The influenza virus

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Influenza is a severe cause of morbidity and mortality throughout the world, resulting in annual outbreaks in all age ranges of the population. With an extensive animal reservoir the threat of emergence of a novel influenza virus, capable of causing a pandemic, has spurred research into novel therapies with which to fight the virus.

Influenza is a small, enveloped, negative-sense RNA virus belonging to the orthomyxoviridae family. There are three types of influenza — A, B and C — which are classified according to the serological properties of the two types of internal proteins, the nucleoprotein (NP) and matrix (M) (*Figure 1*). Influenza A and B have eight segments, while influenza C has only seven (Fields, 1996). Influenza A can be further classified according to the serological properties of two external proteins — the haemagglutinin (HA) and the neuraminidase (NA). There are 15 different HA types (H1-15) and nine different NA types (N1-9) (World Health Organization (WHO), 1980; Rohm et al, 1996). The natural host of influenza B and C is man, whereas the natural host for influenza A viruses are aquatic birds. In humans only influenza types A and B are known to cause severe disease, with influenza C causing mild illness.

VIRUS REPLICATION

Replication of the influenza genome requires RNA-dependant RNA polymerase activity, which is specified by the virus. This enzyme lacks a 5' to 3' exonuclease activity (proofreading ability) and therefore has limited ability to correct mistakes during replication. As a result, there is a high frequency of mutations in any newly replicated population of influenza. Mutations that confer a selection advantage result in rapid expansion of the population of variant viruses, reflecting the plasticity of RNA virus genomes (Domingo et al, 1998). Accumulation of mutations leads to progressive genetic drift, and eventually confers sufficient changes for the virus to evade humoral antibody responses and reinfect, a phenomenon known as antigenic drift.

The segmented nature of the influenza virus genome also allows the possibility of reassortment of virus segments. If a single cell is infected by two viruses simultaneously, recombination of the segments of RNA from different hosts allows the emergence of viruses with novel constellations of surface and internal proteins, a process known as antigenic shift.

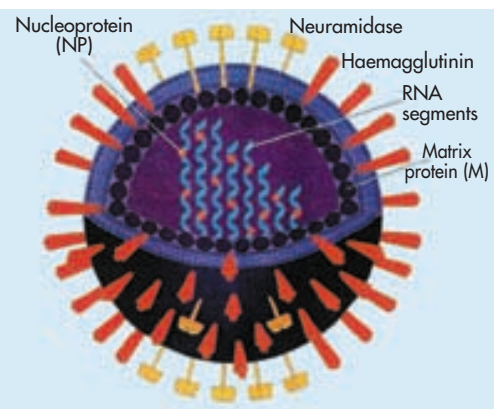

Figure 1. Diagrammatic representation of an influenza virion.

GENETIC DIVERSITY

Thus genetic diversity among influenza A viruses is maintained by an intrinsically high-mutation rate, coupled with the potential for segment reassortment and a number of host species, as described below. Influenza B and C have intrinsically lesser rates of mutation, a single animal reservoir and do not have multiple subtypes of HA and NA. The rate of mutation of avian influenza A virus genes in avian species, the natural host, is much more similar to the rate of mutation observed in influenza B segments in the human host (Gorman et al, 1990; Cox and Bender, 1995). This is taken to indicate the adaptation of the virus to the natural host and the coevolution of virulence determinants and host response to infection.

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VIRUS GLYCOPROTEINS: HA AND NA

The virion has an envelope derived from the cell membrane with various virus protein spikes (*Figure 2*). The two main antigenic determinants of the influenza A and B virus are the HA and NA. HA, originally named because it agglutinates red blood cells, makes up a large portion of the envelope spikes. It is synthesized as a single polypeptide chain, which is cleaved into two disulphide-linked chains, HA1 and HA2. This cleavage is essential for virus infectivity and is performed by host proteases (Lazarowitz and Choppin, 1975). HA molecules act as the virus receptor for target cells and bind to sialic acid residues on cell surfaces, following which the virus enters the cell by endocytosis and fuses with endosomal membranes under low pH conditions (White et al, 1981).

The NA protein, which acts as a sialidase enzyme, is less abundant on the surface of the virus, but is the second major antigenic determinant of the virus. The main function of the protein is thought to be the removal of sialic acid residues from newly synthesized viral glycoproteins, allowing newly-formed particles to bud from infected cells and preventing aggregation. Virus mutants defective in NA function are seen to clump at the surface of infected cells instead of being released, and are unable to complete the replication cycle (Palese and Compans, 1976). NA is also involved in the cleavage of the α-ketosidic linkage between a terminal sialic acid and an adjacent sugar residue, which may help to allow the virus to pass through the mucus in the respiratory tract (Colman, 1998).

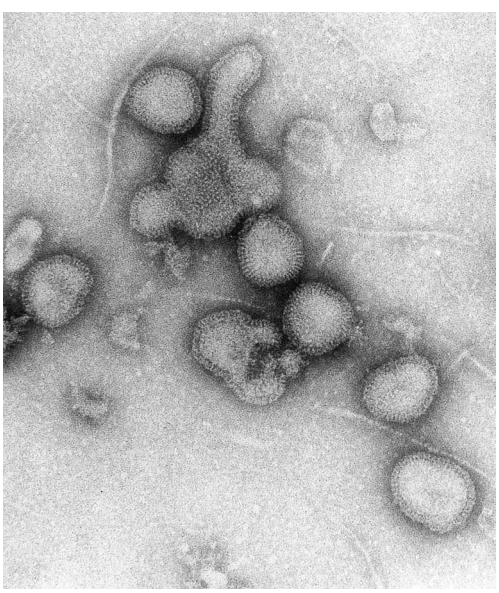

Figure 2. Electron micrograph of influenza A H1N1 (magnification x 62 500).

NATURAL RESERVOIRS OF INFLUENZA VIRUSES

Influenza virus infects and replicates epithelial cells in the respiratory tract in humans and causes respiratory illness, although influenza A viruses can infect a number of mammalian species besides humans, including horses, swine and a variety of sea mammals (Webster, 1998). Only two of the 15 different HA types (H1N1 and H3N2) are commonly found in humans today. However, all 15 subtypes of influenza A HA have been found in aquatic birds and most of these types are associated with asymptomatic infection, although H5 and H7 cause severe infection in domestic poultry.

In avians, influenza A is a disease of the enteric tract and is transmitted via the faecal–oral route. It is thought that migratory birds are important in disseminating the spread of different subtypes of influenza, particularly where there is congregation of birds on migratory flyways. Influenza A has been recovered from unconcentrated lake water. High virus shedding and virus particles that are relatively stable in a moist environment ensures the successful transmission of infection between generations and species of birds. Infections spill over into the domestic bird population (ducks, geese, chickens, turkeys), especially where there is mixing of feral and domestic birds.

RECEPTOR BINDING

Human influenza A HA types preferentially bind to sialic acid in an α-2-6 link to galactosidase residues, whereas avian influenza types preferentially bind to α-2-3-linked sialic acid (Rogers and Paulson, 1983). As a result of this preferential binding, it was thought that direct avian to human transmission of influenza virus was unlikely.

Domestic swine have both α-2-6- and α-2-3-linked sialic acid in their respiratory tract, and it is thought that a dual infection of swine by influenza viruses from different species provides an opportunity for exchange of RNA segments and emergence of an influenza virus capable of infecting and rapidly spreading between humans (Ito et al, 1998). However, in Hong Kong in 1997, a highly pathogenic avian influenza virus, H5N1, directly infected several humans causing severe illness and six deaths (Shortridge et al, 1998). The source of the H5N1 outbreak in 1997 was infected poultry in live bird markets in Hong Kong, and more widespread dissemination was prevented by a cull of approximately 1.5 million chickens. Although this particular virus was not highly transmissible from human to human, the potential threat of the avian reservoir of influenza subtypes to human health is also clearly demonstrated. Other sporadic cases of animal to human transmissions of

TABLE 1.
Sporadic cases of influenza A viruses variants over the past three decades

Virus subtype	Year	Transmission	Origin	Symptoms	No. of individuals affected	References
H1N1	1976	Swine to human	USA	Respiratory (deaths)	230*	Top and Russell (1977)
H7N7	1977	Seal to human	USA	Conjunctivitis	4	Webster et al (1981)
H1N1	1993	Swine to human?	Netherlands	Mild respiratory	2	Claas et al (1994)
H7N7	1995	Avian to human	UK	Conjunctivitis	1	Kurtz et al (1996)
H5N1	1997	Avian to human	Hong Kong	Respiratory (deaths)	18†	Shortridge et al (1998)
H9N2	1999	Avian to human?	China	Respiratory?	2	Anonymous (1999a)

*One death. †Six deaths

unusual influenza A subtypes have occurred (*Table 1*). As influenza surveillance improves, it is likely that more of these events will be identified.

PANDEMIC INFLUENZA

One of the puzzles of influenza epidemiology is the appearance and disappearance of influenza strains, occasionally in a cyclical manner (*Figure 3*). During the 20th century, a number of novel influenza viruses have emerged to cause pandemics. In 1918, 1957 and 1968, H1N1, H2N2 and H3N2 viruses appeared, although the precise origin of these strains remains to be clarified. In 1918, influenza A H1N1 was responsible for more than 20 million deaths worldwide, killing twice as many people than the First World War. This virus killed people of all ages, unlike most winter seasons where excess deaths because of influenza occur primarily in the over-65 age group. The rapid spread of influenza coupled with the possibility of genetic reassortant and an extensive animal reservoir of infection ensures that the threat of a pandemic of influenza is as great at the turn of the 20th century as it was at the beginning (*Table 2*).

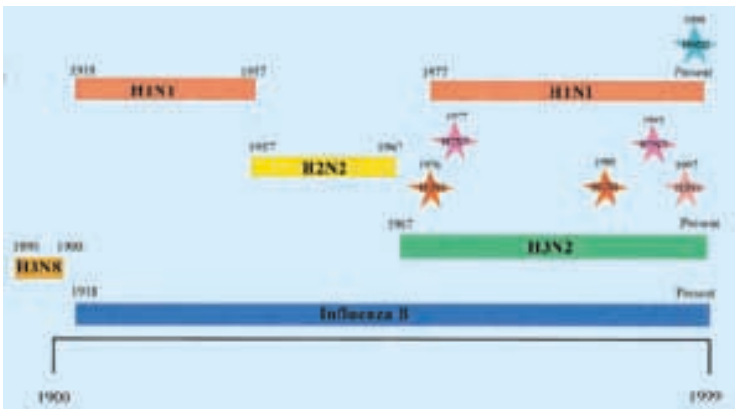

Figure 3. Recycling of influenza viruses throughout this century. Sporadic cases of animal to human transmission of influenza A viruses are indicated in stars (see Table 2*).*

TABLE 2.
Influenza pandemics — past and present

Year	1918	1999
Estimated world population	1.8 billion	6 billion
Transportation	Rail, military ships	Air, rail, sea
Estimated time needed for virus to travel the world	Four months	Four days
Prevention	Disinfectants, masks	Limited supply of vaccine*
Treatments	None	Some antiviral drugs
Estimated death toll	20+ million	60+ million?

*Current vaccine composition would be insufficient to protect against a new antigenic variant

CLINICAL PRESENTATION

Human influenza is spread primarily by the aerosol route or by direct contact. With a short incubation time of 1–4 days and abrupt onset of illness, epidemics can start explosively and on a large scale (Cox and Fukuda, 1998). An adult patient with an influenza infection can have many symptoms, most commonly temperature, muscle aches and fatigue (*Figure 4*). Fever can last between 3 and 6 days at which point the respiratory symptoms may become more marked. Illness can last up 2 weeks and may need hospitalization in severe cases. In children the clinical symptoms can be similar to adults, but fever is higher and there is an increased risk of otitis media. In children less than 3 years old, there may be more pronounced systemic features, particularly abdominal pain and vomiting (Nicholson et al, 1998).

Although the factors that influence the symptoms of an influenza infection are not fully understood, it is most likely that symptoms are caused by a combination of virally-induced cytopathic effects and the host immune response to the virus. This involves the secretion of cytokines, particularly interferon (IFN)-α and interleukin (IL)-6, which are most associated with the early phases of influenza infection (Hayden et al, 1998).

MORBIDITY ASSOCIATED WITH INFLUENZA EPIDEMICS

Influenza is a seasonal disease in the Northern hemisphere, occurring between October and March every year, although the exact timing,

duration, and magnitude of epidemics of influenza vary year to year. Complications associated with influenza infections occur in both the upper and lower respiratory tract. Otitis media is a common complication in children and conjunctivitis occurs in both adults and children.

Primary viral pneumonia or more commonly combined viral and bacterial pneumonia can occur following influenza that has spread to the lower respiratory tract (Nicholson et al, 1998). Every year the total number of deaths from all causes peaks during the time of circulation of influenza viruses (*Figure 5*). In an average H3N2 year, the number of deaths is estimated to be between 10 000 and 13 000 (Fleming, 1996). It has also been estimated that the number of deaths year to year in the interpandemic period cumulatively exceeds the number of deaths because of influenza in pandemic periods.

DIAGNOSIS OF INFLUENZA

The key to assessing the public health impact of influenza is accurate diagnosis. This is also true for outbreak and individual patient management. Hitherto diagnosis of influenza has relied on traditional methods of cell culture, which are still crucial for assessing the antigenic properties of circulating strains. However, newer diagnostic methods, including molecular diagnosis using polymerase chain reaction (PCR), can now contribute to immediate patient management (*Table 3*) and may be very helpful in outbreak situations (Anonymous, 1999b). Additionally, there are several near patient tests either already marketed or about to be launched that may impact on the speed of diagnosis of influenza in various different settings, although their utility in different clinical settings in the UK has not yet been assessed.

PREVENTION AND TREATMENT

The main strategy for controlling influenza has focused on vaccination using trivalent inactivated influenza vaccines. Every year circulating flu strains are monitored by the WHO global influenza surveillance network, and the information used to decide which strains should be incorporated into the vaccine for the following winter season. The vaccine consists of influenza A H1N1 and H3N2 and influenza B virus antigens, and is made from viruses grown in embryonated eggs. Because of the time required to make the vaccine (currently 6–9 months), this decision has to be made months before the influenza season starts (Cox and Regnery, 1996). This can result in a poor match for the next season's circulating strains. Effectiveness of the vaccine depends upon how close the vaccine strains match strains circulating in the population as well as the age and immunocompetence of the recipient. However, there is a large body of evidence that demonstrates both clinical efficacy and cost benefit of influenza vaccination, particularly in the elderly population (Nichol et al, 1995, 1998), and this evidence led to the recommendation in 1998 that all over-75s in the UK should receive influenza vaccine irrespective of risk (Department of Health, 1998).

The current guidelines for vaccination in the UK also include any person over 6 months of age, who because of age or medical condition are at increased risk from influenza infection (Department of Health, 1998; Salisbury and Begg, 1998) (*Table 4*).

Despite efforts at targeting the vaccine, it is clear that individuals in key target groups are not receiving vaccines. Over a 3-year period of monitoring vaccine uptake in England and Wales, 38% of people in the high-risk category did not receive vaccine in any of the 3 years, whereas

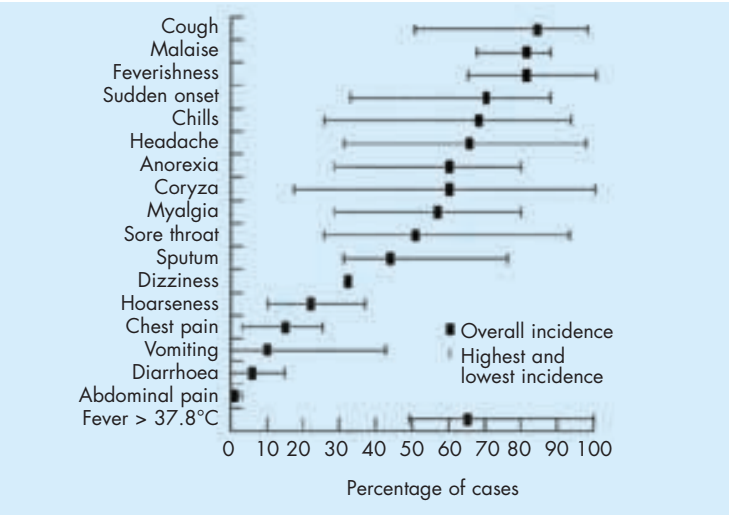

Figure 4. Incidence of symptoms associated with influenza A infection in adults. From Nicholson et al (1998).

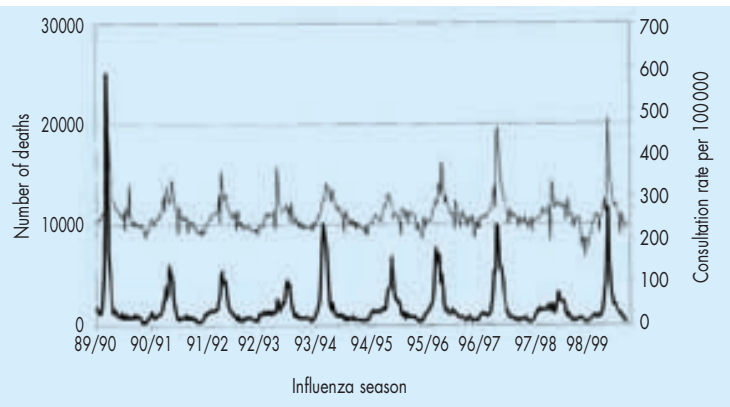

Figure 5. Number of deaths from all causes notified to Office of National Statistics by week of notification 1989–1999, weeks 40–39.

TABLE 3.
Advantages and disadvantages of different diagnostic methods

Method	Sample required	Estimate cost (per sample)	Time taken	Advantages	Disadvantages
Culture	Nasopharyngeal aspirate, nose and throat swab, bronchoalveolar lavage	£10–20	3–7 days	Whole virus measured, virus recoverable, 'gold standard'	Requires infectious virus, requires several cell lines/ embryonated hens eggs, highly skilled
IF	Nasopharyngeal aspirate, nose and throat swab, bronchoalveolar lavage	£5	2 hours–1 day	Rapid	Requires intact cells, highly skilled, no virus recoverable, specialized equipment needed, labour intensive, non-specific, numbers limited
Antigen	Nasopharyngeal aspirate, nose and throat swab, bronchoalveolar lavage	£5–10	15 mins–1 day	No specialized facility needed, can be 'near patient' testing, low skill, rapid	No virus recoverable, poor sensitivity/specificity, often non-proven technology
PCR	Nasopharyngeal aspirate, nose and throat swab, bronchoalveolar lavage, unfixed postmortem tissue	£20–30	1–2 days	Sensitive, allows further molecular analysis	No virus recoverable, specialized equipment/ laboratory needed, highly skilled
Serology HI	Serum	£5	2 days*	Sensitive and specific	Retrospective, paired samples needed
CFT	Serum	£5	2 days*		Insensitive, retrospective, paired samples needed

CFT = complement fixation test; HI = haemagglutination inhibition; IF = immunofluorescence; PCR = polymerase chain reaction. *Acute and convalescent sera required (14 days).

TABLE 4.
Key risk groups for influenza vaccine

Persons over 75 years old
Residents of residential homes and chronic care facilities
Persons with chronic pulmonary or cardiovascular disorders
Persons who require regular medical follow-up for chronic metabolic diseases
People who are immunosuppressed as a result of disease or treatment

23% of persons in a no-risk category received vaccine in all 3 years (*Figure 6*) (Irish et al, 1998; C Joseph, 1998, personal communication). The reasons for this are not clear, but may include under-recognition by medical staff of the impact of influenza and the need for vaccination.

NOVEL VACCINE STRATEGIES

Several novel techniques are being explored in an attempt to produce new vaccines, such as:

- Purified HA vaccines
- DNA vaccines
- Live attenuated vaccines.

Purified HA vaccines

These vaccines circumvent the current reliance on chicken eggs. HA may be synthesized from a variety of sources, including baculovirus or *Escherichia coli*. This is of obvious benefit to people with an egg allergy and may allow more rapid vaccine production. The HA is delivered in the uncleaved form, and may be of lower reactogenicity as it is more highly purified. Vaccine strains of influenza grown in cell culture also avoids the potential to cause egg allergy.

DNA vaccines

Direct inoculation of DNA has caused great interest as a vaccination strategy since proof-of-principle studies showed its potential in the early 1990s (Webster, 1999). The technique is based on the observation that direct intramuscular injection of DNA resulted in expression of genes encoded by the DNA. The basic method has several inherent advantages:

- Stability of DNA relative to live vaccines or proteins
- No antivector immune response
- No egg involvement
- Apparently ideal antigen for MHC (major histocompatibility complex) class I presentation, leading to development of cytotoxic T-lymphocyte response and better crossprotection.

Efficacy of DNA vaccination against influenza has been demonstrated in animals (Fynan et al, 1995), although safety concerns will temper the use in humans for some time.

Live attenuated vaccines

An intranasal cold-adapted vaccine is in late clinical development in several countries (Belshe et al, 1998). Vaccine production relies on the ability of influenza A to reassort. A strain that has become attenuated by cold-adaptation is used as the donor virus, to which is added an appropriate wild-type variant that contains the NA and HA segments against which protection is sought. The

resultant vaccine strain contains an attenuated genome but expresses the wild-type HA and NA surface antigens. The vaccine strain maintains its attenuated phenotype and genotype through passage. Live attenuated vaccines allow:

- Induction of mucosal immunity similar to that induced by natural infection with wild virus
- Induction of significant cytotoxic T-lymphocyte response
- Superior protection from influenza in the upper respiratory tract, limiting viral spread within the population.

This is a much easier, convenient and acceptable method of vaccination. Currently, the best results with live attenuated vaccines appear to be with children (Belshe et al, 1998), and there will be some debate about the place of such vaccines in a national vaccination programme against influenza.

ANTIVIRALS

Until 1999, there were two drugs licensed for use against influenza — amantadine and its methylated derivative rimantadine — although these have not been widely used. These drugs work by blocking an early part of virus replication and act on the influenza A virus M2 (Hay, 1996). M2 is not a constituent of influenza B, so these drugs lack any efficacy against influenza B virus. Although not in widespread use in the UK, amantadine has been used elsewhere in the world and is effective both prophylactically and as a therapeutic agent. It does, however, have a significant list of side-effects including gastrointestinal complaints, sleep disturbance and difficulty in concentrating. Elimination of amantadine is related to renal function, whereas rimantadine is metabolized by the liver and causes fewer side-effects.

NEW TREATMENT OPTIONS FOR INFLUENZA: NA INHIBITORS

The crystal structure of NA was solved in 1983, which laid the foundations for the computer-aided design of inhibitors of NA reported in 1993 (Laver et al, 1999). This work was crucial to the development of NA inhibitors (NIs). One NI, zanamivir (GlaxoWellcome), has already been licensed in the UK and is expected to be available for the 1999/2000 winter season. A second drug, GS 4104 (Roche), is expected to follow closely behind. The two drugs target the NA and both act at the active site of the molecule. Zanamivir is given intranasally and GS 4104 is given orally (Calfee and Hayden, 1998).

NA INHIBITORS AND RESISTANCE ISSUES

As with nearly all antiviral agents, one of the problems with anti-influenza agents is development of strains that are resistant to the drug, yet retain full pathogenicity. Clinical use of amantadine and rimantadine has been tempered by these problems and hence they have tended to be used in a limited number of settings. Resistance was reported from very early in the development of these drugs, with resistant isolates appearing after only one passage in some animal models.

The observation that the active site of the enzyme was highly conserved across all types of influenza A and B may have implications for whether or not NIs may give rise to clinically relevant drug-resistant influenza strains. Resistance to zanamivir and to GS 4104 does not appear to occur as readily as has been seen with amantadine and rimantadine, although the true picture of resistance will not emerge until these drugs are used widescale (Penn, 1999).

Resistance mechanisms

The evidence that has emerged so far from zanamivir indicates that no clinically significant zanamivir-resistant strains have been detected during acute treatment in otherwise healthy individuals. However, mutations in NA may occur and account for relative resistance to zanamivir in vitro. Viruses containing mutations of this type show attenuated sensitivity to zanamivir in vitro and, to a lesser extent, in animal models. However, strong evidence is now emerging that viruses that have undergone these mutations are in some way functionally impaired. As zanamivir binds to the NA active site, it implies that mutations that have any effect on the affinity of NA for zanamivir will affect the affinity of NA for its natural sub-

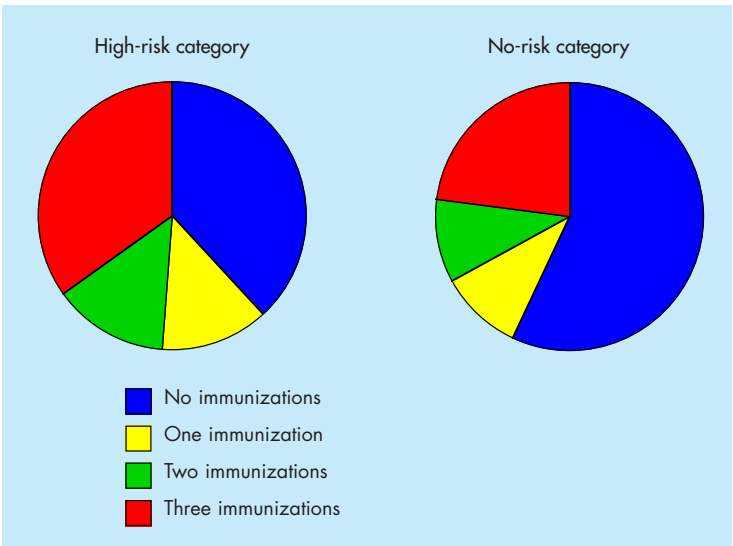

Figure 6. Number of immunizations received annually over 3 study years from July 1993 to June 1996 in England and Wales.

strate, sialic acid, and that this will have an attenuating effect on the virus (Calfee and Hayden, 1998; Penn, 1999).

CONCLUSION

This is an interesting time to be working on influenza, as we hope the above review illustrates. Influenza demonstrates an elegant replication strategy and many as yet undefined interactions with host cell proteins. The continuous genomic variation and rapid molecular evolution means that we are constantly tracking a moving target when monitoring influenza and delivering appropriate control measures. Influenza continues to provide diagnostic, clinical and management difficulties during the characteristic influenza seasons. Clearly influenza and its associated complications can have an enormous impact on the health-care service, and the advent of new therapeutic approaches should be a promising advance. HM

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KEY POINTS

- Influenza infection occurs annually in all age groups of the population.
- Two subtypes of influenza are of public health importance: A and B.
- Influenza is associated with excess deaths every winter, particularly in the elderly.
- There is an extensive animal reservoir of influenza A subtypes.
- Rapid genome mutation of influenza necessitates constant surveillance.
- There is the potential to recombine genome segments and therefore the threat of the emergence of a novel virus.
- The most important method of control of influenza is vaccination.
- The current subunit vaccine is updated annually.
- New vaccine formulations and approaches are currently in development.
- A novel class of anti-influenza drug (antineuraminidases) has recently been licensed.