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# Clinical review

## Influenza pandemics and avian flu

Douglas Fleming

Douglas Fleming is general practitioner in a large suburban practice in Birmingham. In this article he seeks to clarify clinical issues relating to potential pandemics of influenza, including avian influenza



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The word pandemic is used to describe a disease that is epidemic throughout the world at more or less the same time. The other criterion for defining a pandemic relates to the causative virus. A pandemic occurs when a completely new virus emerges—a virus that shows a more radical change (antigenic shift) than the change occurring continuously in influenza viruses (antigenic drift) and which is generally associated with more severe illness. Britain is used to experiencing flu in most winters, but these outbreaks are not pandemics because they are not consistently present in all countries at the same time and not caused by new virus.

### Transmission

Not all flu viruses have the same transmission properties. The virus causing avian flu in poultry spreads by faeco-oral transmission. It is widely believed that humans contracting this condition have acquired it as a result of contact with infected poultry, either by airborne spread from birds or their faeces or by contamination during food preparation. Anxieties surrounding the H5N1 avian flu virus arise for three reasons: it has infected and caused serious illness in humans; further antigenic drift may increase the likelihood of spread to and between humans; antigenic shift (a change to the virus nucleus occurring as a result of simultaneous infection in one species with different strains of virus) may result in a virus transmissible between humans and with a capacity to initiate a new type of flu virus infection and series of annual epidemics.

People typically acquire flu by inhaling the virus or by being in direct contact with the respiratory tract secretions of people who are infected. The potential to infect others lasts as long as viruses are being shed from the respiratory tract. Healthy adults shed viruses from about one day before the onset of symptoms and continue to do so for about five more days. Children shed viruses for about two days longer, and people who are immunocompromised shed viruses for longer still.

### Avian flu

Flu viruses can affect many species including horses, whales, seals, pigs, and birds (particularly duck and wildfowl). The virus now commonly referred to as

avian flu (because of the extensive outbreaks in wild birds and poultry in China and South East Asia) is categorised H5N1, although some other viruses also cause flu epidemics in birds and have been the cause of considerable mortality. In 1983 an epidemic in poultry of an H5N2 virus infection was reported in the United States and was associated with 13 million poultry deaths either as a result of infection or because of the poultry cull instituted to control it.

### Avian flu in humans

Human infection with an avian H5N1 virus was first described in Hong Kong in 1997: 18 people were affected, six of whom died. Close links with domestic birds were a common feature, but there was no good evidence of spread between people. Episodes caused by various avian viruses (including H5 and H7 strains) have continued to appear. These occurred mainly in clusters, although not solely in South East Asia: an H7N7 infection has been described in Dutch poultry workers, which caused the death of a veterinary surgeon.

So far, episodes have occurred in individuals or communities with close links with poultry; none has occurred where human to human transmission was implicated beyond doubt. Where human infection has occurred, the symptoms were not solely respiratory.

### What should GPs be doing about the pandemic threat?

It is important that general practitioners take the recent threat of a flu pandemic seriously. In the United Kingdom, the contingency plan for flu pandemic published by the Department of Health is essential reading.<sup>1</sup> The plan includes provision to strengthen healthcare capacity in primary care, but if a pandemic does occur, general practice is likely to carry the major burden of disease management in the community, and it is unrealistic to think that it will be contained in routine office hours. Pandemics causing severe illness occurred in 1919, 1957, and 1969. These pandemics undoubtedly pressurised the health services, but the country did not come to a halt.

Medical and non-medical staff in practices should meet formally to consider the implications of running the practice. These meetings should be minuted so that

**Sample questions**

Here is a small sample of the questions that you can find at the end of this module. To see all the questions and to get the answers, go to [www.bmjlearning.com/](http://www.bmjlearning.com/) and search for "influenza pandemics: bird flu"

- Which one of the following statements is correct about avian flu?
  - Avian flu H5N1 is now a pandemic flu virus
  - Humans cannot be infected by avian flu viruses
  - Avian flu does not spread between humans
  - Avian flu has spread throughout the whole of South East Asia
- Which one of the following statements is correct about pandemic planning?
  - Pandemic planning in most countries is focused on vaccinating high risk individuals
  - Planning cannot start until a pandemic virus strain has been identified
  - In the UK the Department of Health has published a pandemic contingency plan
  - Pandemic planning is based solely on the use of antiviral drugs
- Which one of the following statements about the commercial issues surrounding the manufacture of pandemic flu vaccine is correct?
  - They provide considerable potential for entrepreneurial manufacturers
  - They present considerable problems for testing new vaccines
  - They are being addressed by the manufacture of a pandemic virus vaccine
  - They cannot be addressed until a pandemic occurs
- How long do antibody levels typically take to rise after influenza vaccination?
  - 3-6 days
  - 7-13 days
  - 14-21 days
  - 21-27 days

the practice can prepare a document outlining its contingency plans. You need to consider how to advise patients, target those at risk, cope with demand, and continue giving routine care.

**Advising patients**

You and your staff will be responsible for providing accurate information to a fearful and anxious population. This will involve minimising rather than inflaming the hype that is likely to occur.

A pandemic is likely to cause illness in several members of a household. You can use your experience of the first person to become ill to brief the entire family on management and alert them to risk symptoms. However, the advice you give to the 30 year old man consulting you today might not be appropriate for his three month old son, who may be the next family member to become ill.

The media coverage during the 1918 pandemic, the recent incidence of severe acute respiratory syndrome (SARS), the emergence of avian flu, and the coverage of the pressures imposed by flu over the millennium period all demonstrate the reaction of the public to health risks: some people will not accept the principles of prioritisation and rationing, and general practitioners will need to stand firm.

**Symptoms and complications of flu\*****Typical symptoms (last about five to seven days)**

- Dry cough
- Muscle pains
- Sore throat
- Raised temperature (not always present in elderly people)
- Headache
- Feeling weak and tired

**Typical complications**

- Otitis media
  - Primary influenza pneumonia
  - Secondary bacterial bronchitis and pneumonia
  - Encephalitis (rare)
  - Worsening or destabilisation of pre-existing diseases, such as cardiac failure and diabetes
- \*The time between exposure to the flu virus and the onset of symptoms is usually two days, but it can vary from one to five days

**Targeting patients**

General practitioners in the UK will be required to implement policies determined by the Department of Health. You will need to consider how best you can contact target groups for vaccination (subject to vaccine availability), though appropriate national publicity will be available.

You will need to consider whether you have registration procedures that reliably identify patients in the likely risk categories. Have you generated lists of such patients, and were they reliable and comprehensive? You will also have to deal with aggrieved people who do not accept their exclusion from a priority group.

**Coping with demand**

You should be thinking about how best to cope with a large increase in demand, especially for home and out of hours visits. Can you learn from your experience of telephone consultations and think of ways you can use these to best effect? You may be working with a depleted staff. Can you simulate the situation and test your capacity to deal with such a contingency?

Flu infection is associated with high fever, and febrile convulsions are likely to lead to fears about meningitis. Flu spreads rapidly, and it will therefore be preferable to keep those affected out of hospital, but can we do this safely? Hospital beds will be at a premium.

In recent years, medical care has increasingly used triage methods, which have usually involved nurses.

**Learning point: Example 1**

**You advise a 70 year old man to have the flu vaccine, but he says he had it last year and still got flu. What should you say to him?**

He may not have had flu; many respiratory pathogens circulate each winter, and flu vaccination won't prevent infections with other respiratory viruses. The vaccine does not prevent every attack of flu, but it does reduce the likelihood of complications and death. So you should urge him to have the vaccine.

**Learning point: Example 2**

**A 69 year old woman comes to see you in December. She forgot to have the flu vaccine, and now there is a flu outbreak. What should you advise her?**

She can still have the vaccine if it is still available. But after vaccination, antibody levels take 7-13 days to rise. If she has been exposed to the flu virus in the past 48 hours, you could give her oseltamivir to prevent her getting flu.

The art of triage is not learnt overnight. Do you need to train certain staff so they can select who needs to consult a doctor? During a severe pandemic your nurses are likely to be engaged in disease management and may have limited time for triage.

**Continuing routine care**

To restrict spread of infection in the event of a severe pandemic, schools and places of congregation may be closed. Health centres may become places where people are likely to catch flu. How will you care for people with chronic disease who will still need their routine medication? And what about people needing to consult for other conditions? How many of these could you manage by telephone?

**Commercial and ethical issues**

In the commercial world, products are developed and sold according to their usefulness and price, as judged by the consumer. The pharmaceutical industry operates within this framework. New vaccines and drugs are developed according to likely sales and the potential for profit. Manufacturing protocols are observed; products are tested, licensed, and marketed; and manufacturing capacity is adapted to the market potential. There are successes and failures in all manufacturers' programmes. But the threat of a pandemic brings a new perspective to these familiar commercial principles.

It is usual to license new drugs or vaccines for age groups in which they have been tested. In a pandemic the opportunity to test a new vaccine will be limited and will certainly not be possible in the people who may be at most risk (for example, young children). This poses a dilemma when determining appropriate use of vaccines and antiviral drugs. Because of the fear of litigation arising out of the use of a vaccine in "uncharted

**Learning point: Example 3**

**A 76 year old woman says she had the flu vaccine two years ago and it gave her flu. She says she never wants to have it again. What should you advise her?**

Flu vaccine can't cause flu because it is an inactivated vaccine. The symptoms of flu come from the destruction caused by a replicating virus. As inactivated vaccines contain no living flu virus, virus replication cannot occur. However, she might have contracted the flu before she could mount an immune response to the vaccine. The delay between vaccination and effective protection is about two weeks. The best time to be vaccinated is therefore at the start of the flu season.

**Learning point: Example 4**

**A 66 year old man with a history of stroke has read that the flu vaccine can cause strange neurological illnesses. What should you say to him?**

Flu vaccine does not cause strokes. He may have read about Guillain-Barré syndrome, but this condition is extremely rare, perhaps occurring at a rate of about one additional case per million people vaccinated. A history of Guillain-Barré syndrome is no longer considered to be a contraindication for vaccination. Pregnancy is not a contraindication for vaccination. True hypersensitivity to eggs is also a contraindication because flu vaccines are developed from virus material grown on hens' eggs.

waters," a pharmaceutical manufacturer is likely to seek government assurances on product liability.

**Vaccine production**

An appropriate vaccine cannot be developed before a virus emerges that can be replicated in sufficient quantities to manufacture the vaccine. Experimental work with potentially serious pathogens is conducted only in laboratory conditions of high security, and the availability of such conditions is limited. Although there may be some benefit in developing a vaccine against an H5 virus, the chances of a good match with a truly pandemic strain may be low and certainly not such that it might tempt a manufacturer to incur the costs of preparing a vaccine on a substantial scale (which would require using the facilities normally used to produce routine flu vaccines).

Even if there were considerable assurance about the protective value against all H5 viruses, the commercial risk would be considerable: an H5 virus might never cause a pandemic and there might never be a market for it. Developing a suitable vaccine, manufacturing and testing it, and, finally, licensing it is unlikely to take less than six months. Normally, a new vaccine is subjected to detailed clinical trials before licensing. This step may have to be curtailed in a pandemic situation.

Limited supplies of vaccine against the existing H5N1 avian virus are now being manufactured and used for studying likely dosing schedules and the immune response that might be expected. The possibility that such a generic H5 vaccine might at least be used to prime selected persons in special situations is under consideration.

**Antiviral drugs**

Antiviral drugs against flu have scarcely been used in Europe, and the manufacturing capacity has accordingly been matched to current rather than exceptional use. Manufacturers cannot accommodate a surge in demand without sufficient notice. If these drugs are to be made available to manage a pandemic, they will have to be manufactured (and sold) well in advance.

For these reasons, many European governments (including the UK, which has ordered 14 million treatment courses) have placed orders so they can stockpile these drugs. They will buy the stockpiles regardless of whether there is ever a pandemic in which the drugs will be used. The drugs may well be used in situations in which doctors have limited knowledge of optimum use (as opposed to use in the conditions of a clinical

trial). Furthermore, it is not clear how useful they would be to treat a completely new virus or how great the risks from resistant strains would be.

Neuraminidase inhibitor antiviral drugs are licensed for prophylaxis in high risk groups (as recommended by the National Institute for Health and Clinical Excellence). However, prescribing them for prophylaxis in a pandemic might be an extravagant use of limited resources. This could be justified only if there were good grounds to think a vaccine was imminent. It might be preferable to institute early treatment rather than offer prophylaxis, because the stimulus of infection will prompt an antibody response.

### Supply shortages

Vaccines and drugs will be manufactured at selected plants. In the event of a serious pandemic, countries may suspend routine trading practices. Governments will be strongly tempted to suspend the export of drugs in short supply, and in some countries there may be no local manufacturer and no drugs or vaccines available. There is clearly an ethical dilemma between the competing interests of countries with manufacturing capacity and those without. An ethical dilemma also exists with respect to people in countries with inadequate resources to meet the cost of vaccines and drugs.

Should a pandemic emerge within 12 months, the availability of antiviral drugs will be limited, and people at high risk will need to be given priority; the groups at risk may differ from those conventionally associated with the routine annual vaccination programme. Healthcare workers and people operating essential services might be the most important groups to protect. Serious illness in children might result in redefining the concept of risk.

### Summary points

Now is the time for general practices to plan their response to managing a pandemic

Engage your entire practice team in those discussions

Familiarity with the national plan and cooperation in it are essential

Be prepared for an illness in which the principles of prioritisation of treatment groups will be needed

Improve your capacity to manage illness on the basis of telephone contact

Obtain and provide accurate information: do not be swayed by media hype

The author is also director of the Birmingham Research Unit of the Royal College of General Practitioners. The unit is funded by the Department of Health and is particularly concerned with routine surveillance of common diseases presenting in primary care. The contents and opinions expressed in this article are exclusively those of the author.

Competing interests: The author has provided consultancy services to several pharmaceutical companies engaged in drug and vaccine manufacture of flu related products.

<sup>1</sup> Department of Health. *UK health departments' influenza pandemic contingency plan*. London: DoH, 2005 (October). ([www.dh.gov.uk](http://www.dh.gov.uk), search with ref 4615).

### Hide the title

As anybody knows who has sat on an interview panel, people choose a career in medicine for different reasons—interests, steady job, tradition—but if you speak in depth to most medics we all feel that we are “doing our bit.” Working as hard as we do to help others is the crux of our career choice and, in spite of all the surrounding difficulties, is the main joy of being a doctor. Now for this we get reasonable remuneration and hopefully some degree of job satisfaction. Do other members of the public see us in this light, or are we seen as fat cats and fair game because of the image of the rich doctor on the golf course?

My wife and I recently moved house and, because of several incidents, decided to use this (unpleasant) experience to see how your average workman reacted to us being a couple who both happen to be doctors. Our “hypothesis” was a rather cynical one—that people who knew of our profession were apt to change their quotes accordingly. The house we moved to is in a fairly affluent area of Cheshire with a semi-professional population—we have several medical colleagues living in the same postcode.

We chose four jobs to be quoted for—removal expenses, fitting the house with a burglar alarm, garden fencing, and an extra television aerial to be fitted in the bedroom. For each job, we got three quotes from firms advertising in the local

telephone book. For two of these quotes we were simply Mr and Mrs, but for the third we introduced ourselves as Dr.

The results spoke for themselves. Of those companies who knew we were doctors, the removals company quoted in excess of £250 more than the other two companies, the garden fencing was about £200 more expensive, and the aerial doubled in price. Our only piece of good news was the alarm company, which turned out to be the cheapest of the three (name supplied on request) and which was promptly hired.

This is something I have long wondered about, but have been told that I am a cynical old man (at 29) and that the British public should be trusted. I would just like to point out that, even though we gain satisfaction from helping our fellow humans at work, after having trained for many years, the fact that we are doctors means to some that we are targets for inflated costs. I for one am now going to keep my job under wraps and use any money I save to put myself through a DIY course.

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Competing interests: My wife and I have a definite, significant financial interest in this study.