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Seminar

Influenza

Karl G Nicholson, John M Wood, Maria Zambon

Although most influenza infections are self-limited, few other diseases exert such a huge toll of suffering and economic loss. Despite the importance of influenza, there had been, until recently, little advance in its control since amantadine was licensed almost 40 years ago. During the past decade, evidence has accrued on the protection afforded by inactivated vaccines and the safety and efficacy in children of live influenza-virus vaccines. There have been many new developments in vaccine technology. Moreover, work on viral neuraminidase has led to the licensing of potent selective antiviral drugs, and economic decision modelling provides further justification for annual vaccination and a framework for the use of neuraminidase inhibitors. Progress has also been made on developing near-patient testing for influenza that may assist individual diagnosis or the recognition of widespread virus circulation, and so optimise clinical management. Despite these advances, the occurrence of avian H5N1, H9N2, and H7N7 influenza in human beings and the rapid global spread of severe acute respiratory syndrome are reminders of our vulnerability to an emerging pandemic. The contrast between recent cases of H5N1 infection, associated with high mortality, and the typically mild, self-limiting nature of human infections with avian H7N7 and H9N2 influenza shows the gaps in our understanding of molecular correlates of pathogenicity and underlines the need for continuing international research into pandemic influenza. Improvements in animal and human surveillance, new approaches to vaccination, and increasing use of vaccines and antiviral drugs to combat annual influenza outbreaks are essential to reduce the global toll of pandemic and interpandemic influenza.

Influenza is a globally important contagion. About 20% of children and 5% of adults worldwide develop symptomatic influenza A or B each year.[1] It causes a broad range of illness, from symptomless infection through various respiratory syndromes, disorders affecting the lung, heart, brain, liver, kidneys, and muscles, to fulminant primary viral and secondary bacterial pneumonia. The course is affected by the patient's age, the degree of pre-existing immunity, properties of the virus, smoking, comorbidities, immunosuppression, and pregnancy. Most influenza infections are spread by virus-laden respiratory droplets several microns in diameter that are expelled during coughing and sneezing. Fomites represent another mode of transmission. Occasionally, influenza is transmitted to people by pigs or birds.

Although the initial site of replication is thought to be tracheobronchial ciliated epithelium, the whole respiratory tract may be involved. Virus can be detected in secretions shortly before the onset of illness, usually within 24 h. The viral load rises to a peak of 10^3–10^7 $TCID_{50}$/mL of nasopharyngeal wash, remains high for 24–72 h, and falls to low values by the fifth day. In young children, virus shedding at high titres generally persists for longer, and virus can be recovered several weeks after symptom onset. Although most influenza infections are self-limited, few other diseases exert such a huge toll of absenteeism, suffering, medical consultations, hospital admission, and economic loss.

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Infectious Diseases Unit, Leicester Royal Infirmary, Leicester, UK (Prof K G Nicholson MD)**; National Institute for Biological Standards and Control, Potters Bar, Hertfordshire** (J M Wood PhD)**; and Central Public Health Laboratory, London** (M Zambon PhD)

Correspondence to: Prof Karl G Nicholson, Infectious Diseases Unit, Leicester Royal Infirmary, Leicester LE1 5WW, UK
(e-mail: karlgnicholson@doctors.org.uk)

Virology

Influenza viruses have segmented genomes and show great antigenic diversity. Of the three types of influenza viruses—A, B, and C—only types A and B cause widespread outbreaks. Influenza A viruses are classified into subtypes based on antigenic differences between their two surface glycoproteins, haemagglutinin and neuraminidase. 15 haemagglutinin subtypes (H1–H15) and nine neuraminidase subtypes (N1–N9) have been identified for influenza A viruses (figure 1). Viruses of all haemagglutinin and neuraminidase subtypes have been recovered from aquatic birds, but only three haemagglutinin subtypes (H1, H2, and H3) and two neuraminidase subtypes (N1 and N2) have established stable lineages in the human population since 1918. Only one subtype of haemagglutinin and one of neuraminidase are recognised for influenza B viruses.

Selection criteria and search strategy

We reviewed international reports published in English before December, 2002. The data for this non-systematic review of articles were identified by searches of MEDLINE, EMBASE, Integrated Science Citation Index, PubMed, and the Cochrane Library electronic databases with relevant keywords. We also searched cited references in retrieved articles, reviewed articles we have collected over many years, referred to the *Textbook of Influenza*,[2] and used knowledge of new data presented at international scientific meetings. Because of the large number of articles that are published every year and limitations on the number of citations, we gave emphasis to clinically relevant issues, particularly disease burden, the emergence of new subtypes, vaccines, and antivirals, and diagnosis. We gave priority to randomised controlled trials when available, to larger studies, articles published in high-impact journals that have a wide readership, and the systematic review and economic decision modelling, for the prevention and treatment of influenza, commissioned by the Health Technology Assessment Programme on behalf of the National Institute of Clinical Excellence.[1] We also drew on our own knowledge when it seemed appropriate to fill in the gaps in the published work and included several recent pertinent articles.

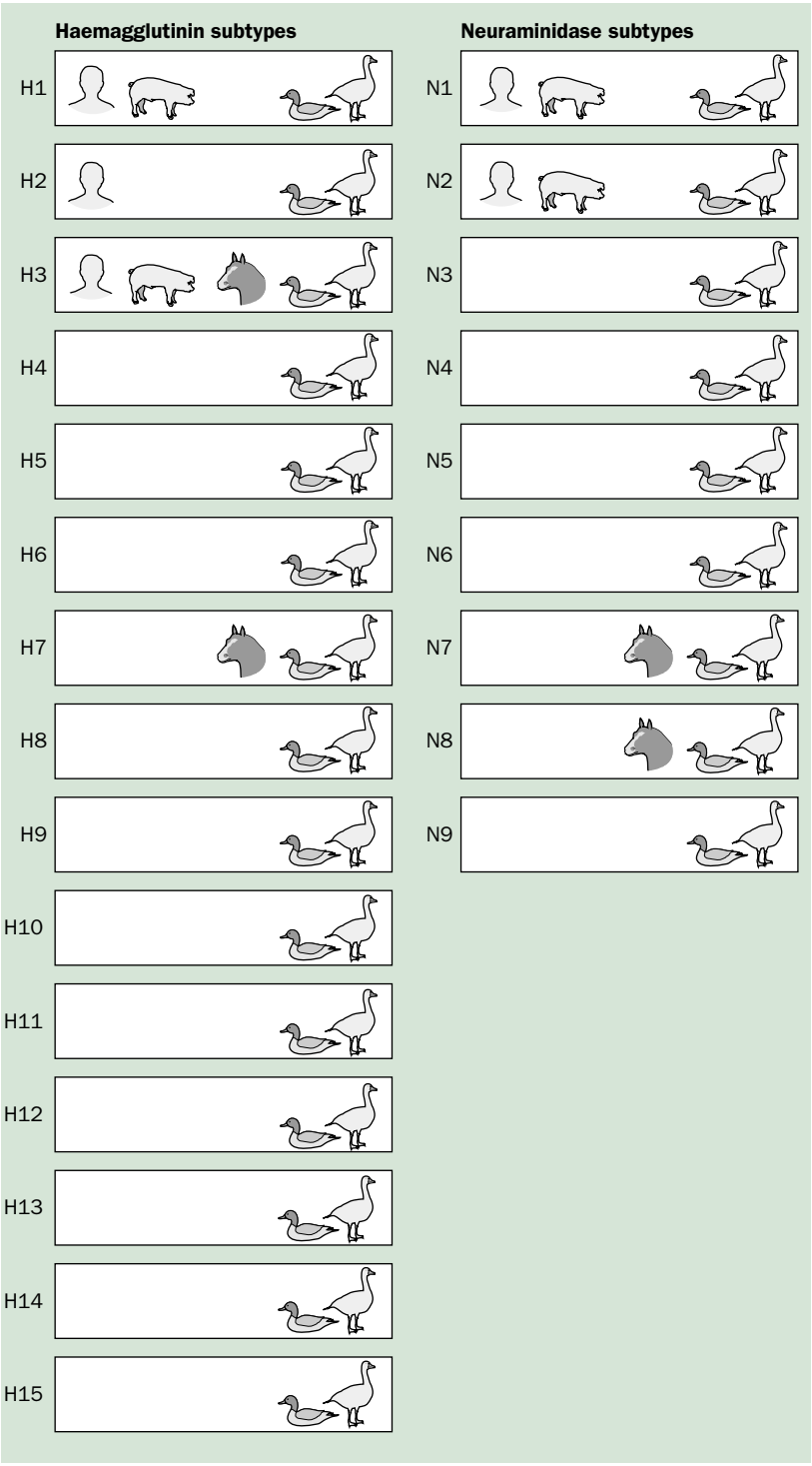

Figure 1: **Natural hosts of influenza viruses**

Haemagglutinin facilitates entry of the virus into host cells through its attachment to sialic-acid receptors. It is the major antigenic determinant of type A and B viruses to which neutralising antibodies are directed and the crucial component of current influenza vaccines. An important function of neuraminidase, the second major antigenic determinant, is to catalyse the cleavage of glycosidic linkages to sialic acid, thereby assisting in the release of progeny virions from infected cells. Accordingly, neuraminidase has become an important target for antiviral activity. The M2 ion channel of influenza A, which is blocked by the antiviral drug amantadine, regulates the internal pH of the virus, which is crucial during early viral replication.

The epidemiological behaviour of influenza in people is related to the two types of antigenic variation of its envelope glycoproteins—antigenic drift and antigenic shift. During antigenic drift, new strains of virus evolve by accumulation of point mutations in the surface glycoproteins. The new strains are antigenic variants but are related to those circulating during preceding epidemics. This feature enables the virus to evade immune recognition, leading to repeated outbreaks during interpandemic years. Antigenic shift occurs with the emergence of a "new", potentially pandemic, influenza A virus that possesses a novel haemagglutinin alone or with a novel neuraminidase. The new virus is antigenically distinct from earlier human viruses and could not have arisen from them by mutation (figure 2).

Burden of influenza

Four or five pandemics of influenza occurred during the 20th century with intervals of 9–39 years. The H1N1 pandemic of 1918–19 was the most devastating, with 40–50 million deaths; an estimated 4·9 million excess deaths, representing 2% of the population, occurred in India alone. However, the cumulative mortality from influenza during the intervening years is generally many times greater than that associated with pandemics.[3]

Although influenza A or B viruses circulate virtually every winter in temperate zones of the northern and southern hemispheres, quantification of the burden of influenza on consultations, emergency-department examinations, hospital admissions, and mortality has been difficult because influenza lacks pathognomonic features, it cocirculates with other respiratory pathogens, and it causes a range of non-specific complications, such as exacerbations of chronic cardiopulmonary disease. Nevertheless, there is much evidence that the H3N2 subtype of influenza A virus causes more severe illness than H1N1 or influenza B,[4–6] more hospital admissions for pneumonia and influenza,[7] and higher numbers of excess deaths.[3]

During outbreaks, sentinel schemes, such as the Royal College of General Practitioners' network in England, report increased consultation rates for influenza-like illness and other respiratory syndromes that are strongly associated with excess mortality.[8] In England and Wales, an estimated 6200–29 600 people died during each of the epidemics between 1975–76 and 1989–90.[8] These estimates are about ten times the number of death certifications for influenza, because the disease is the cause of many "hidden deaths". In the USA, during the

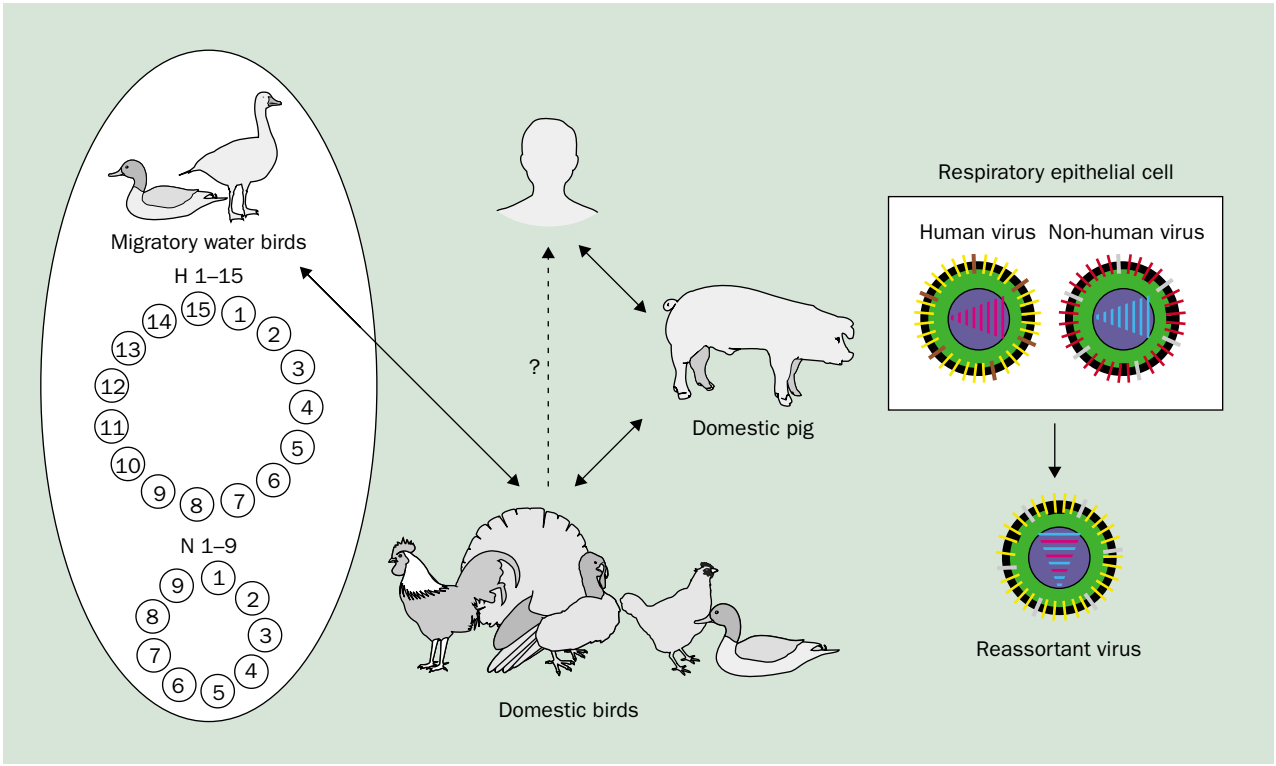

Figure 2: **Origin of antigenic shift and pandemic influenza**
The segmented nature of the influenza A genome, which has eight genes, facilitates reassortment; up to 256 gene combinations are possible during coinfection with human and non-human viruses. Antigenic shift can arise when genes encoding at least the haemagglutinin surface glycoprotein are introduced into people, by direct transmission of an avian virus from birds, as occurred with H5N1 virus, or after genetic reassortment in pigs, which support the growth of both avian and human viruses.

period 1976–99, influenza viruses were associated with annual means of 8097 deaths from pneumonia and influenza, 11 321 respiratory and circulatory deaths, and 51 203 all-cause deaths.[9] About 90% of these influenza-associated excess deaths are among people aged 65 years and older. Although there are age-related increases in deaths from influenzal illness in both at-risk and low-risk groups,[10] most deaths and hospital admissions occur in elderly people with chronic cardiopulmonary disorders.

Among toddlers, rates of influenza-associated hospital admission in the USA have ranged from about 500 per 10^5 population for those with high-risk conditions to 100 per 10^5 for those without high-risk conditions.[11–14] Admission rates are highest among children younger than 1 year and are similar to rates found among people aged 65 years and older.[13,14] Among children in Hong Kong, China, the numbers of excess hospital admissions attributed to influenza are very high in children younger than 12 months (2785 and 2882 per 10^5 in 1998 and 1999, respectively) and decrease with age (2184 and 2093 per 10^5 children aged 12–23 months; 1256 and 773 per 10^5 children aged 2–4 years; 573 and 209 per 10^5 children aged 5–9 years; and 164 and 81 per 10^5 children aged 10–15 years).[15] In the tropics and subtropics, influenza occurs either throughout the year with no distinct seasonality or visible excess mortality, or twice a year, with the more intense activity during the rainy season. Consequently, the morbidity and mortality from influenza are probably greatly underestimated in these regions. During summer, 2002, an epidemic of respiratory illness with 22 646 cases and 3% case-mortality affected Madagascar; it was attributable to influenza A/Panama/2007/97-like (H3N2) virus. The loss of life was greatest in young children and was ascribed to malnutrition and poor access to health care.[16] Another outbreak attributable to influenza A/Panama/2007/97-like (H3N2) virus occurred during November and December, 2002, in the district of Bosobolo, Democratic Republic of Congo. The case-fatality rate was 3·5% in children younger than 5 years and 3·2% in people over 65. These rates illustrate the seriousness of such outbreaks and are one of the reasons why improved linkage of morbidity and mortality analysis with virological surveillance is one of the key objectives of the WHO Global Agenda on Influenza, formulated in 2002.

Emergence of new subtypes in human population

In southern China, influenza viruses circulate throughout the year. There is evidence for the origin in China of the viruses that caused the pandemics of H2N2 influenza in 1957, H3N2 influenza in 1968, and the re-emergence of H1N1 influenza in 1977. Recent outbreaks of avian influenza A H5N1 and H9N2 in people in Hong Kong show the importance of virological surveillance in this region for the early detection of potentially pandemic viruses. There is also evidence that some drift variants circulate in China for up to 2 years before causing epidemics in Europe and North America.[17,18] This region is thought to provide an appropriate ecological niche for the emergence of new influenza viruses with pandemic potential, owing to the proximity of dense populations of people, pigs, and wild and domestic birds, thereby facilitating genetic reassortment of viruses from different species (figure 2), or for the emergence of drift variants, given the high human population density and year-round virus circulation. These observations provided the impetus for improving the WHO global influenza surveillance programme in China that has provided many of the vaccine strains recommended by WHO in the past decade.

The examples cited below indicate the unpredictability of influenza-virus variation and the great capacity for evolution, but they also show that novelty alone is insufficient for the emergence of pandemic influenza. Adaptation to replication in human beings, the ability to spread from person to person, and a susceptible population are also prerequisites. Thus, the emergence of new influenza-virus variants in the human population does not necessarily herald pandemic influenza.

Influenza A/Hong Kong/97 (H5N1)

In May and November–December, 1997, 18 cases of influenza H5N1 infection were identified in people in Hong Kong. This outbreak, which followed serious outbreaks of avian H5N1 influenza in chicken farms, signalled the possibility of an incipient pandemic. The human influenza isolates were of avian origin and were not derived by reassortment.[19] The high mortality (six of 18 patients died from acute respiratory distress syndrome or multiple organ failure, most previously healthy young adults[20]) suggested an unusually aggressive clinical course. Deterioration was rapid, with pneumonia necessitating ventilatory support developing within a few days of illness onset. Striking features of severe cases were the early onset of lymphopenia and high concentrations of serum transaminases. Fortunately, there were few if any secondary infections, and the H5N1 outbreak ceased when all chickens in Hong Kong (about 1·5 million) were slaughtered. The territory's poultry stocks were again depopulated when highly pathogenic A/Hong Kong/97 (H5N1) virus re-emerged in flocks in May, 2001, and February and April, 2002. However, no further human cases of H5N1 influenza were identified until February, 2003, when two cases were confirmed in a family of Hong Kong residents.

The first patient, a 9-year-old boy who was admitted to hospital in Hong Kong and recovered, became unwell during travel to Fujian Province, mainland China. The boy's 33-year-old father died in a Hong Kong hospital and his 8-year-old sister died in a hospital while the family was in China; the cause of her death is not known. Genetic analysis of the two H5N1 isolates showed that the virus genes were purely avian in origin, but differed from the 1997 strains that infected human beings.

Influenza A/Hong Kong/99 (H9N2)

After the H5N1 outbreak in Hong Kong, heightened surveillance in the adjoining Guandong Province led to recovery of nine human isolates of H9N2 virus during July–September, 1998.[21] In March, 1999, influenza H9N2 viruses were isolated from two children in Hong Kong. The illness in both was mild and self-limited.[22] No serological evidence of H9N2 infection was found in family members or health-care workers who had close contact with the children; thus, H9N2 viruses, like H5N1 viruses, seem not to be easily transmitted from person to person.[23] Three lineages of H9 virus have been defined, with the prototype viruses being G1, G9, and Y439.[24] The G1 "avian" H9N2 viruses isolated from human beings have some receptor properties similar to those of other human viruses—ie, binding to α2,6 sialic acid linkages, in contrast to the binding preference to the α2,3 linkages normally found with avian influenza viruses. In Hong Kong, antibody to H9 viruses was found in about 4% of blood donors,[22] which suggests that human infection with H9N2 may occur in this locality. Surveillance of pigs in southern China has shown that H9N2 viruses are cocirculating with human A/Sydney/97-like H3N2 viruses and other porcine H1N1 and H3N2 viruses. Together, these observations indicate that all the precursors of potentially pandemic H9 human-avian reassortants are in place.

H1N2

During February, 2002, a new influenza H1N2 virus was isolated from patients with influenza-like illness in England and the middle East.[25] In the UK it affected mainly young children.[26] These H1N2 viruses arose after reassortment of the segments of the currently circulating influenza A (H1N1) and A (H3N2) subtypes.[25] Although influenza A (H1N2) viruses have been identified previously, during 1988–89, when 19 influenza A (H1N2) viruses were isolated in six cities in China, the virus did not spread further.[27,28] The limited effect of H1N2 in 1988 and during the 2001–02 and 2002–03 seasons is attributable to the good pre-existing immunity in the population.

H7N7

In 1980, four people contracted purulent conjunctivitis within 2 days of post-mortem examination of harbour seals that died during an outbreak of influenza A/Seal/Mass/1/80 (H7N7), an A/Fowl Plague/Dutch27 (H7N7)-like virus, in Cape Cod, MA, USA.[29] Subsequently, A/Seal/Mass/1/80 (H7N7) was recovered from the conjunctiva of an investigator who developed conjunctivitis when an infected animal sneezed into his face.[29] In 1996, avian H7N7 virus was isolated in the UK from a woman with conjunctivitis who kept ducks.[30]

Although none of these six patients had respiratory symptoms, an outbreak of highly pathogenic avian H7N7 influenza in poultry farms in the Netherlands, which began at the end of February, 2003, was associated with fatal respiratory illness in one of 82 human cases by April 21. The person who died was a previously healthy 57-year old veterinary surgeon who developed severe headache, renal impairment, interstitial pneumonia, and acute respiratory distress after visiting an affected poultry farm.[31] Most patients presented with conjunctivitis (n=79), and only seven (<10%) had respiratory illness. Transmission of H7N7 influenza from poultry workers to family members was found on three occasions.[31] Most virus isolates obtained from human beings had not accumulated significant genetic changes, including those from cases of human-to-human transmission. However, the virus isolated from the person who died had 14 aminoacid substitutions, which suggests a role in pathogenicity.

Diagnosis

Rapid, near-patient tests for influenza can aid clinical management, but the usefulness of existing tests for decisions on whether to start antiviral drug treatment is limited because they are complex or have low sensitivities (table 1).[32–41] However, rapid influenza tests can show whether virus is circulating in specific populations or localities, and they may become a useful adjunct to surveillance programmes.[42] Thus, treatment with anti-influenza drugs commonly depends on patients' symptoms. Although influenza has no pathognomonic features, it was diagnosed correctly in clinical trials in about two-thirds of adults when the clinical entry criteria were met.[43] Cough and fever (temperature 37·8°C or above) are the most predictive symptoms of influenza,[43] but fever may not be present in

elderly people.[44] In primary care, about 25–50% of patients with influenza-like illness have the disease during outbreaks.[45–47] Thus, optimum implementation of guidelines for antiviral treatment depends on continuous community-based clinical and virological surveillance and awareness by general practitioners that influenza is circulating.

Pathogenesis

Most of what we know about highly pathogenic influenza viruses derives from studies with avian influenza viruses in birds. This situation is potentially relevant to disease in human beings because some mechanisms of pathogenicity in birds may operate in mammals and new human influenza A strains may come ultimately from the avian reservoir.[48] Tissue tropism and the capacity for systemic spread are the most important determinants of pathogenicity in birds. The molecular correlates of these pathogenic properties reside in the viral haemagglutinin and have been well studied.[49–51] However, in mammals, factors other than viral haemagglutinin are involved in determining pathogenicity, including viral non-structural protein 1, PB2, and neuraminidase.

Recovery of nucleic acid of the 1918 pandemic virus from post-mortem tissue or preserved human remains has shown that this highly pathogenic virus did not have the molecular motifs in haemagglutinin associated with virulence in avian strains.[52,53] The use of reverse genetics techniques has allowed the direct manipulation of influenza-virus gene products and creation of new recombinant viruses. Selective testing of specific mutations engineered into recombinant viruses in a mouse model has shown that greater virulence is obtained by specific molecular properties of haemagglutinin, but these do not fully explain pathogenicity.[54]

The balance between viral replication and host immune response determines the outcome of viral infection. Highly virulent viruses, such as H5N1, have a remarkable capacity to resist the antiviral effects of host cytokines.[55] Infection of human macrophages also results in induction of high cytokine expression, suggesting that severe outcome of infection is due both to lack of inhibition of viral replication by cytokines and to excess induction of cytokines leading to tissue damage in the infected host.[56] The key genetic component determining replication of highly pathogenic virus may be the non-structural protein 1 of the virus, which has been identified as the major immune modulator.[57]

Factors contributing to the pathogenesis of influenza in people are incompletely understood. These include understanding of the nature of tissue restriction of proteases, differences in reactivity of the innate immune system at different stages of life, and varying susceptibilities in different human populations, leading to different ranges of disease in certain populations; for example, encephalopathy is well recognised in Japan, but less so in other populations.[58,59] Study of mechanisms of virulence should provide more than simply elucidation of pathogenesis, notably development of alternative means of attenuating influenza viruses (eg, by deletion of non-structural protein or M2 [matrix protein 2] genes) to make safer vaccine strains.

Current vaccines

Current vaccines are produced from virus grown in fertile hens' eggs and inactivated by either formaldehyde or β-propiolactone. They consist of whole virus, detergent-treated split product, or purified haemagglutinin and neuraminidase surface antigen formulations of the three virus strains currently recommended by WHO. About 50 countries have government-funded national immunisation programmes, and influenza vaccine is available in many others. About 234 million of the world's population of 6 billion were vaccinated during 2000. Specific vaccine recommendations vary, but most involve annual vaccination of elderly people and those with certain chronic medical disorders. These recommendations were founded on proven morbidity and mortality in the at-risk groups, consistent demonstrations of vaccine efficacy in military recruits, recognition of the relation between antibody and protection, and proof of vaccine antigenicity.

Safety of current inactivated vaccines

Whole-virus vaccines are not widely available because they cause adverse reactions in young children, whereas split-product formulations and those containing purified surface antigen are well tolerated and extremely safe. The virtual absence of published reports suggests that hypersensitivity reactions are rare. Recent randomised controlled trials[60–62] and a large cohort study have confirmed the safety of influenza vaccine in patients with

Test name and manufacturer	Format	Time to completion (min)	Readout	Number of studies	Sensitivity (%)	Specificity (%)	Comment and references
Directigen Flu A; Becton Dickinson (www.bd.com)	Membrane adsorption EIA: detection of influenza NP	15	Colour change in small cassette	11	62–100 (median 89·7)	84–100 (median 97·2)	Detects influenza A only[32–35]
Directigen A/B; Becton Dickinson	Membrane adsorption EIA: detection of influenza NP	15	Colour change in small cassette	2	Median 90 influenza A, 71 influenza B	Median 99·8 influenza A, 98·5 influenza B	Detects A and B and distinguishes between them[36,37]
Biostar; Biota (www Biostar.com)	Optical immunoassay; detection of influenza NP	15	Change in refractive index on silicon chip embedded in small cassette	8	37–93 (median 52·7)	73·1–95·7 (median 86)	Detects A and B; does not distinguish between them[38]
Z Stat; Zyme Tx Inc (www.zymetx.com)	Membrane adsorption EIA; detection of influenza neuraminidase	30	Colour change in small cassette	6	65–96 (median 71)	63–92 (median 83)	Detects A and B; does not distinguish between them[38,39]
QuickVue; Quidel (www.quidel.com)	Membrane capillary flow; detection of influenza NP	10	Dipstick; colour change	3	74–95 (median 79·2)	76–98 (median 82·6)	Detects A and B; does not distinguish between them[38,40,41]

NP=nucleoprotein.

Table 1: **Summary of near-patient tests**

Population	Vaccine and dose	Study	Outcome	Efficacy (%; 95% CI)
Children	Split product and surface antigen, 15 μg	Random-effects meta-analysis[1] of RCTs[64–68]	Symptomatic laboratory-confirmed influenza	80 (74–90)
Adults of working age	Split product, 15 μg	Random-effects meta-analysis[1] of RCTs[69,70]	Symptomatic laboratory-confirmed influenza; laboratory-confirmed influenza	77 (66–85)
Community-dwelling elderly	Surface antigen, 15 μg	RCT[71]	Laboratory-confirmed influenza	52 (29–67)
Elderly people in welfare nursing homes	Split product, 15 μg	Prospective cohort study[72]	Symptomatic laboratory-confirmed influenza	60 (NA)

NA=not available; RCT=randomised controlled trial.

Table 2: **Efficacy of influenza vaccine in preventing laboratory-confirmed symptomatic influenza in populations of children, working adults, and community-dwelling elderly people**

asthma. Guillain-Barré syndrome, arising within 6 weeks of vaccination, occurs at a rate of slightly more than one additional case per million vaccinees.[63] Searches of the world literature have shown weak associations between vaccination and the rare occurrence of miscellaneous events.[1] Recently, oculorespiratory syndrome, a "new" adverse event, defined as redness of both eyes with or without respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness, or sore throat), or facial oedema, occurring within 2–24 h of vaccination, was identified in Canada at low frequency (13·9 and 19·3 per 100 000 doses distributed) with vaccine from two manufacturers.[73,74] Few cases have been reported elsewhere, and the pathophysiological mechanism underlying the syndrome remains obscure.

Efficacy and effectiveness of current vaccines

Studies on the efficacy and effectiveness of inactivated influenza vaccines reveal substantial benefits. In children, meta-analysis[1] of double-blind[64–66] and single-blind[67,68] randomised controlled trials estimated the efficacy of vaccine in preventing symptomatic laboratory-confirmed influenza at 80% (table 2). Other benefits include reductions in school absenteeism, otitis media, asthma exacerbations, and febrile respiratory illness in unvaccinated household contacts.[67,75–79]

In adults of working age, meta-analysis[1] of two randomised controlled trials of split influenza vaccines[69,70] estimated the efficacy in preventing laboratory-confirmed influenza at 77% (table 2). Associated benefits include reductions in absenteeism, consultations, antibiotic use, and use of over-the-counter medication.[80–82]

The frequency of laboratory-confirmed influenza fell by 52% in vaccinees in a randomised controlled trial (table 2)[71] and by 94% in a prospective cohort study of elderly people living in the community.[83] Many cohort and case-control studies have shown lower rates of hospital admissions for pneumonia and influenza,[84–92] all respiratory disorders,[85,87] respiratory disorders and heart failure,[93] deaths from pneumonia and influenza,[84,87] and all-cause mortality[85,86,94] in vaccinees than in controls (table 3). A meta-analysis of reports published before 2001 showed that vaccination reduces numbers of cases of influenza-like illness by 35%, hospital admissions for pneumonia and influenza by 47%, and all-cause mortality by 50%.[95]

A prospective observational study of 22 462 nursing-home residents in Japan showed a 60% reduction in laboratory-confirmed influenzal illness among vaccinees.[72] Vaccination also reduced numbers of hospital admissions among vaccine failures and thus appears to ameliorate illness severity. Gross and colleagues[96] did a meta-analysis of 20 cohort studies. The odds ratios for development of respiratory illness (0·44) or pneumonia (0·47), hospital admission (0·50), and mortality (0·32) indicate substantial protection.

Vaccination of elderly patients with chronic lung disease reduces hospital admissions for pneumonia and influenza by 52%,[97] all-cause mortality by 70%,[97] and complications (death, exacerbations of lung disease, pneumonia, heart failure, angina, and myocardial infarction) by 50%.[98] Influenza vaccination also prevents heart failure,[85] brain infarction,[99] recurrent myocardial infarction,[100] and primary cardiac arrest,[101] indicating important benefits in patients with cardiovascular disease. Vaccination of patients with diabetes mellitus is associated with an estimated 79% reduction in hospital admissions, mostly (86%) for reasons of diabetic control.[102] Thus, influenza vaccine protects against several potentially fatal events that explain the many hidden deaths that accompany epidemics.

Staff have been implicated as the source of influenza in several outbreaks in nursing homes. Evidence is

Outcome and studies	Study period	Risk status	Effectiveness (%; 95%CI)
Hospital admission for pneumonia and influenza			
Retrospective cohort study[84]	1980–81 to 1988–89	Low	40 (1 to 64)
		High	30 (17 to 42)
Retrospective cohort study[85]	1990–91 to 1995–96	Low	49 (29 to 69)
		Intermediate	32 (−8 to 71)
		High	29(11 to 47)
Retrospective cohort study[86]	1996–97	Elderly	20 (5 to 31)
	1997–98		24 (14 to 34)
Case-control study[87]	1982–83	Elderly	37 (15 to 53)
	1985–86		39 (19 to 53)
Case-control study[88]	1989–90	Elderly	63 (17 to 84)
Case-control study[89]	1989–90	Elderly	45 (14–64)
Case-control study[90]	1990-91	Elderly	31 (4 to 51)
	1991-92		32 (7 to 50)
Case-control study[91]	1994-95	Elderly	79 (45 to 91)
Case-control study[92]	1994-95	Elderly	33 (5 to 52)
All respiratory admissions			
Retrospective cohort study[85]	1990–91 to 1995–96	Elderly	32 (29 to 40)
Case-control study[87]	1982–83	Elderly	17 (1 to 32)
	1985–86		32 (20 to 43)
All respiratory admissions and heart failure			
Retrospective cohort study[93]	1994–95 to 1996–97	Elderly	20 (10–30)
Pneumonia and influenza deaths			
Retrospective cohort study[84]	1980–81 to 1988–89	High	33 (−7 to 58)
Case control study[87]	1982–83	Elderly	64 (19 to 84)
	1985–86		54 (7 to 77)
All-cause mortality			
Retrospective cohort study[94]	1989–90	Elderly	75 (21 to 92)
Retrospective cohort study[85]	1990–91 to 1995–96	Elderly	50 (44 to 56)
Retrospective cohort study[86]	1996–97	Elderly	60 (55 to 65)
	1997–98		39 (33 to 44)

Table 3: **Effectiveness of influenza vaccine in community-dwelling elderly people**

accumulating that influenza vaccination of staff caring for elderly people in long-stay facilities provides benefits to residents.[103–105] One study showed substantial herd immunity (68–87% protection) among patients exposed to staff with high vaccine coverage.[105]

Newly licensed vaccines

During the past decade, there have been many new developments in vaccine technology that have aided vaccine production or aimed to improve vaccine immunogenicity and acceptability.

Adjuvant-treated vaccines

Subunit influenza vaccine with adjuvant MF59, an emulsion of squalene in water for parenteral use, is licensed in some European countries but not the UK. MF59 significantly increases haemagglutination-inhibition antibody responses to interpandemic influenza A H3N2 and influenza B antigens, particularly in older people with chronic diseases, and is well tolerated despite slightly higher rates of transient mild local reactions than with other vaccines.[106]

Virosomes consist of bilayers of phospholipids (liposomes) containing virus surface proteins embedded in the bilayer. Virosomes have been extensively evaluated in various human populations.[107] Typically, virosomes induce higher concentrations of antibody after vaccination, higher rates of seroconversion, and a greater proportion of individuals with "protective" antibody titres than conventional inactivated vaccines. Virosomal influenza vaccine for parenteral use became available in the UK during the 2002–03 season.

Cell-culture vaccines

Cell-culture vaccines offer the potential of being able to respond quickly to epidemics or a pandemic at any time of the year and avoid the risk of contaminated eggs, which could affect the bioburden and endotoxin content of vaccines. Moreover, influenza viruses grown in mammalian cells more closely resemble those present in clinical samples than viruses isolated and grown in eggs, hence offering the potential for more effective vaccine. Influenza vaccines prepared with Madin Darby canine kidney (MDCK) and African green monkey (Vero) cells as substrate have been licensed in the Netherlands but are not yet available commercially.

New approaches to vaccination

Live attenuated influenza vaccines

Intranasal delivery of live influenza vaccines offers the advantage of mimicking natural infection, thereby providing a broader immunological response and more durable protection than with inactivated vaccines. Strategies for use of live influenza vaccines based on the transfer of genes coding for cold adaptation (*ca*) and temperature sensitivity from an attenuated parental virus donor have been used in Russia for many years and were approved in June, 2003, by the US Food and Drug Administration for use in healthy children and adolescents aged 5–17 years, and in healthy adults aged 18–49 years after three decades of clinical evaluation. Vaccines based on *ca* replicate well at the temperatures found in the nasopharynx but not at temperatures in the lower airways. In young children, a recent study of US *ca* vaccine showed very high protection with benefits in terms of both influenzal illness and otitis media.[108] During the second year of this study, *ca* vaccine afforded a high degree of protection against a variant not closely matched to the vaccine antigen.[109] Studies in nursing-home residents have suggested that a combination of live and inactivated influenza vaccines may improve protection in these communities.

Parenteral adjuvants

Immunostimulating complexes are cage-like structures that were originally formed as a complex between cholesterol and saponin derived from the tree *Quillaia saponaria*. Vaccines containing a defined saponin called Iscoprep 703 stimulated an accelerated serum antibody response in human beings compared with conventional inactivated vaccines, an improved proliferative T-cell response, and a cytotoxic T-cell response.

Mucosal adjuvants and delivery systems

Although nasally delivered influenza vaccine could greatly increase vaccine coverage and provide mucosal immunity, intranasal administration of conventional inactivated influenza vaccines has typically been unsuccessful. In animals, incorporation of a mucosal adjuvant derived from bacteria has been necessary to improve immunogenicity, and several such vaccines administered intranasally have been evaluated clinically, with promising results. An intranasal spray formulation containing trivalent subunit influenza vaccine prepared from virosomes and wild-type *Escherichia coli* enterotoxin was licensed briefly in Switzerland. Although it met the immunogenicity criteria set for yearly relicensing of conventional influenza vaccines, it was withdrawn after a possible association with Bell's palsy could not be discounted.

Various microparticles are being investigated as adjuvants and delivery systems, for parenteral delivery of influenza-virus antigens or delivery to mucosal sites including the gut.

Recombinant vaccines

Subunit influenza vaccines have been prepared from recombinant haemagglutinin and neuraminidase proteins expressed in insect cells by baculoviruses. The recombinant haemagglutinins are well tolerated by young adults and elderly people, and there are significant dose-response effects for both H1 and H3 haemagglutinin vaccines. Phase I and virus-challenge studies of baculovirus-expressed recombinant neuraminidase in healthy volunteers have had promising results.

Reverse genetics

The development of reverse-genetics techniques for negative-sense RNA viruses has allowed the direct manipulation of influenza-virus gene products and creation of new recombinant viruses. This approach offers enormous potential for preparing interpandemic vaccines.

Nucleic-acid vaccines

DNA vaccines present a promising new approach to vaccination, evoking a full range of immune responses, including antibody, cytotoxic, and helper-T-cell responses. DNA vaccines with constructs encoding the nucleoprotein (NP), haemagglutinin, neuraminidase, matrix protein 1 (M1), and non-structural protein 1 of influenza virus have been studied extensively, either singly, in combination with one another, or together with DNA encoding various cytokines.

Antiviral drugs

Currently, two drug classes are available to manage influenza: the inhibitors of M2, amantadine and rimantadine, and the neuraminidase inhibitors, zanamivir

Drug and patients treated	Reduction (median days) in treatment groups compared with placebo (95%CI)			
	Symptom alleviation		Time to return to normal activities	
	ITT population	Influenza positive	ITT population	Influenza positive
Zanamivir				
Healthy individuals, aged 12–65 years	0·78 (0·26 to 1·31)	1·26 (0·59 to –1·93)	0·51 (–0·02 to 1·04)	0·46 (0·02 to 0·90)
At-risk individuals, including older than 65 years	0·93 (–0·05 to 1·90)	1·99 (0·90 to 3·08)	0·09 (–0·78 to 0·95)	0·2 (–0·79 to 1·19)
Healthy children	1·0 (0·50 to 1·50)	1·0 (0·40 to 1·60)	0·5 (–0·30 to 1·30)	0·5 (–0·40 to 1·40)
"All" individuals	0·94 (0·65 to 1·23)	1·26 (0·90 to 1·61)	0·37 (0·01 to 0·74)	0·37 (0·02 to 0·72)
Oseltamivir				
Healthy individuals, aged 12–65 years	0·86 (0·31 to 1·42)	1·38 (0·79 to 1·96)	1·33 (0·70 to 1·96)	1·64 (0·69 to 2·58)
At-risk individuals, including older than 65 years	−0·34 (–0·71 to 1·40)	0·45 (–0·97 to 1·88)	2·45 (0·05 to 4·86)	3·0 (0·13 to 5·88)
Healthy children	0·87 (0·25 to 1·49)	1·49 (0·76 to 2·20)	1·25 (0·70 to 1·80)	1·86 (1·06 to 2·65)
"All" individuals	0·80 (0·41 to 1·18)	1·33 (0·90 to 1·77)	1·32 (0·91 to 1·73)	1·64 (1·17 to 2·10)

ITT=intention-to-treat.

Table 4: **Summary results of the Health Technology Appraisal meta-analyses of zanamivir and oseltamivir for the treatment of influenza[1]**

and oseltamivir. Rimantadine causes less neurotoxicity than amantadine but is not available in most parts of the world and is not discussed further.

Amantadine

Amantadine inhibits the M2 membrane protein ion-channel activity of the influenza A virus but has no effect on influenza B. Amantadine has three important limitations: its range of activity excludes influenza B; it has adverse side-effects, including insomnia, light-headedness, hallucinations, dizziness, headache, and falls, which are particularly troublesome in elderly people; and drug resistance emerges rapidly during treatment. The genetic basis of resistance is a single nucleotide change, resulting in an aminoacid substitution at position 26, 27, 30, 31, or 34 in the membrane-spanning region of M2.

Estimates of amantadine's therapeutic effectiveness are uncertain owing to the clinical and methodological heterogeneity of clinical trials, a paucity of data by dose, the small number of trials in children and elderly people, and low trial-quality scores.[1] Treatment of healthy adults with 100–300 mg daily of amantadine cuts the duration of fever compared with placebo by 1 day.[110] There are few data on use of the currently licensed dose in the UK, 100 mg daily.[1] At this dose, amantadine reduced the duration of fever compared with placebo by 1 day, but in a meta-analysis of data from six trials involving a total of 232 patients the effect did not attain statistical significance.[111] There is no high-quality evidence from randomised controlled trials of the effectiveness of amantadine 100 mg daily for the treatment of influenza in at-risk individuals, and illness was significantly shortened with treatment by 1·2 days in only one of two small randomised controlled trials in children.[1,111] No randomised trial has tested amantadine during outbreaks in nursing homes. Moreover, its use in this setting is complicated by toxicity, treatment failures, and frequent recovery of drug-resistant virus (about 32%). Amantadine prophylaxis of other populations during interpandemic outbreaks is precluded by the lack of high-quality evidence from randomised controlled trials at the licensed dose and the high incremental cost per quality-adjusted life-year gained.[1]

Zanamivir

This second-generation neuraminidase inhibitor is a potent and specific inhibitor of a wide range of influenza virus types A and B. It has poor oral bioavailability and is delivered through an inhaler. Zanamivir is licensed for the treatment of influenza A and B in people aged 12 years and over. It is well tolerated; the number, type, and severity of adverse events in healthy adults or people with stable chronic underlying medical disorders differ little from those with placebo.[112] The main safety concern is that inhaled zanamivir may cause bronchospasm.[113] However, respiratory viruses including influenza regularly exacerbate asthma and chronic obstructive pulmonary disease, so the role of zanamivir in bronchospasm is unclear. Zanamivir was administered with apparent safety in two studies involving patients with asthma or chronic obstructive pulmonary disease.[114,115]

Difficulty in using the inhaler may limit use of zanamivir. In one study, half of a very elderly group were unable to use the inhaler after training, and two-thirds

Drug and patients treated	Complications necessitating use of antibiotics						Pneumonia					
	ITT population			Influenza positive			ITT population			Influenza positive		
	Placebo group (%)	Treatment group (%)	Odds ratio (95% CI)	Placebo group (%)	Treatment group (%)	Odds ratio (95% CI)	Placebo group (%)	Treatment group (%)	Odds ratio (95% CI)	Placebo group (%)	Treatment group (%)	Odds ratio (95% CI)
Zanamivir												
"All" individuals	18	13	0·71 (0·56 to 0·90)	18	13	0·82 (0·61 to 1·10)	1	<1	0·49 (0·21 to 1·06)	2	<1	0·43 (0·15 to 1·10)
High-risk individuals	..	..	..	24	15	0·55 (0·24 to 1·23)	4	3	0·90 (0·21 to 3·62)	4	3	0·69 (0·10 to 3·64)
High-risk children and adults	25	16	0·57 (0·31 to 1·03)	24	13	0·49 (0·23 to 1·04)	..	..	..	..	..	..
Oseltamivir												
"All" individuals	..	..	..		..	..	..	..	..	2	<1	0·37 (0·15 to 0·86)
Healthy individuals	..	..	..	5	2	0·32 (0·16 to 0·59)	..	..	..	1	<1	0·15 (0·06 to 0·72)
High-risk individuals	..	..	..	18	12	0·62 (0·40 to 0·94)	..	..	..	2	2	0·76 (0·24 to 2·23)

Table 5: **Effect on complications necessitating use of antibiotics and pneumonia of zanamivir and oseltamivir[1]**

were unable to use it the next day.[116] However, in three other studies, it was used successfully by about 80% of more than 400 elderly people.[1]

Summary results,[1] which draw from published[117–122] and unpublished treatment studies with zanamivir, are shown in table 4. Overall, symptoms were alleviated sooner with zanamivir than with placebo—a median of 0·9 days on an intention-to-treat basis and 1·3 days for the influenza-positive subgroup. With zanamivir, the median time to return to normal activities was 0·4 days shorter for the treatment group, for both the intention-to-treat and influenza-positive populations. In a pooled analysis of intention-to-treat data from trials including both otherwise healthy and at-risk individuals, antibiotics were given to a smaller proportion of patients receiving zanamivir than of those assigned placebo (table 5).[123] Similar, but non-significant, reductions in need for antibiotics in high-risk individuals and in pneumonia were seen with treatment in published[124] and unpublished[1] marginal analyses.

Seasonal prophylaxis with zanamivir 10 mg daily of mostly unvaccinated healthy adults provided an estimated 69% reduction in the incidence of laboratory-confirmed clinical influenza compared with placebo,[125] and meta-analysis of two randomised controlled trials of postexposure prophylaxis, with treatment given for 5 days[126] or 10 days,[120] suggested 81% protection against symptomatic laboratory-confirmed influenza.[1]

Oseltamivir

This third-generation neuraminidase inhibitor is an orally active prodrug of oseltamivir carboxylate. It is licensed for the treatment of influenza A and B in people aged 1 year or older and for the prophylaxis of influenza A and B in people aged 13 years or older. The frequency of nausea is 3–7% higher and of vomiting up to 2% higher than with placebo;[127,128] these gastrointestinal side-effects can be ameliorated if the drug is taken shortly after food.

Summary results,[1] which draw from published[129–131] and unpublished treatment studies with oseltamivir (table 4) Show that for all treatment groups combined, symptoms were alleviated sooner with oseltamivir than with placebo, by 0·8 days on the basis of intention to treat and 1·3 days for the influenza-positive subgroup. Similarly, normal activities were resumed 1·3 days and 1·6 days sooner with oseltamivir for the intention-to-treat and influenza-infected group, respectively.

Treatment with oseltamivir reduces the frequencies of otitis media, antibiotic use, pneumonia, and hospital admissions. In children with influenza, the frequency of otitis media was 21% with placebo and 12% with oseltamivir.[131] The rate of antibiotic use in the intention-to-treat population in one study was 3·4% (eight of 235) with placebo and 0·4% (one of 241) with treatment.[129] Pooled marginal analyses showed lower rates of antibiotic use for lower-respiratory-tract complications in "healthy" and "high-risk" people with influenza with oseltamivir than with placebo;[1] a lower frequency of pneumonia in the influenza-positive group of ten studies (2% among placebo recipients *vs* <1% with oseltamivir; table 5); [1] and a significant reduction in the occurrence of hospital admissions in influenza-positive populations of ten trials (1·7% *vs* 0·7%).[1]

Three different strategies in preventing laboratory-confirmed symptomatic influenza with oseltamivir have been investigated in randomised controlled trials. Meta-analysis of data from two trials of seasonal prophylaxis in non-vaccinated healthy adults with oseltamivir, 75 mg once daily,[127] gave an estimate of 74% protection.[1] In households, postexposure prophylaxis with oseltamivir, 75 mg once daily for 7 days, gave 89% protection.[128] Similarly, seasonal prophylaxis of mostly vaccinated elderly people receiving residential care with oseltamivir, 75 mg daily for 6 weeks, provided 91% protection.[132]

Resistance to neuraminidase inhibitors

Influenza viruses with low susceptibility to the neuraminidase inhibitors have been isolated in vitro and in vivo. Resistance involves either a mutation in the active site of the neuraminidase, altering its sensitivity to inhibition, or a mutation in the haemagglutinin. Mutations in haemagglutinin that confer drug resistance decrease the affinity of the protein for the cellular receptor, thus enabling virus to escape from infected cells without the need for viral neuraminidase.

To date, few viruses with altered susceptibility to neuraminidase inhibitors have been recovered from patients. The first report of emergence of neuraminidase-inhibitor resistance (R152K) during treatment with zanamivir involved a recipient of a bone-marrow transplant.[133] During clinical trials with oseltamivir, 1·3% (four of 301) of post-treatment isolates from adults and adolescents and 8·6% (nine of 105) from children had low neuraminidase-inhibitor susceptibility,[134] indicating that such viruses are likely to emerge in clinical practice. Three resistant variants with neuraminidase mutations (E119V, H274Y, and R292K) that have emerged in clinical trials show low infectivity and virulence in animal models, thus the relevance of these mutations in clinical practice remains uncertain. In 1999, an international Neuraminidase Susceptibility Network was established to oversee global surveillance of neuraminidase-inhibitor resistance.

National recommendations for the use of anti-influenza drugs

The UK National Institute for Clinical Excellence (NICE) has recently issued new guidance on the interpandemic use of antivirals for the treatment of influenza.[111] Amantadine is not recommended. Neither zanamivir nor oseltamivir is recommended for the treatment of influenza in children or adults unless they are at risk. Within their licensed indications, zanamivir and oseltamivir are both recommended for the treatment of at-risk adults, and oseltamivir for the treatment of at-risk children, who present with influenza-like illness and can start therapy within 48 h of the onset of symptoms, when it is known that influenza A or B is circulating in the community. NICE guidance on the use of antiviral drugs for the prevention of influenza was also issued lately.[135] Oseltamivir is recommended for postexposure prophylaxis of influenza in at-risk people aged 13 years and older, who can begin prophylaxis within 48 h, if they live in a residential care establishment, whether or not they have been vaccinated, and a resident or staff member has influenza-like illness; or if they are not effectively protected by vaccination and can begin prophylaxis within 48 h of exposure. Oseltamivir is not recommended for postexposure prophylaxis of healthy people up to age 65 years or for seasonal prophylaxis. Amantadine is not recommended for either postexposure or seasonal prophylaxis. This guidance does not cover the circumstances of a pandemic.

Use of vaccines and antivirals in a pandemic

The Hong Kong "chicken flu" situation in 1997 and the rapid global spread of severe acute respiratory syndrome highlighted how ill prepared we are to introduce preventive measures for pandemic influenza. The

problems encountered in 1997 were due mainly to the dangers of working with the chicken H5N1 virus and the need to produce a safe vaccine strain. Conventional technology was unable to produce a safe productive vaccine strain. However Li and colleagues[136] were able to modify the haemagglutinin gene of the A/Hong Kong/97 virus. They deleted the series of basic aminoacid residues at the cleavage site associated with virulence, then by use of reverse genetics rescued the modified haemagglutinin gene and the neuraminidase gene from the wild-type A/Hong Kong/97 virus into *ca* A/Ann Arbor/6/60 virus. The resultant *ca* virus was non-pathogenic in animal models of infection, grew well in eggs, and protected chickens from challenge with lethal virus; it could be a suitable candidate vaccine strain. These experiments show the potential for using reverse genetics technology to develop live and inactivated vaccines for both pandemic and interpandemic use.

A second strategy for pandemic vaccine development is the use of recombinant haemagglutinin. However, the disappointing results from clinical trials of baculovirus-expressed haemagglutinin from the A/Hong Kong H5N1 virus, even after two doses of up to 90 μg,[137] question the role of this strategy alone. Clinical trials of conventional inactivated-surface-antigen vaccine produced from an H5N3 virus showed that extremely poor antibody responses were stimulated, even after two doses, whereas an H5N3 subunit vaccine with MF59 adjuvant was much more immunogenic.[138] The benefit of adjuvants for use in naïve populations has also been shown with a whole-virus H2N2 vaccine with aluminium salts adjuvant.[139] Thus, like MF59, aluminium salts have promise in increasing vaccine coverage in response to pandemic influenza by allowing scarce antigen to be used more efficiently.

From the limited information available, conventional influenza vaccines seem not to be sufficiently immunogenic in a pandemic situation and two doses in conjunction with an adjuvant may be needed. Different dosing strategies with various influenza-virus subtypes should be investigated so a robust strategy can be developed. Vaccines will be in very short supply during the first stages of a pandemic, and antiviral drugs could have an important role in prevention. WHO has recently prepared draft guidelines for use of both vaccines and antiviral drugs during a pandemic;[140] they emphasise the need to stockpile drugs and to develop plans for their distribution and use. As with vaccines, there are gaps in our knowledge as to how antiviral drugs should be used. Research is urgently required to ensure effective use of both vaccines and drugs in response to an emerging pandemic.

Conflict of interest statement

KGN has received fees or honoraria from Roche Pharmaceuticals, Wyeth, and Berna Biotech for speaking at meetings on influenza; research has been supported by Chiron Vaccines, Aventis Pasteur, Wyeth, and Berna Biotech. Solvay and Berna Biotech have provided H9 avian influenza viruses free of charge for a project on candidate pandemic vaccines. MZ has received honoraria from Berna Biotech to speak at pharmaceutical-industry conferences on influenza and has been supported in attendance at an international WHO workshop on virus neutralisation sponsored by GlaxoSmithKline. The Health Protection Agency has received funding from Chiron Vaccines, Wyeth Vaccines, Aventis Pasteur, Roche, and GlaxoSmithKline, to carry out analytical work on a contractual basis in MZ's laboratory. JMW has no conflicts of interest to declare in relation to this paper. None of these sources of funding had any role in the writing of this seminar.

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Uses of error

Learning from experience?

Martin Tattersall

Reflecting on my medical errors over 35 years of clinical experience, I was disturbed to note that most errors that came to my mind were from the early part of my career. Is this a sign that I really did become a better doctor or is it a symptom of ageing? Were my early errors more influential on my subsequent practice or are my current errors not recognised or not made known to me by sympathetic colleagues?

During my first house job, a middle-aged man was under my care for several months with an infected pleural cavity following a plombage operation for tuberculosis some years previously. He was memorable not only because of his sickness, but also because he was the first patient to give me a present, which I have to this day. 18 months later, I was a casualty officer at a teaching hospital. An intern showed me the chest radiograph of a man with a febrile illness and an opaque hemithorax. I lectured the intern on my patient with the infected plombage, not thinking for a moment that this story was directly relevant to the radiograph I was shown. The patient died of a cardiac arrest in the casualty department. The autopsy showed an infected plombage site and death from untreated septicaemia.

3 years after qualifying, while a locum physician in the northern parts of Canada, I was required to do a coroner's post-mortem on a middle-aged man found dead in his cabin. Fortunately, the policeman knew what to do and this overcame my anxiety. 2 hours later, I had no doubt that the man was dead, but knew neither why nor how. I dissected the heart and coronary vessels and decided they were atheromatous and that death was from natural causes, probably from myocardial ischaemia. In the coroner's court, I presented my conclusions and the case was closed. I received the pathologist's report as I was due to finish the locum . . . normal heart!

Being on-call for a unit and not just one's own patients can be an onerous task, particularly as the staff become more numerous and anonymous. In the past 5 years, I have been required to be on-call for a unit of ten consultants at two hospitals, one of which I visit only when on call. I was telephoned in the middle of the night about a patient who had had a cardiac arrest. I did not recognise the patient's name. I was told the arrest team wanted me to advise on their "enthusiasm" for resuscitation. I said that if she was not readily resuscitated, they should not resort to extreme measures, presuming she was a cancer patient admitted under the care of one of my oncology colleagues. On visiting the ward the next morning, I learnt that the patient who had died was a young woman under my care. (I had been given her first name and not her surname). She had been successfully treated for ovarian cancer 10 years previously and had been diagnosed with metastatic disease a couple of weeks earlier. She was neutropenic after the first chemotherapy treatment and a fatal outcome was not anticipated, particularly since she was being treated with curative intent.

Department of Cancer Medicine, University of Sydney, NSW 2006, Australia (Prof M H N Tattersall MD)