likelihood that a skilled person would be instantly available to perform such tests is remote and not justifiable economically. Selected medical practices in a locality could be designated to undertake these to identify influenza in that area, but increased use of near patient tests must not interfere with current virological surveillance based on culture and strain type identification.

● Influenza management

The mainstay of influenza control is based on annual vaccination of risk populations. Risk is defined in relation to co-morbidity (chronic respiratory disease, ischaemic heart disease, diabetes, immunocompromised), age (currently 75 years and over), or institutional living. There is good evidence showing these people are at increased risk if they get influenza, though severe illness due to influenza is not confined to these groups. Vaccination has been shown to be clinically effective in almost all populations in which it has been

examined. However, there is a need for improvement in the logistics of the annual vaccination programme which favours targeted vaccination, though uptake in risk groups is less than desirable.

Amantadine and rimantadine have been available for treatment (and prophylaxis) for several years, but in the UK only amantadine is licensed. Amantadine is infrequently prescribed because it is only effective against Influenza A. It is not well tolerated with adverse central nervous system (CNS) effects, particularly in the elderly. Resistant strains of influenza virus emerge during treatment and these are transferable to other people.

In 1999, the first neuraminidase inhibitor (zanamivir) received a licence in the UK for the treatment of Influenza A and B in adults. Two drugs in this class (zanamivir, an inhaled topical preparation and oseltamivir, an oral systemic preparation) have been shown to be clinically effective against influenza provided they are given early in the course of the illness (up to 48 hours). They have also been shown to be effective for prophylaxis. These drugs block the function of the neuraminidase enzyme which is essential to the release of daughter virions after replication in the epithelial cells lining the respiratory tract. The clinical trials involving these drugs have shown benefits between 1 and 3 days. The degree of benefit is influenced by the severity of illness at recruitment, and the age and risk status of the patient. Clinical trials have involved recruitment of subjects who in some cases have had a comparatively minor illness (temperature <37.8 °C at recruitment) and people infected with differing virus strains, some more pathogenic than others. In its interim evaluation of zanamivir, the National Institute for Clinical Excellence considered the results in patients at most risk from influenza were inconclusive and that the overall benefits of the drug were insufficient to recommend prescription on the National Health Service. They entered a caveat emphasizing the responsibility of the individual doctor in making prescribing decisions. The decision presents considerable difficulty for the general practitioner. There are people who show signs of severe illness and who present early in the illness who would benefit from a neuraminidase inhibitor. The licensing mechanism involves assessment of efficacy and safety. The adverse effects and viral resistance associated with amantadine, the only reasonable alternative, makes this a less attractive option in the patients who are most likely to benefit. National policy should be directed towards identifying the sensible use of neuraminidase inhibitors rather than blanket discouragement.

● *Dr D.M. Fleming is Director of The Royal College of General Practitioners, 54 Lordswood Road, Birmingham B17 9DB
Tel. 0121 426 1125; Fax 0121 428 2084;
email dfleming@rcgp-bru.demon.co.uk*

Further reading

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