*Fortnightly Review*

# Influenza: diagnosis, management, and prophylaxis

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**Summary**

- Influenza causes enormous morbidity, death, and economic loss
- Annual vaccination is strongly recommended for groups at high risk
- Amantadine is effective treatment for and prophylaxis against influenza A during epidemics
- New developments include rapid laboratory diagnosis, live attenuated vaccines, and antiviral drugs

Outbreaks of influenza have been recognised since ancient times and are responsible for devastating global morbidity and mortality. The characteristic epidemiological features of influenza include the occurrence of frequent, but unpredictable epidemics and periodic worldwide pandemics. Four pandemics have been recorded this century (table I). The potential consequences of a future pandemic can be judged by the impact of the 1918-19 pandemic, which was known as Spanish flu. Over a period of months influenza caused more deaths than the first world war. An estimated 200 000 people died as a result of influenza in England and Wales alone, with over 20 million deaths worldwide. Influenza remains a great challenge to modern medicine. In this review I will discuss the epidemiology and surveillance of influenza outbreaks and recent advances in the diagnosis and management of infection.

TABLE I—*Recent global pandemics of influenza*

| Year | Influenza A subtype |
|---|---|
| 1918-9 | H1N1 |
| 1957 | H2N2 |
| 1968 | H3N2 |
| 1977 | H1N1 |

Pandemics are caused by antigenic shift of influenza A resulting in the appearance of an influenza virus with a novel haemagglutinin (H antigen) or neuraminidase (N antigen) subtype. Influenza pandemics usually arise in China and spread westward to the rest of Asia, Europe, and America. Influenza viruses have been isolated from many different animal species, and recent evidence suggests that antigenic shift results from genetic reassortment of virus between humans and the animal reservoir. This process is facilitated by farming practices in south east Asia, which allow close proximity between humans, ducks, and domestic pigs.[1]

During interpandemic periods outbreaks of influenza A or B infection are reported nearly every winter and vary in severity. Antigenic variability during interpandemic periods is less marked and is caused by antigenic drift. This describes a process of minor antigenic changes resulting from the accumulation of random point mutations. These mutations lead to alterations in the amino acid composition of haemagglutinin and neuraminidase. New strains of influenza A and B are constantly being generated by antigenic drift, and epidemics arise if circulating strains are significantly different from previous strains encountered by the population. The last major epidemic in England and Wales occurred during 1989-90.

**Laboratory diagnosis of influenza**

- Virus isolation
  - Amniotic cavity of chicken embryos
  - Tissue culture
- Serological tests
  - Complement ixation
  - Haemagglutination inhibition
- Antigen detection
  - Immunofluorescence
  - Enzyme linked immunosorbent assay (ELISA)
- Gene amplification
  - Polymerase chain reaction

## Diagnosis of influenza

Influenza causes an acute febrile illness associated with myalgia, headache, and cough. The median duration of fever is three days, but cough and malaise often persist for 1-2 weeks.[2] The clinical features of influenza are often indistinguishable from those caused by other respiratory viruses that may be circulating in the community at the same time. Laboratory confirmation of influenza infection therefore has a vital role in surveying influenza outbreaks and is essential for assessing the efficacy of vaccines and antiviral agents. The first box summarises the laboratory diagnosis of influenza.

The diagnosis of influenza is usually confirmed by isolation of virus or from serological results. Influenza is transmitted by spread of airborne droplets, high titres of virus being shed by patients with symptoms. Influenza A and B replicate in several primary kidney cell lines, and influenza may be shown in tissue culture by adsorption of guinea pig erythrocytes, even if there is no obvious cytopathic effect.

Isolation of the virus is labour intensive and takes several days. Serological tests include complement fixation and haemagglutination inhibition. These tests provide useful epidemiological information but will only confirm a diagnosis after the patient has recovered from the acute illness. Diagnosis needs to be more rapid, particularly in severely ill patients who might benefit most from prompt antiviral treatment. Techniques for the rapid diagnosis of influenza include gene amplification and antigen detection by immunofluorescence or enzyme linked immunosorbent assay (ELISA).[3]

Immunofluorescence is comparatively inexpensive

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and straightforward; sensitivity is poor compared with standard tissue culture. A capture ELISA has been described for the detection of influenza antigen in clinical specimens. The test uses a monoclonal antibody to nucleoprotein and has a high sensitivity and specificity.[4] The polymerase chain reaction has recently been used to identify influenza virus genome in clinical material, and several methods have been described. The procedure uses reverse transcriptase (to convert viral RNA to DNA) and type specific primers based on highly conserved sequences. The technique offers greatly enhanced sensitivity and gives a result within 24 hours. Influenza primers may be combined with specific primers for a range of other respiratory viruses in a more comprehensive assay known as a multiplex polymerase chain reaction.

INFLUENZA SURVEILLANCE

Influenza surveillance provides important information on the timing and potential impact of an influenza outbreak. This information is used to coodinate an appropriate public health response, including issuing guidelines on vaccination and antiviral treatment and assessing the need for additional medical resources. Influenza epidemics usually follow a characteristic pattern. Small, isolated outbreaks are followed by a steep rise in the number of reported cases, which reach a peak after 3-4 weeks and decline over a similar time. The most susceptible group is young children, who are the first to be affected during an epidemic. Absence from work, hospital admissions, and influenza related deaths reach a peak later in the epidemic.

The Communicable Disease Surveillance Centre in Colindale monitors the incidence and spread of influenza in England and Wales and publishes regular information on influenza activity. The second box shows the methods used to monitor the spread and impact of influenza. Most cases are diagnosed clinically,

**Monitoring spread of outbreaks**

- Weekly number of confirmed cases of influenza reported by public health virology laboratories
- Weekly incidence of influenza-like illness reported by spotter practices
- Weekly incidence of epidemic influenza reported by spotter practices
- Total recorded number of deaths in which influenza is certified as being a component factor
- Excess number of cases of pneumonia reported during an epidemic period
- Total excess number of deaths occurring during an epidemic period

but laboratory confirmation has a crucial role in verifying the scale of an influenza outbreak. The weekly incidences of influenza-like illness and epidemic influenza are reported by a network of spotter general practitioners established by the Royal College of General Practitioners. Epidemic influenza refers to more severe disease and is considered to be the most accurate indicator of influenza activity. An influenza epidemic is declared if the weekly incidence of reported epidemic influenza is greater than 100 cases per 100 000 patients.

## Management and complications of influenza

The mangement of influenza includes relief of symptoms, treatment of complications, and specific antiviral treatment. The clinical severity of influenza is variable, and most patients with uncomplicated infection will require symptomatic treatment alone. Mild attacks of influenza are associated with a 20-40% impairment of reaction times.[5] This has implications for those who continue performing demanding work while suffering from symptoms.

**Complications of influenza**

*Respiratory*

- Otitis media
- Influenza pneumonitis
- Secondary bacterial pneumonia, particularly *Staphylococcus aureus*
- Exacerbations of chronic respiratory disease
- Croup and bronchiolitis in infants and young children

*Non-respiratory*

- Febrile convulsions
- Toxic shock syndrome
- Reye's syndrome
- Myositis and myoglobinuria
- Myocarditis
- Neurological sequelae, including Guillain-Barré syndrome, transverse myelitis, and encephalitis
- Subsequent meningococcal infection
- Possible increased incidence of schizophrenia if exposure is in utero during second trimester

The third box summarises the complications of influenza. Respiratory complications are encountered most often. Influenza virus is rarely identified outside the respiratory tract, and complications in distant sites usually result from immune mechanisms rather than a cytopathic effect of the virus itself. Influenza pneumonitis may occur in previously healthy people but is most commonly seen in patients with underlying chronic heart or pulmonary disease, when it is associated with a high mortality. A chest *x* ray film shows interstitial changes, which may be localised or widespread (fig 1). Secondary bacterial pneumonia is usually caused by *Staphylococcus aureus*, although infection with *Streptococcus pneumoniae* and *Haemophilus influenzae* may also follow influenza. Staphylococcal pneumonia (fig 2) is an important cause of death, and patients usually present with a rapid deterioration in health and hypoxia.[6] Findings on a chest *x* ray film include lobar consolidation, bilateral nodular shadowing, cavitating pneumonia, or a lung abscess. The toxic shock syndrome may further complicate associated staphylococcal infection. Mortality from pneumonia associated with influenza remains high. Thirty nine per cent of patients admitted to hospitals in Nottingham with proved influenza during the 1989-90 epidemic

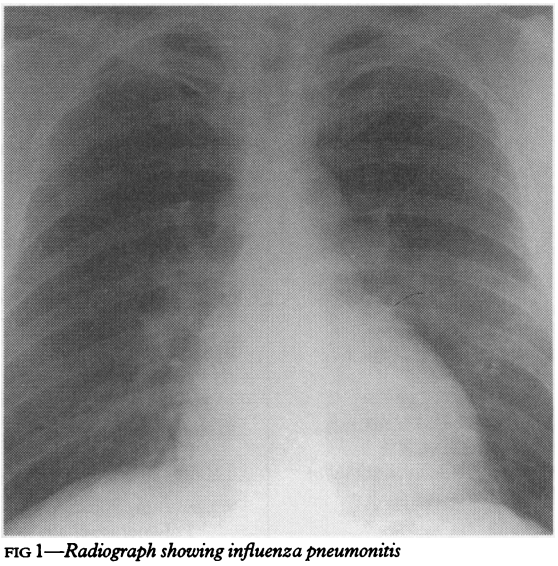

FIG 1—*Radiograph showing influenza pneumonitis*

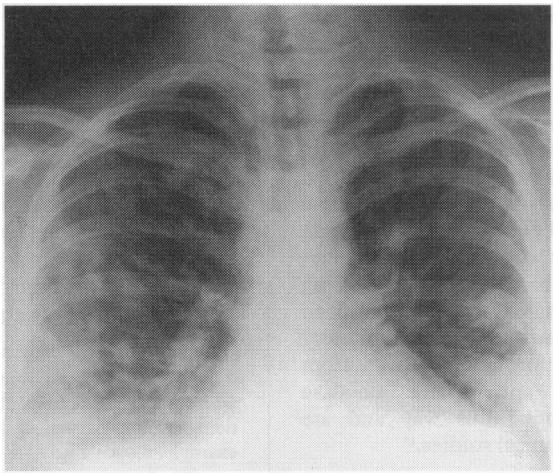

FIG 2—*Radiograph showing staphylococcal pneumonia as complication of influenza*

died as a result of their illness.[7] Factors associated with poor outcome included confusion, uraemia, and lack of focal chest signs. The British Thoracic Society recommends that antibiotics against staphylococcus infection should be included when patients present with evidence of pneumonia during an influenza epidemic.[7]

Abnormalities in the function of small airways and sensitivity to histamine may be detected for several weeks after uncomplicated influenza infection in previously healthy people. Influenza is an important cause of exacerbations in patients with chronic respiratory disease,[2] and bronchitis was the presenting complaint in nearly a fifth of all cases of clinically diagnosed influenza seen by general practitioners during the 1989-90 epidemic.[8] These patients need appropriate treatment for their underlying condition and antibiotics if secondary infection is suspected.

A significant association has been observed between influenza and subsequent meningococcal infection.[9] General practitioners and hospital physicians should therefore be particularly alert to the possibility of meningococcal disease during an outbreak of influenza.

Influenza may be particularly severe in pregnancy, but there is no conclusive evidence of any associated congenital abnormality. Several studies have suggested that fetuses exposed to influenza during the second trimester of pregnancy may have an increased risk of subsequently developing schizophrenia,[10] although the importance of this observation is hotly disputed.

### MORTALITY ASSOCIATED WITH INFLUENZA

Mortality from influenza increases dramatically with age and the presence of underlying medical conditions (table II).[12,13] The 1989-90 epidemic in England and Wales was the worst since 1976 and was thought to be responsible for over 29 000 excess deaths.[14] Influenza was specified on the death certificate in only 2440 cases and pneumonia in a further 5260 cases. Increased numbers of deaths from cerebrovascular or cardiac disease were also recorded during the epidemic, and influenza probably played a part in these excess deaths.

TABLE II—*Mortality from influenza by age[11] and number of underlying medical conditions[12]*

| | Mortality (SE) (per 100 000 population) |
|---|---|
| Age (years): | |
| 5-14 | 0·04 |
| 15-24 | 0·12 |
| 25-34 | 0·16 |
| 35-44 | 0·24 |
| 45-54 | 0·44 |
| 55-64 | 1·3 |
| 65-74 | 4·0 |
| ≥75 | 30·6 |
| No of medical conditions: | |
| 0 | 4 (3) |
| 1 | 157 (35) |
| ≥2 | 615 (167) |

*In patients aged ≥45.

### USE OF AMANTADINE

Amantadine is the only anti-influenza drug currently licensed in the United Kingdom. Amantadine and its analogue rimantadine inhibit all subtypes of influenza A but have little action against influenza B or C or other respiratory viruses.[15,16] They have a tricyclic chemical structure with an amine side chain and a cage-like configuration, and they are believed to act by inhibiting virus uncoating.

Amantadine and rimantadine have been used for both treatment of and prophylaxis against influenza A. Treatment leads to a reduction in virus shedding and shortens the duration of symptoms by about a third if the drug is started within 48 hours of the onset of symptoms. Prophylactic efficacy is high, with several studies in children and adults showing protection against proved influenza infection in at least 50% and prevention of symptomatic illness in over 70%. Indications for the use of amantadine are summarised in the fourth box.

The recommended dose of amantadine is 200 mg daily, which is reduced to 100 mg in people over 65. There are few serious adverse effects, although epilepsy has been reported in patients with underlying cerebral disease. More common problems include headache, light headedness, dizziness, difficulty in concentrating, and insomnia. These effects occur in 5-29% of patients. High doses of amantadine are teratogenic in rats, and the drug should be used only for life threatening infection in women who might be pregnant. Amantadine should be prescribed with caution in patients with cardiovascular or cerebral disorders. Unfortunately, these groups of patients are precisely those who are at particular risk of developing complications. The use of amantadine in families or institutions seems to favour the development of resistance, and drug resistant viruses may be recovered within 2-3 days of starting treatment. The spread of resistant viruses has been documented during clinical trials, and these strains seem to be fully pathogenic. The long term implications of drug resistance are uncertain as no reduction in efficacy of rimantadine was observed after 20 years of follow up in over 142 000 patients in the former Soviet Union.[17]

Well designed clinical trials have convincingly shown the prophylactic and therapeutic efficacy of amantadine. However, its use is limited in the United Kingdom owing to a lack of awareness among medical practitioners and concern over possible adverse effects. The use of amantadine in patients in hospital with severe or complicated influenza would undoubtedly increase if rapid diagnostic tests were to become widely available.

### OTHER ANTIVIRAL AGENTS

Interferon and ribavirin have activity against influenza and have been investigated in clinical trials.[16] Clinical studies of interferon alfa in experimental and

**Clinical use of amantadine**

*Prophylaxis*

- Unvaccinated people at high risk should be vaccinated at the start of an influenza epidemic and given amantadine for two weeks until a protective antibody response is induced
- If vaccination is contraindicated or likely to be ineffective as a result of immunodeficiency, patients at high risk, can be given amantadine for the entire epidemic period
- Amantadine prophylaxis should be considered for unvaccinated health care workers and other key staff during an influenza epidemic
- Vaccinated people at high risk can be given additional amantadine prophylaxis if the vaccine and epidemic strain vary greatly
- When outbreaks of influenza occur in residential homes amantadine should be considered for all residents and staff regardless of vaccination status as it will augment the protection afforded by vaccination

*Treatment*

- Amantadine should be considered for patients at high risk who develop symptoms of a flu-like illness during an influenza outbreak
- Treatment should be started within 48 hours of the onset of symptoms and continued for 5-7 days

naturally occurring influenza infection have been disappointing. Ribavirin is a synthetic triazole nucleoside with a broad spectrum of antiviral activity. Clinical trials of oral ribavirin in influenza infection have failed to show any substantial benefit, and inhibitory concentrations of ribavirin against influenza viruses are difficult to achieve orally. Aerosolised ribavirin is effective against influenza in animal challenge studies and may be beneficial in treating influenza infection in patients who are desperately ill.[16] A neuraminidase inhibitor is currently undergoing clinical trials. A recent exciting development has been the use of computer programs to design inhibitory drugs based on structural information derived from crystallography. Two new and potent sialidase inhibitors have been developed this way and are currently being evaluated in clinical studies.[18]

## Prophylaxis against influenza

### INFLUENZA VACCINE

The use of killed influenza vaccine was first described by Salk in 1945. Early whole virus vaccines contained intact, formalin inactivated virus and were associated with many adverse effects. Modern subunit vaccines are well tolerated and evoke a good serological response.[19] Two forms of subunit vaccine are available: split virus vaccine contains disrupted virus particles that have been partially purified by extraction with organic solvents, and surface antigen vaccine is composed of highly purified haemagglutinin and neuraminidase antigens. Current commercial influenza vaccines are usually trivalent, containing two influenza A subtypes and influenza B. The antigenic composition of the vaccine is reviewed annually and depends on the strains prevalent in the community. The amount of haemagglutinin in each dose of vaccine is standardised, but the titre of neuraminidase is more variable.

The titre of antibody induced by influenza vaccine is determined by the dose of vaccine and the host's immune response, which is influenced by previous exposure to vaccine or infection. The vaccine is effective in patients with cardiac or respiratory disease and in renal impairment. Serological response to influenza vaccine in elderly people may be diminished or enhanced compared with that in younger subjects and depends on the characteristics of the population group studied.

The antibody titres induced by influenza vaccine decline over a period of three to six months. Annual vaccination is recommended, although the value of repeated annual vaccination has been questioned.[19] A study of children at boarding school who were given H3N2 vaccine over seven years showed that the efficacy of the vaccine against clinical illness was 50% in the first year but vaccination had no effect against two subsequent epidemics.[20] The importance of these observations have been disputed, and further longitudinal studies are clearly required.

The efficacy of a vaccine is also dependent on the degree of antigenic similarity between strains of vaccine and circulating strains of influenza. Protection against infection of 70-90% can be achieved in young healthy adults when vaccine and epidemic strains are closely matched, but protection is much lower in elderly patients living in institutions. A summary of 17 trials of influenza vaccine in nursing homes found that the mean efficacy against clinical influenza A and B infection was only 27% and 21% respectively.[21] More importantly, studies in elderly people have shown that vaccination is associated with a significant reduction in the severity of disease, incidence of bronchopneumonia, rate of admission to hospital, and mortality (by a mean of 69%).[11] In addition, the herd immunity achieved by vaccinating at least 70% of residents in nursing homes will help to limit the spread of influenza.

Each year the chief medical officer issues recommendations on the use of influenza vaccine. The fifth box shows current recommendations.[22] Routine vaccination of all people over the age of 65 is not advised in the United Kingdom because about half of this age group will have no underlying medical disease[23] and are at low risk of developing serious complications.

**Department of Health recommendations**

Immunisation is strongly recommended for:

- People of all ages, but especially elderly people, who are at increased risk of influenza related complications or exacerbations of their underlying disease—for example, those with
  - Chronic respiratory disease, including asthma
  - Chronic heart disease
  - Chronic renal failure
  - Diabetes and other endocrine disorders
  - Immunosuppression due to disease or treatment
- Residents of nursing homes, old people's homes, and other long stay facilities where rapid spread is likely to follow introduction of infection

Virus used to make the vaccine is grown in allantoic fluid, and contraindications to vaccination include hypersensitivity to eggs, polymyxin, or neomycin. Adverse effects include local erythema and tenderness at the site of injection, low grade fever, myalgia, and headache in the first 24 hours after vaccination. In 1977 the incidence of the Guillain-Barré syndrome during a vaccination programme against swine influenza in the United States was 1 in 100 000. The cause remains controversial, and this effect has not been observed in subsequent vaccines. Anecdotal cases of attacks of asthma after vaccination have been reported, but their significance and true relation to the administration of vaccine is uncertain. Concern over possible adverse effects is often cited as a reason not to vaccinate, but the incidence of severe side effects with modern subunit vaccines is exceedingly low.

### UPTAKE AND DELIVERY OF INFLUENZA VACCINE

The rate of vaccination in patients at high risk is surprisingly poor despite good evidence of vaccine efficacy. Connolly *et al* found that only 4·5% of such patients had been vaccinated during the 1989-90 epidemic,[8] and other recent studies have shown vaccination rates of about 19·5% in patients over 65,[24] 15% in patients with chronic asthma,[25] and 17% in patients with serious cardiac disease.[26] The reasons for the low vaccination rate are thought to include a poor perception of the potential severity of influenza, concern over vaccine efficacy and possible adverse effects, and logistic difficulties in identifying and targeting people at high risk. The last box shows strategies associated with improved uptake of vaccine in general

**Strategies to improve uptake of influenza vaccine in general practice**

- Having an agreed written practice policy
- Sending reminder letters to patients at high risk and those in residential institutions
- Having regular vaccination sessions, including home vaccination for immobile patients
- Using computer generated reminders on repeat prescriptions
- Printing a vaccination reminder on daily appointment lists

practice.[24 27 28] The costs and benefits of vaccination strategies for influenza have not been adequately assessed and should be a priority for further investigation.

NEWER APPROACHES TO INFLUENZA VACCINATION

Options other than killed influenza vaccines include recombinant fusion proteins and live attenuated vaccines.[19] Live attenuated, cold adapted, reassortant influenza virus vaccines have been investigated extensively in the former Soviet Union and in the United States. They may be given intranasally and are well tolerated. Potential advantages over inactivated vaccines include good immunogenicity in children, induction of nasopharyngeal IgA, and a longer lasting antibody response. Cold adapted vaccine can be given as an adjunct to inactivated vaccine and has been shown to confer additional protection.[29] The long term benefits of cold adapted live virus vaccines have yet to be established, and a proportion of subjects fail to respond. Whether lack of response is influenced by previous vaccination or exposure to influenza is unclear. Live virus vaccines will also need to be updated regularly as antigenic changes arise.

## Conclusion

Although epidemics and pandemics of influenza have been documented throughout history, the mechanisms underlying the global spread of infection are still poorly understood. Effective antiviral agents and vaccines are currently available but are not used to their full potential. Newer developments include the introduction of intranasal cold adapted live virus vaccine and further antiviral drugs. The responsibility for the management and control of influenza is shared by general practitioners, hospital physicians, public health officers, and national government.


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## A PATIENT WHO CHANGED MY PRACTICE

### Screening in obstetrics

Several years go I was nearing the end of an antenatal clinic when the sister in charge asked me to go and counsel a woman who had been screened for toxoplasmosis and had a positive result. She had asked for the investigation because she had heard about testing in the media and had not been counselled before the serum was taken. I made several urgent telephone calls to get some information about the implications of a positive result and then approached the woman and her husband.

They were an intelligent couple and were rather aggressive in their questioning. I was guarded in my response to their questions. The positive IgM level meant that infection had occurred sometime within the past three months (she was 10 weeks' pregnant at the time of testing). It was difficult to predict the risk of transplacental infection of the fetus, although it was probably fairly low in the early part of pregnancy. But if the fetus had acquired the infection in the first trimester then the chance of serious malformation was higher than if acquired later.

How were we to find out if the baby was infected? Unfortunately, we would have to wait another eight weeks until she was 21 weeks' pregnant when the fetus would start producing its own immunoglobulins. We would then have to take blood from the umbilical cord to investigate further; this procedure carried up to a 5% risk of causing a miscarriage. In the meantime, she should take spiramycin until the time of cordocentesis to reduce the risk of fetal infection. If she continued the pregnancy after this she should take the spiramycin for the rest of the pregnancy in case the fetus became infected subsequently. Even I was finding the logic of this suggestion hard to comprehend.

I saw the couple several times before the 21 weeks were up and admitted that our knowledge of toxoplasmosis in pregnancy was far from complete. I tried to deal with their questions by reference to expert colleagues and felt that I was becoming quite an expert myself. Fortunately the cordocentesis was uncomplicated and the result was negative. My relationship with the patient and her husband improved after this and I saw her regularly throughout the pregnancy, during labour, and after delivery. She had a healthy baby and continued to send me literature on toxoplasmosis for some time afterwards.

There are a large number of conditions we can screen for in pregnancy and at the moment there is a national debate on the introduction of serum testing for Down's syndrome risk in pregnancy. Following my experience I am convinced that all the implications of screening tests should be considered before their introduction and in particular the benefits must outweigh the disadvantages. I also emphasise the importance of considering the implications of a "positive" result to my patients when embarking on screening procedures.—ROBERT HAMMOND *is a consultant obstetrician and gynaecologist in Nottingham*