Seasonal Human Influenza and Vaccination – The Facts

Human influenza viruses - microbiology

Human influenza viruses are RNA viruses from the family Orthomyxoviridae.
They are usually classified into three broad types A, B and C according to differences in the antigenic properties of their external coat. Influenza A viruses, clinically the most important, are further divided into subtypes based on two proteins on the external coat , the hemagglutinin (HA) (H1 – H16) and the neuraminidase proteins (NA) (N1 – N9). Type C viruses do not cause significant human disease, so, only type A and B viruses are of concern. Currently circulating A virus subtypes are A(H3N2) and A(H1N1). Like other RNA viruses, the genome of influenza viruses is subject to a significant spontaneous mutation rate. In addition, the genome consists of 8 separate segments. Significant mutation rates and reassortment of the genome segments result in considerable antigenic variability, particularly of the HA and NA of the influenza A viruses. Partially for this reason the mix and severity of circulating viruses changes year on year with either small changes or occasional major changes so called antigenic 'drift' and 'shift'.

'Drift' and 'Shift'

Changes in the level and type of human seasonal influenza is the result of what is known as *antigenic drift*, the continuous change of the viral HA and NA facilitated by the high mutation rate of the genome to evade the human immune response. Pandemics are the result of so-called *antigenic shift*, large changes for example through inclusion in the virus of HA and NA subtypes from avian origin by reassortment or direct adaptation of avian viruses to humans, for which many or most humans lack immune protection. (see pandemics of the 20th Century)

Influenza Transmission and Epidemiology

Influenza spreads predominantly via the droplet and contact routes when people cough and sneeze and by indirect spread from respiratory secretions on hands, tissues, etc. The incubation time for influenza ranges from 1 to 5 days, but the average is 2 days. In most cases, virus is found in specimens from nose and throat from 1 day before symptoms to 4 to 5 days after onset of disease. However, the level of virus shedding before symptoms is low and highest in the few days after symptoms start when the patient is feeling worse. Viral shedding continues for somewhat longer in young children than in adults. Cases of influenza where people cannot recall any contact with ill people suggest there are some cases where the person catches infection and passes it on without any symptoms at all or only very mild symptoms. Virus types A and B cause acute respiratory illness. Although both types can cause epidemics and significant disease and some deaths, type B infections are usually milder and therefore are more often detected in the context of localized outbreaks. In contrast, type A viruses, which cause more severe symptoms, are those responsible for the highest burden of disease during seasonal epidemics and are responsible for the occasional worldwide pandemics. In Europe, influenza occurs in regular annual epidemics in the winter. These usually affect most of the countries for one to two months and last in Europe for about 4 months.(Paget 2007) Sporadic infections also occur outside of the influenza season, though the incidence is very low in the warm summer months when infections may be the result of imported cases from equatorial areas (where transmission is more year round) and the southern hemisphere where most infection takes place in the European 'summer'. A global overview is always available from WHO Global Influenza Programme summaries. All age-groups are affected, though the proportions of the exact groups vary from year to year and according to the dominant viruses and the level of population immunity. Some years it's mostly children, other years it's other age-groups.

In the first years of the new Millennium the annual epidemics have been mild compared to previous years. Some experts believe that this might be due to the many years since the last pandemic in 1968. The usual experience after a pandemic is that the new pandemic strain comes to dominate the annual epidemics for some years which are then more vigorous and severe than in the years before the pandemic. Details of the decade or so are available via the EISN web-site .

Is it Influenza?
It needs to be appreciated that influenza is only one of the many infections that contribute to colds and respiratory tract infections in the winter. There are many other important viruses that cause these, notably **respiratory syncytial virus** (RSV) which can mimic influenza. Additional confusion arises is that in a number of counties relatively mild infections are also referred to as 'flu' or 'grippe' by the public, when they are in fact due to other viruses entirely. That is why combined epidemiological and virological surveillance such as performed by EISN is so important.

Influenza - the Symptoms
Straightforward influenza disease usually presents as rapid onset of the following combination of systemic and respiratory (both upper and lower) symptoms though not every suffer all the symptoms:

- fever or feverishness,
- headache
- muscle pain
- runny nose,
- sore throat,
- non-productive cough,
- a general feeling of ill-health,

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The more serious symptoms usually last for only a few days but cough, sore throat and runny nose may last longer. Mild and asymptomatic cases also occur, but with the more typical infections a person is rarely properly recovered until a week has passed. However, it should be realised that many other infections with viruses and some bacteria can cause similar symptoms.

More Severe Disease and Complications – Groups at Greater Risk
In some cases the disease becomes more severe due to more extensive spread of the virus in the body (viraemia) or a second usually bacterial infection due to organisms like the *Streptococcus pneumoniae,Staphylococcus aureus* or *Haemophilus influenzae*. These can be fatal and most commonly they result in severe lung infections (pneumonias). Quite often the initial cause of influenza is not recognised and the death is not classified as being due to influenza. These complications can occur in anyone, but are commoner among the elderly and in people of any age with chronic medical conditions.

Groups of the elderly and people with chronic ill health are especially at risk. The list of conditions which make people vulnerable is long and includes the following broad groups of conditions:

- Metabolic diseases (e.g. diabetes)
- Chronic lung conditions (e.g. chronic bronchitis)
- Cardiovascular disease (e.g. coronary artery disease)
- Chronic kidney diseases (e.g. chronic renal failure)
- Conditions and treatments that suppress the immune function (e.g.people receiving chemotherapy)

The Burden of Disease from Influenza

The burden from influenza is two-fold. Firstly there is the severe disease and deaths. Secondly, but of greater economic impact, are the large numbers of mild to moderate cases which result in time off work and losses to production and pressure and costs on the health and social care services. The burden varies from year to year which makes it hard to estimate the annual number of deaths or economic impact. One estimate looking at excess deaths due to influenza found that in milder influenza seasons there were around 8 deaths per 100,000 population while in more severe but non-pandemic years the figure would be 44 per 100,000 (Tillett 1980). Another independent estimate found something similar with an average estimated excess deaths of 25 per 100,000 on average between 1989 and 1998 (Fleming 2000). Applying these figures to the EU population as a whole (around 500 million in 2008) would result in up to 40,000 excess death in a moderate to severe season.

These are rough crude figures and are not adjusted for example for the levels of influenza vaccine used in the vulnerable groups or the rising proportion of the very old and vulnerable people in European countries.

Though much attention is paid to the impact of pandemics, many more people die in the intervening years because of the seasonal influenza epidemics than during the pandemics themselves. Applying the average estimate of 25 per 100,000 population would mean that over a theoretical hundred years there would be 12.5 million excess deaths from seasonal influenza. This compares to the estimated 1.1 million that would die from a re-run of the worst recorded pandemic in the EU (Murray 2006). Certainly in the 20th Century the combined mortality from influenza in seasonal or inter-pandemic influenza considerably exceeds that seen in the pandemic years.

Seasonal Influenza Vaccination

Human immunity to influenza

Human influenza viruses are well adapted to their hosts. That is they infect humans easily and transmit easily from one human to another, usually without killing their hosts. Immunity comes either from experiencing infection or from vaccination. Immunity following infection by one strain or vaccination with a specific type or subtype often does not protect completely against subsequent variants of the same type or subtype. The extent to which influenza A(H3N2), A(H1N1), and B viruses circulate may vary by season. In addition, as the antigenic properties of these viruses might change due to continuous evolution of these viruses under immune pressure (*antigenic drift*), the virus strains of A(H3N2), A(H1N1) and B included in the vaccine have to be reviewed by the WHO annually and possibly changed. Also new vaccines may have to be made when variants of the virus emerge through antigenic shift.(Gerdil 2003)

Most of the acquired protection against influenza comes from antibodies in the blood. Some additional protection comes from cell-based immunity and IgA antibodies produced on mucous membranes, like those of the respiratory tract. After the first (primary) infection, or vaccination, virus neutralizing antibodies to the haemagglutinin and neuraminidase appear in the blood in about one to two weeks and rise to a peak in about four weeks. Antibodies inhibit haemagglutination, agglutination of red blood cells due to multiple red blood cells bound by one virus, and so this is referred as haemagglutination inhibition (HAI). HAI correlates fairly well with virus neutralisation (Ada, 1986). Hence often the levels of these specific antibodies are used as a proxy for the presumed level of protection with higher titres more than 1: 40 or 1:80 (in the older person) taken to indicate immunity.* After a second or further infection or repeat vaccination the antibodies appear and rise more quickly. The antibodies usually persist for months or years, although in people with weaker immune systems like the elderly and those with chronic illness they decline more quickly. However, the problem with influenza is that antibodies to one type or subtype of influenza do not

necessarily give protection to other influenza virus types or subtypes (so called *cross-protection*). Equally they do not give full protection against subsequent drift variants of the same type or subtype. That is why seasonal influenza vaccines contain a mix of influenza virus types and subtypes and the composition has to be reviewed each year by the WHO (Gerdil 2003).

Treatment and Public Health Management of Influenza

Most simple seasonal influenza cases, are just treated symptomatically, that is the patient is sent home to bed and isolated so that they cannot infect other * What this means is that the serum has to be diluted 40 or 80 times before the HAI effect is lost persons and given medicines that will reduce their temperatures and relieve the general feeling of illness and sore muscles. Doctors may or may not attempt to confirm the diagnosis by taking specimens for laboratory analysis. It is important that patients are monitored to detect if patients are deteriorating and perhaps develop a secondary infection for which intensive medical interventions are needed. Many doctors will take a risk based approach considering whether the patient is at greater risk of developing complications and secondary infections. Recently, antiviral drugs, first the M2 inhibitors like amantadine and rimantidine (acting only against type A viruses) and then the neuraminidase inhibitors like oseltamivir and zanamivir (acting against both A & B viruses), have been found to be effective for treatment and for prophylaxis (Moscona 2005a). However, they have to be used early in the infection (best within 24 hours after the symptoms start and certainly within 48 hours is recommended). Licensing of amantadine, rimantadine and zanamivir varies by country and by its expected use, treatment or prophylaxis. For oseltamivir there is a European license for treatment and prophylactic use. The use of these drugs is very variable between countries. Although vaccination is the preferred option for preventing influenza, antivirals can be particularly useful when the vaccine fails (due to antigenic mismatch with circulating virus, waning immunity in elderly, patient being immunocompromised, etc), when vaccine is not (yet) available, as well as during an outbreak of 'avian' influenza or an emerging pandemic. At least one EU country (the UK) makes specific recommendations on when to use anti-virals according to the levels of circulating influenza viruses as determined by surveillance.

In addition to the above measures the **public health management** includes the strong promotion and adoption of the ECDC recommended personal protective measures:

- Regular hand washing
- Good Respiratory Hygiene – covering mouth and nose when coughing or sneezing, using tissues and disposing of them correctly
- Mask-wearing in health care settings by those with symptoms of acute febrile respiratory infections
- Early isolation, usually at hope of those feeling unwell and feverish and having other symptoms of influenza which are considered to reduce the risk of people acquiring or transmitting infections.

Resistance to Antivirals

Resistant mutants to the M2 inhibitors have been detected in a number of countries to the extent that these are not always recommended. There had been few instances of resistance to the neuraminidase inhibitors in seasonal influenza until the emergence of resistant seasonal A(H1N1) viruses that were capable of transmiting on. (Moscona 2005b) Antiviral resistance in Europe is monitored by the VIRGIL project in collaboration with the European Influenza Surveillance Network Scheme (EISN) and by a number of individual National Influenza Centres (Meijer 2006).

The contribution of virological surveillance

For selection of vaccine candidate viruses matching the virus strain expected to circulate in the coming season and for keeping a close watch on the evolution of influenza viruses there is a Global Influenza Surveillance Network, managed by WHO. and comprised of National

Influenza Centres including those that are part of the Community Network of Reference Laboratories for Human Influenza in Europe. These continuously report and share influenza viruses with a series of four highly specialist WHO Collaborating Centres. In Europe, a WHO Collaborating Centre is located in the UK (Mill Hill), where there is also the National Institute of Biological Standards and Controls (NIBSC) which further refines and prepares suitable viruses for passing onto industrial vaccine producers (ECDC 2007). Based on data arising from this surveillance each year WHO convenes specialist meetings at which it agrees on recommendations on the composition of the influenza vaccine for the next season. Separate meetings and recommendations are made for the northern hemisphere (which includes Europe) and the southern hemisphere. Current influenza vaccines (2007) are recommended to contain antigens protecting against two influenza A subtypes, H3N2 and H1N1, and one of the two lineages of type B virus.

The Influenza Vaccines

Currently there are 3 types of vaccines used in Europe, all of them inactivated, some formulations are also adjuvanted:

- split virus vaccines consisting of virus particles disrupted by detergent treatment;
- subunit vaccines consisting essentially of haemagglutinin and neuraminidase from which other virus components have been removed;
- whole virus vaccines consisting of inactivated viruses;
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Live attenuated influenza vaccine given by nasal sprays are available in North America, though they have been mostly been developed for use in children for whom vaccination is not generally recommended in Europe (Fukuda 2006).

Vaccine Strategies

The approach with influenza is generally to reduce the risk of people at greater risk of complications from becoming infected. Hence, the approach is one of *protecting the most vulnerable* or *selective vaccination*.

People to whom influenza vaccine is recommended

A survey by ECDC in 2006 of EU and EEA counties found that all the reporting countries were recommending annual vaccination to the two largest groups which are highlighted by WHO (WHO 2002)

1. Older people above a nationally-defined age
2. All people over 6 months of age with chronic medical conditions: notably chronic heart or lung diseases, metabolic or renal disease, or immunodeficiencies.

Many countries especially emphasise the importance of annual vaccination of people living in residential care for the elderly and disabled. Few EU countries recommend vaccination of children or offering vaccines to pregnant women. This is different from policy in the United States (CDC 2007). An expert panel convened by ECDC considered there was as yet insufficient evidence on the burden of infection in children to take any view for or against vaccination. (ECDC Scientific Panel report 2007)

Health Care Staff

Health care staff are expected to protect themselves and their patients from influenza by use of protective measures. The majority of countries in Europe recommend that all health care staff should be immunised against influenza. This is partially to protect the staff who are more likely to be exposed through their work than other people. However it is more to protect their patients, especially those at higher risk of infection and disease. However all reports are that only a minority of health care workers take up this offer.

Vaccine Efficacy and Effectiveness

Estimates of vaccine efficacy and effectiveness, the extent to which vaccine protects in optimal circumstances (efficacy) and in practice (effectiveness), vary according to the match between vaccine and the circulating viral strain and by age group and clinical category. Generally, the vaccines work somewhat less well in the elderly and those with chronic ill-health. In trials, inactivated influenza vaccines have consistently been shown to prevent laboratory-confirmed illness in between 70% and 90% of healthy adults though the results are less in field effectiveness studies.(Turner 2003, Treanor J et al 1999, Nichol 2007, Skronowski 2007, Wilde 1999) The reduction in hospitalisations and deaths is less dramatic but still significant.(Mangtani 2004) Trial data cannot help here as hospitalisations, pneumonia and deaths are too uncommon to be revealed by trial data which also usually exclude those most at risk. Instead, observational data have to be used. These data are more subject to bias (Simonsen 2007). However modern epidemiological studies can compensate for these biases and when this is done positive effects are consistently observed, though there are minority opinions that disagree (Jefferson 2005, 2006).

Contraindications to Vaccination

On empirical grounds, as most viruses used for influenza vaccines are grown in eggs, egg-based vaccines should not be used for individuals with a definite history of serious allergic reactions to egg products.

Giving Vaccines

Most inactivated influenza vaccines are injected into the muscle in the outer upper arm. A single injection annually is sufficient except for previously unvaccinated preschool children with medical conditions for whom WHO recommends 2 doses at least one month apart.

Reactions to vaccines

The three groups of inactivated influenza vaccine show minor differences in the mild reactions that sometimes follow vaccination. In trials, when whole virus vaccines are used, between one in five and one in six of those vaccinated experience local reactions in the arm, lasting for one or two days. Short term reactions such as mild fever, malaise and muscle pains are reported in a much smaller proportion in the first few hours following vaccination. In contrast, trials of the split and subunit vaccines show even fewer reduced systemic reactions. There have been no strong temporal associations of the current vaccines with more severe reactions.

Vaccination Coverage Targets

The World Health Assembly, which includes all EU/EEA countries, supported a proposal in 2003 that there should be targets for uptake in the elderly of 50% by 2005 and 75% by 2010. As consistently shown by a survey conducted at EU level in 2000 (Kroneman 2003), and subsequently by ECDC for EU and EEA countries in 2006, only 15 out of 28 eligible countries could provide data and for those where data were available remarkable differences were observed indicating that efforts need to be made in Europe to improve vaccination coverage rates and meet the 2010 WHO target.

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