Pandemic (H1N1) 2009: The Role of Pharmacy

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Background

This article is based on a presentation given by Dr Martin Henman at the joint PSI/ICCPE educational sessions held earlier this summer. The sessions around pharmacy and the influenza pandemic were held under the auspices of the Expert Pharmacy Advisory Taskforce, which comprises representatives of the PSI, IPU, academic pharmacy, hospital pharmacy, HSE pharmacists and public health doctors. The taskforce was established to advise and inform Government and the Health Services of the relevant issues, and to support pharmacists in their role. The taskforce is fortunate in having Pamela Logan from the IPU as a member as Pamela has been nominated to represent European community pharmacists on the European Scientific Working group on Influenza (ESWI).

The email database of the PSI Register of Pharmacists is being used as a communication channel by the HSE, and clinical information and updates are disseminated to pharmacists via this database. The most recent letter to all clinicians dated 29 July was sent to pharmacists by email and is also available on the PSI website at www.pharmaceuticalsociety.ie. Pharmacists are kindly requested to ensure that the email addresses on the PSI database are the correct and most convenient ones for them to continue to receive updates on the pandemic.

Pharmacists are also advised to regularly consult the websites of the HSE www.hse.ie, Department of Health and Children www.dohc.ie, and the Health Protection Surveillance Centre www.hpsc.ie. The HPSC site has a link for advice for health professionals on Pandemic (H1N1) 2009, as the virus is now termed, with a further link for pharmacists and pharmaceutical information.

The website of the Irish Medicines Board www.imb.ie is another useful resource, including the SPCs of the antivirals and information on the reporting of adverse events and the extension of the shelf-life of Tamiflu from 5 to 7 years.

The European Centre for Disease Prevention and Control www.ecdc.europa.eu and the European Medicines Agency www.emea.europa.eu are also useful resources.

Introduction

In Mexico in March of this year, and then in the US in April, health authorities began to report cases of influenza caused by a novel form of influenza virus. Influenza is an acute, easily transmitted infection of the upper respiratory tract that can cause extensive morbidity even in its mildest forms and considerable mortality when complications such as pneumonia also occur. Influenza viruses cause infections each autumn/winter, known as seasonal influenza, and each autumn a new vaccine is made available to protect those at risk of serious complications. This annual undertaking is necessary because influenza viruses are uniquely and rapidly able to change their genes.

Viruses can only live by infecting the cells of a host organism and using that cell's genetic machinery to read the virus's genes and replicate new viral particles. Influenza viruses are made up of an outer coat which protects the viral genes and other proteins which are carried inside the spherically shaped particle. The outer coat contains a number of types of proteins; one of these, the M protein, enables influenza viruses to be identified, because its structure is highly stable. Influenzas are grouped into three types, A, B and C, and the A and B types infect humans. The infectivity of each influenza virus strain is largely determined by two other proteins found in the outer coat, the H and N proteins. The H protein - haemagluttinin, enables the virus to bind to the surface of the cell, and to trigger the process that brings the virus inside the cell and initiates viral replication. The new viral particles are attached to the outside of the host cell. The N protein – neuraminidase – is an enzyme that cuts the bond holding these new viral particles to the cell wall, allowing them to pass on in the fluids of the body to infect other cells. The haemagluttinin and neuramidase proteins can be classed into particular variants (for influenza A there are 16 variants of the haemagluttinin and 9 of the neuramidase) and within each variant changes in structure can, and do occur regularly; for example, not all H1 or N1 variants are the same, giving rise to different strains. Hence, when influenza viruses are named they are typed according to their group, A, B or C, and according to the variants of the haemagluttinin and neuramidase – thus, influenza A/H1N1 is a general name, but more detailed analysis of the H1 and N1 proteins is used to identify the strain. Given the importance of the H and N proteins to the infectivity and transmission of the virus, analysing and recording the H and N protein sequences is crucial. When the immune system detects influenza viruses, it recognises these unusual proteins as antigens and it produces antibodies against them. Specific antibodies for the particular variants of the H and N proteins in the viral coat circulate in the blood. It also establishes 'memory cells' that enable a quicker immune response if the virus returns, but with so many possibilities for variation and such potential for rapid change, influenza viruses present a difficult target for the immune system.

Minor variations in influenza occur when a small change in the sequence of a gene occurs. Every gene in the virus contains the code for a protein through its sequence of nucleic acid bases. The genes of the influenza virus are divided up into eight separate segments that work together to produce the virus. When the virus replicates, it produces a new set of genes, and during replication all genes can undergo small changes in their sequences – mutations, that in turn slightly alter the structure of the protein that is produced from the gene. This is one level at which changes in influenza viruses occur, leading to slightly different influenza viruses each autumn. This means that the new strain of influenza virus may be just different enough so that the immune system's response is only partially effective, even though antibodies to the previous virus may still be present in the blood. Small changes in the influenza viral genome are known as antigenic drift.

Another level at which change can occur is that of an entire gene and this can bring about major changes in the virus, known as antigenic shift, because the extent of change makes it unlikely that the viral antigens have been in circulation before. The segmentation of the influenza genes means that each segment, and therefore each gene in its entirety, can be swapped, without affecting the ability of the virus to operate. Since it is also possible for more than one virus to infect a cell at once, reassortment of the genome is not difficult. Exactly how this happens is not known but what is known is that influenza viruses are often made up of genes that originated in a different species to their present host. Birds and humans have different receptors on the surfaces of some of their respiratory tract cells that allow only avian or human influenza haemaglutttinin protein to bind to them. Consequently viruses usually remain within the species in which they originated, infecting birds or humans, not both, which is why influenzas are usually referred to also by their host species. Rarely, they 'jump', as avian influenza H5N1 ('bird flu') did when its avian haemagluttinin had changed sufficiently to enable it to infect human cells.

However, the most likely way in which influenza is thought to move between species and swap segments of genetic material involves pigs. These animals have receptors that can accept swine, avian and human influenza haemagluttinin proteins on to the cells of their respiratory tracts, so they can become infected with viruses that originated in any of the three species. A pig cell that is simultaneously infected by two viruses from different species provides a place in which swapping of viral genes can occur, potentially leading to influenza viruses made up of mixtures of avian, human and pig genes – a reassortant virus. Influenza A/H1N1 (recently re-named by WHO as Pandemic (H1N1) 2009), the virus causing this pandemic, contains just such a mixture. It represents a 'new' virus, a major change. Analysis of the genes of this virus and comparison with isolates of

virus kept in reference laboratories show that it originated in swine, and has presumably been evolving there for some time. But, unlike H5N1, the ease with which Pandemic (H1N1) 2009 is transmitted from one human to another shows that it has become completely adapted to humans and there is no evidence that contact with swine or consumption of swine tissues causes infection. Pandemic (H1N1) 2009 is now officially considered to be a human influenza, but is named human swine influenza to reflect its origins.

These two mechanisms for antigenic change give influenza the capability to produce epidemics and pandemic in the human population. Small changes mean the immune system can still detect and respond to a virus relatively quickly, since the virus is similar to the one(s) for which its has built up immunity, and this usually results in mild symptoms in a limited proportion of the population and serious complications in a much smaller group. Epidemics of seasonal influenza occur every year and strains of Pandemic (H1N1) 2009 viruses have circulated as recently as 2006-2007. Its characteristics were only slightly different to other H1N1s from previous years and so its impact was limited. In contrast, antigenic shift, with big changes in the H and N proteins enables the virus to infect many cells and to pass from host to host before the immune system has time to mount a substantial response. The Human Swine Influenza of this pandemic is the result of antigenic shift and crucially, its H and N proteins are substantially different to those seen in seasonal influenzas. This usually results in more severe symptoms in a larger proportion of the population and also leads to a significant number of this larger total infected population at risk of developing serious complications. If the combination of these two groups is sufficient, the numbers of patients seeking treatment and care could overwhelm the capacity of the health service.

Antiviral drugs

The main class of antiviral drugs is the neuraminidase inhibitors, and both oseltamivir and zanamivir have been stockpiled by the government, and the distribution of a portion of those stocks to community and hospital pharmacies has now taken place. Both are authorised by the Irish Medicines Board for the treatment and prevention of influenza in adults and children.

They inhibit the working of the neuraminidase enzyme, the N protein referred to earlier, thus preventing any new viral particles from being released from the cell surface into the surrounding tissue fluid. This localises the infection, but it can only do so efficiently if the drug is taken within 48 hours of infection, since the virus replicates and spreads quickly in the body. Both types A and B of influenza, and all nine types of neuraminidase proteins, are susceptible to oseltamivir and zanamivir. Some studies, including a recent clinical trial in general practice in Japan, provide evidence that zanamivir may be more effective against influenza B than oseltamivir.

Randomised, controlled clinical trials have shown that both drugs are effective against seasonal influenza virus strains, when used to treat infected adults and also when used in post-exposure prophylaxis. Systematic reviews in the Cochrane library have shown that, when used as treatment, they reduce the severity of symptoms and the duration of symptoms in adults by approximately 1 day and in children by around 36 hours. Notably, oseltamivir also reduces the incidence of complications, which include bronchitis and pneumonia. An updated Cochrane Review shows that oseltamivir may only reduce the complication of otitis media in children between 1 and 5 years of age. Viral shedding, the excretion of virus into the nasal mucus, is reduced, thus potentially limiting the spread of virus from one person to another.

Both drugs can reduce the spread from cases (people with an infection) to contacts (those who look after, live or work with them), and there is good evidence that oseltamivir reduces the spread of seasonal influenza among groups, such as would be found in residential homes, and there is rather less evidence that zanamivir is effective in this form of prophylaxis as well.

However, all of this evidence was obtained in cases in which the infecting virus was one of a number of seasonal influenza strains. Observational evidence from this pandemic suggests that oseltamivir, the drug that has been most frequently used, is effective against Pandemic (H1N1) 2009, and so for the moment it can be assumed that the drug's characteristics will be the same as those reported in clinical trials involving other influenza A strains.

Oseltamivir

Oseltamivir is orally active and available in capsules and as a suspension. The two dose forms seem, from a small study to be bioequivalent. It is quickly and almost completely absorbed from the gastro-intestinal tract and its absorption is not significantly affected by food, or by the common ingredients of antacid preparations, magnesium and aluminium hydroxides and calcium carbonate. It has low protein binding and distributes rapidly into the tissues of the respiratory tract. It is converted in the body to a carboxylate, which is the pharmacologically active molecule, and this is excreted unchanged in the urine by a combination of glomerular filtration and tubular secretion. There is evidence that the pharmacokinetic properties of the drug are similar in patients suffering from an influenza infection to the properties established in studies in healthy volunteers. The conversion to the active metabolite is catalysed by hepatic esterase enzymes of which there are a substantial excess and, consequently, in studies with patients with impaired liver function no change in the conversion of oseltamivir into the carboxylate was found. However, in patients with moderately impaired renal function (creatinine clearance >10 to ≤30ml/min) the dose for treatment of an adult should be reduced to 75mg once daily or 30mg twice daily, while in patients with poor renal function (creatinine clearance ≤10ml/min) the drug is not recommended.

Since oseltamivir is not metabolised by any of the enzymes most commonly associated with drug metabolism (cytochrome P450), and since studies show that it does not bind significantly to these enzymes, drug interactions of this sort have not been reported. Studies of patients who took paracetamol or amoxycillin on the fifth day of a course of oseltamivir did not show any evidence of interactions. However, if a patient were concomitantly taking probenecid, this would reduce the tubular secretion of oseltamivir carboxylate and increase the serum concentration of the drug, although the size of this effect is not considered clinically significant. Oseltamivir's low protein binding eliminates the possibility of drug interactions from this route. However, the SPC for Tamiflu (oseltamivir) recommends that care should be taken with *'co-excreted agents with a narrow therapeutic margin (e.g., chlorpropamide, methotrexate, phenylbutazone)'.*

Oseltamivir is well-tolerated. Pre-clinical studies showed that the drug was of low toxicity and that the difference between the concentration required to inhibit neuraminidase and the concentration required to cause cytotoxicity was several orders of magnitude. In clinical trials and from subsequent pharmacovigilance reports it is apparent that nausea, vomiting and headache are the most frequently experienced side effects. Nausea and vomiting can be significantly reduced by ensuring that patients take the drug with food and since food does not alter the absorption of the drug this will not affect the drug's activity. Headache will be noticed by patients using the drug for prophylaxis but has not usually led to discontinuation. Neuropsychiatric and neurological events are discussed below.

Zanamivir

This drug is not orally active. Its bioavailability by the oral route is approximately 2%. It is available in this country as an inhaled formulation, as a dry powder in blister packs, for use with the Diskhaler®. Zanamivir is active within minutes of being taken and is well tolerated, partly because it has low toxicity for mammalian cells and partly because only trace amounts are absorbed into the circulation. The drug does not seem to be metabolised and shows low protein binding thus having very little potential for drug interactions. No reduction in dose is required for patients with impaired kidney or liver function.

The principal limitation on the use of zanamivir is that patients must be able to use the Diskhaler effectively, hence the drug is not approved for use by children below the age of five and frail patients may not be capable. The European Medicines Agency has approved, in principle, the distribution of Relenza® (zanamivir) with a Rotacap®/Rotahaler® inhalation device during influenza pandemic, but it is up to the Irish Medicines Board to decide whether to authorise, temporarily, the national distribution and use of the Relenza Rotacap/Rotahaler during the pandemic.

Dosing and use in special groups of patients

Oseltamivir has been authorised for use in adults and children over 1 year of age for treatment and prevention. Infants over 1 year and children under 13 years of age may be dosed according to their body weight. In all age groups, two doses are taken daily for 5 days for a course of treatment, whereas one dose is taken daily for 10 days for prophylaxis. There has been no change to these dosing recommendations and they are can be found in the SPC and PIL for the product Tamiflu®.

Oseltamivir capsules, 30mg, 45mg and 75mg are all available and for those who are unable to swallow capsules, they may be opened and the contents mixed with a teaspoon of a liquid food such as yoghurt or a similar

food, as described in the PIL for Tamiflu®. There are also instructions on how to dissolve in the product in water, oseltamivir is water soluble, and these can also be found in the PIL or as a single page printable sheet on the Health Protection Surveillance Centre's website (http://www.hpsc.ie/hpsc/ —> Advice for Health Professionals —> Pharmacists and Pharmaceutical Information). Information on an extemporaneous preparation is available (www.extemp.ie).

In May the European Medicines Agency published an opinion of certain aspects of the Market Authorisations of Tamiflu® and Relenza®. A group of experts assessed evidence from the Market Authorisation Holders, from ongoing and unpublished studies and reports and evaluations from within the EMEA. Based upon this review they recommended that, in the event of a pandemic being declared by the WHO that;

- Infants below 1 year of age with A/H1N1 influenza could be treated with oseltamivir at a dose of 2-3mg/kg body weight twice daily for 5 days. The paediatric suspension or the use of capsules as outlined above would be suitable for this age group.
- The use of the drug for prophylaxis of A/H1N1 at the same dose for 10 days would be acceptable if this was in line with national policy.
- Side effects of diarrhoea and vomiting were reported in the studies, so administration with food would be advisable.
- Both oseltamivir and zanamivir would be suitable for use in women who are pregnant or breastfeeding in cases of A/H1N1 infection. The EMEA did not consider that there were additional risks to the foetus based on pre-clinical studies and case reports and case series of the use of the drugs in pregnancy.

The IMB has discretion in the measures it adopts in this country and together with the EMEA may change the conditions of the Market Authorisation of the products as new information and evidence alters their assessment of the benefits and risks and any changes can remain in force only while a Pandemic criteria are considered to be fulfilled.

An older drug, amantadine, which is licensed for prophylaxis of seasonal influenza, is of limited usefulness because of side effects (mainly CNS and GIT) and because resistance occurs easily, is widespread and is probably inherited by influenza strains before exposure to the drug. The Pandemic (H1N1) 2009 influenza carries a genetic marker of resistance. However, in these special circumstances it may be used in hospital practice in serious cases in combination with other antiviral drugs.

In the US and some other countries, rimantadine, a derivative of amantadine, is licensed.

Distinguishing influenza from the common cold and responding accordingly

The symptoms and signs of minor upper respiratory tract infections are well known to pharmacists and their staff but it is essential that this knowledge is reviewed by the pharmacist with their staff team, whether pharmaceutically qualified or not. Distinguishing between the different conditions is based upon a combination of the symptoms experienced and the timing of those symptoms. Influenza produces its symptoms within a few hours and they are noticeable, discomforting and even disabling. A fever of 38°C or more, prominent headache, muscle aches and pains (myalgias), cough (dry) and sore throat accompanied by the feeling of fatigue are the most common symptoms with influenza infections. Pandemic (H1N1) 2009 also seems to produce rather more gastro-intestinal disturbance than seasonal influenza and estimates of up 25% of patients experiencing nausea and diarrhoea have been reported.

By contrast, the adenoviruses and corona viruses that cause coughs and colds have a gradual onset over a day, with runny nose (rhinorrhoea) and sneezing as prominent symptoms early on, with sore throat and cough (dry or productive) and occasionally fever (never as high as 38°C), but rarely myalgia and fatigue. Patients can usually keep on going about their normal activities for a day or so as the symptoms are annoying rather than incapacitating.

Medicines such as paracetamol and ibuprofen are recommended as symptomatic relief for fever and myalgia in otherwise healthy patients. There is a reluctance in official pandemic planning documents to discuss other non-prescription medicines, probably because the evidence base for their use and efficacy is much less substantial than that for the antipyretics. However, patients clearly obtain relief from their symptoms since they make repeated requests for such products. If dry cough is a problem then suitable antitussive preparations are available, bearing in mind that dextromethorphan and pholcodeine do not possess the constipating effect of codeine, and that patients taking an analgesic preparation, whether prescription or non-prescription, need to know its constituents so that they do not unwittingly take two doses of codeine or two of paracetamol. Products for sore throats can be recommended, while those for other symptoms require some confirmation of the history. For example, antihistamines such as diphenhydramine and triprolidine are used to dry up secretions in colds and are likely to be less needed in influenza since excessive respiratory tract secretions are not usually a notable feature of the illness. Preparations containing these ingredients might be suitable for otherwise healthy patients, but in those with COPD or a history of bronchitis, particularly elderly patients, it would be prudent to avoid using these drugs since any generalised drying up of respiratory secretions might adversely affect mucus production and clearance. Although Pandemic (H1N1) 2009's capacity to damage the respiratory mucosa in these patients is somewhat greater than seasonal influenza, it still seems to be moderately active, and patients with COPD and other chronic obstructive respiratory conditions are at risk of complications. In addition the anticholinergic activity of the sedating antihistamines produces some degree of cognitive slowing and this too should be avoided in elderly patients who may live alone and have to care for themselves.

Advice about the treatment of young children was updated in the letter to medical practitioners from Public Health that was circulated via the PSI in July. Teenagers and children over 6 years of age with mild to moderate symptoms and without a concomitant condition can take an antipyretic.

In young children, those under 6 years of age, without any other conditions, antipyretics, such as paracetamol, should be used alone rather than in combination with other drugs, and the recommended dose and frequency of dosing should be followed.

Children under two years of age are a risk group and should be offered paracetamol and referred for assessment and monitoring.

Patients at these younger ages (under 5 years) present with different symptoms/combinations of symptoms to adults and so these cases should be considered by the pharmacist and referred to a GP if there is any uncertainty about their cause or course; fever, cough and rhinitis may be the only symptoms – myalgia, headache, chills and sweats and fatigue are more often absent. Non-specific symptoms such as, irritability, unwillingness to feed, vomiting, diarrhoea, abdominal pain, difficulty breathing and lethargy, may be present, but may be attributed to other possible causes.

Several complementary and alternative approaches have been promoted for their 'antiviral' activity over the years, but almost all of the studies reported have involved the common cold and not influenza. Echinacea, Chinese medicinal herbs, garlic, vitamin C, and zinc have all been the subject of Cochrane Reviews.

Echinacea is widely used as a prophylactic by patients and is being extensively promoted at the moment, largely upon the results of individual studies. However, as a systematic review of all the clinical trials has found, there is no substantial evidence for any efficacy. There is no standardisation of echinacea products and those available at the moment contain extracts of different types, varying amounts of different echinacea varieties and different components of the plant. Some of the products that are available have no clinical studies to support their use. This is not to say that the right components of the right variety at the right dose may not, one day, demonstrate efficacy, but at the moment, recommending echinacea as an effective prophylactic for Pandemic (H1N1) 2009 infection or as an alternative to rest and symptomatic relief would be inappropriate. Patients may choose to use the products in this way but it should be in the knowledge that there is no evidence of efficacy. The German Medicines Regulatory Authority recommends that echinacea products should not be used for longer than eight weeks. Rash has also been reported as a side effect of echinacea use.

In Chinese medicine, mixtures of herbs are used to treat acute upper respiratory illness; the permutations used depending upon the nature of the condition. A Cochrane Review has reported that the poor quality of the evidence currently available does not allow a judgement for or against to be made.

Garlic has not been extensively studied and, although the only trial of suitable quality for assessment showed some reduction in incidence, the number of days to recovery was similar. Not surprisingly, odour, but also rash were the side effects reported.

Vitamin C has long been put forward for the treatment and prevention of the common cold, there is no substantial evidence to support its use, although regular use may slightly reduce the severity and duration of common cold symptoms.

Zinc deficiency is known to impair the immune response but unless the patient has been severely malnourished for some time they are highly

unlikely to be deficient and, if not, there is no evidence that additional zinc intake will augment the immune response.

Promotional material for some products containing these ingredients imply that they have antiviral activity or improve the functioning of the immune system and so would be effective against viruses and other infectious agents. There is, however, no evidence for this and a pandemic influenza, such as Pandemic (H1N1) 2009, is, by its very nature, substantially different and so may well be an exception to this hierarchy of assumptions.

Complications of influenza and at risk patients

In most people's minds, the terms epidemic and pandemic imply the seriousness of the situation, and the WHO number scale has probably helped reinforce this. In fact, these terms are used to describe the geographical spread of the disease, not its seriousness. All influenza viruses can produce complications and mortality rates from influenza have increased in most industrialised countries over the past 30 years, probably because of an ageing population and of increased numbers of 'at risk' patients as a result of more effective treatment of their conditions.

Antivirals such as neuraminidase inhibitors act rapidly and treated patients develop less severe and fewer noticeable symptoms than untreated patients. Mitigation of symptoms should occur within 48 hours, if it does not and the severity of the symptoms does not diminish or if the patient deteriorates then they should be referred immediately because they may be developing a more serious infection and be at risk of complications. The warning signs for adults shown below are indications for immediate referral:

- shortness of breath, either during physical activity or while resting
- difficulty in breathing
- turning blue
- bloody or coloured sputum
- chest pain
- altered mental status
- high fever that persists beyond 3 days
- low blood pressure.

Bronchitis, sinusitis, otitis media and pneumonia are all obvious potential complications of influenza. Although influenza damages cells in the respiratory tract directly, particularly through the actions of neuraminidase, elsewhere in the body another mechanism(s) may be responsible. It is thought that some of the other genes of the virus are responsible for the complications and that they may act in two ways to bring about their effects. First of all, when the virus enters the respiratory tract it elicits a response from the immune system that helps to begin the process of containing the infection and of producing antibodies to the virus. Highly pathogenic virus strains interfere with this early phase of the immune response and this gives the virus a head start. Secondly, it has been shown that later on in the course of the infection, an excessive, dysfunctional immune response floods the tissues with immune system messengers, cytokines, and that it is these molecules that cause much of the additional damage. This 'cytokine storm', as it is known, has been shown to occur with the 1918 pandemic influenza strain ('Spanish Flu') and other highly pathogenic strains.

Complications occur in a small proportion of otherwise healthy patients and some of those who are at risk, even with strains of influenza that cause mild disease, and they occur every year with seasonal influenza. However, in strains that produce more severe symptoms, these complications occur with greater frequency and in patients who are otherwise healthy. Pandemic (H1N1) 2009 has some of the characteristics of a highly pathogenic virus in laboratory experiments but it has not produced these complications very frequently so far in the populations infected. In 'at risk' patients their concomitant conditions and/or their drug treatment make them especially vulnerable to the complications of influenza and their conditions can deteriorate rapidly if the functioning of other major organs, such as the liver or kidneys, is affected by the excessive cytokine concentrations.

Patients with risk factors who remain at home and are being monitored can use paracetamol as an antipyretic. As a precaution, pharmacists should ensure that whichever prescriber is monitoring the patient, reconciles the list of medicines in their records with the PMR kept in the Practice.

The most common forms of complications, those in the respiratory system, frequently involve other infectious agents. Respiratory Synctial Virus and Parainfluenza viruses cause acute respiratory illnesses by themselves to varying extents in different age groups. Additional, initially empirical, antiviral drug use, particularly ribavirin, often in combination with a neuraminidase inhibitor and possibly also amantadine, will be considered in tertiary referral centres and published reports suggest benefit in some patient groups. More frequently, secondary bacterial pathogens, Streptococcus pneumoniae, Staphylococcus aureus and Haemophilus influenza, are detected. However, other organs and tissues may also be affected and myocarditis, myositis, encephalopathy and Reye's syndrome are among other potential complications.

Treatment of the complications of influenza involves intensive monitoring and support of the respiratory, renal, hepatic and cardiovascular systems. Where bacterial infection occurs, either as secondary infection or as mixed viral and bacterial pneumonia, antibiotics will be used. In the National Pandemic Influenza Plan, drawn up in 2007, a standard approach using certain antibiotics and dose regimens was envisaged, based upon the common bacterial pathogens listed below (Table 1). Some purchase ordering and stockpiling of antibiotics have been undertaken but whether the antibiotics listed in the table are the ones that will be recommended for this pandemic is not yet clear, and what arrangements may be used to distribute these medicines to hospital pharmacies around the country or whether hospital pharmacists should be taking the initiative are also unanswered questions at the time of writing.

Table 1: Antibiotics for Secondary Infection

Preferred	Alternative
Doxycycline 200mg immediately, then 100mg daily	Clarithromycin 500mg bd for penicillin allergy
—— or ——	
Co-amoxiclav 625mg tds for 1/52	

Patient groups who are at risk are shown in the table below (Table 2). Most of these groups are familiar, since they are patients with chronic disease and they are usually the groups who are encouraged to seek vaccination against seasonal influenza. The extremes of age are risk factors in themselves and add to the risk of chronic disease.

Children in the first year of life and adults over 65 years of age have essentially similar risks of hospitalisation for influenza-related complications. A high fever, without any other signs in an infant of 6 months or less, or a persistent or recurrent fever and cough in a child of less than 2 years of age, may be warning signs of complications and are all indications for referral. Prematurity and cardiopulmonary disease predispose children to exacerbations of pulmonary disease and to complication of influenza. Exacerbations of asthma and antibiotic use do not seem to be reduced in oseltamivir-treated children, nor was the incidence of otitis media altered in children of 6–12 years of age according to the most recent Cochrane Review. Table 3 is an appendix from the US Committee on Infectious Diseases regarding antiviral therapy and prophylaxis for influenza in children, published in 2007, which outlines the paediatric patients at high risk from complications from influenza.

Several clinical trials of oseltamivir, some in patients from risk groups are underway and so new information and guidance may be released.

One group of patients in particular, those receiving drugs that produce immunosuppression (e.g. oral corticosteroids, azathioprine, mycophenolate), can be easily identified by pharmacists from their Patient Medication Records and may otherwise be overlooked. In immunosuppressed patients the symptoms and signs of infection are masked and the consequences of infection are much more serious than in immunocompetent patients.

Another group who should be actively monitored are pregnant women, and so far those with asthma have comprised many of the reported cases. Rapid referral and frequent monitoring are essential. Conflicting advice has already been given out in the UK which added to a feeling of unease there about the NHS response. Oseltamivir, because of its systemic activity, would be the drug of choice and is the drug recommended in the US; in Ireland it is recommended that, pregnant women in the first trimester with severe symptoms, and those in the second and third trimester with influenza-like illness should receive the drug. A letter has been sent to obstetricians from the national committee about this issue and there is also guidance for GPs about 'at risk' groups on the Health Protection Surveillance Centre's website. An example of one of the cases reported by the Centers for Disease Control in May in the USA is given in Box 1.

Box 1: Extract from Case Report

A 29-year old woman at 23 weeks' gestation had a one-day history of cough, sore throat, chills, subjective fever and weakness. One of her sons, aged 10 years, had similar symptoms a week before the mother and another son, aged seven years, had become ill on the same day as the mother. A specimen from the mother was confirmed positive for A(H1N1)v. After being prescribed oseltamivir her pregnancy proceeded normally.

Obesity has not been identified as a risk factor for influenza complications previously. Reports of case series in the US have raised this possibility. In July, the US authorities published a report of 10 Intensive Care Cases, 9 of whom were obese. These patients were treated with antivirals even though more than 48 hours had passed since their symptoms began and they received higher than recommended doses (up to 150mg bd), depending upon their kidney function. None of the cases had evidence of bacterial infection in the respiratory tract. Empirical antiviral treatment outside the usual guidelines, coupled with intensive monitoring has been effective in many of these hospital cases.

Table 2: At-risk Patient Groups

- 65+ years of age
- Chronic respiratory disease – including asthma, COPD, cystic frbrosis
- Chronic heart disease – hypertension with cardiac abnormalities, congestive heart failure
- Chronic renal disease
- Chronic liver disease
- Diabetes mellitus and chronic metabolic disorders
- Immunosuppression and malignancy – HIV+ve, chemotherapy patients, corticosteroid (prednisolone/equivalent) 20mg or more for longer than one month
- Long-stay residents – nursing homes

Referral of patients who may be at risk should be made quickly and clearly, i.e. pharmacists should not worry about overloading the health service. It would be better to assess 20 patients and find one who needs specialist care rather than have that patient delay and present as an acute, deteriorating case, and referral made with justification – a note of the symptoms, patient's report of their history and their medicines use and, of course, include the pharmacist/pharmacy contact details – is the appropriate action. Consider this case (Box 2):

Box 2: Extract from Case Report

In February 2007, fever developed in a previously healthy 15-year-old girl, with a peak temperature of 102°F (38.9°C) and mild upper respiratory congestion. The next day she was seen by her primary care physician. A rapid screening test for group A streptococcus was negative, and oseltamivir was prescribed. After two doses, she continued to have fever and also had nausea and emesis, malaise, and restlessness but could not get out of bed. Two days later, she was taken to the local emergency room, where she was found to be hypotensive.

It is easy to be wise in hindsight, but this patient was taken to the emergency room (A&E in an Irish context), three days after starting oseltamivir (2 doses plus two days). The recommended period during which symptoms should be monitored for improvement is two days, and if no response has occurred, the patient should be re-assessed. In this case the outcome was tragic (Box 3).

Box 3: Extract from Case Report

Despite intensive resuscitative efforts, she died 12 hours later; the postmortem examination showed necrotizing pneumonia and extensive alveolar hemorrhage. A viral culture confirmed an influenza A (H1N1) infection, and methicillin-resistant Staphylococcus aureus was isolated from a tracheal aspirate.

The case report shown above is taken from the seasonal influenza cases of 2006–2007 in Texas, USA.

Table 3: Infants and Children at High Risk of Complications from Influenza[3]

- High-risk children during the 2 weeks after influenza immunisation, if influenza is active in the community
- High-risk children for whom influenza vaccine is contraindicated
- Family members or healthcare providers who are unimmunised and are likely to have ongoing, close exposure to (1) high-risk, unimmunised children or (2) infants who are younger than 6 months
- Control of influenza outbreaks for unimmunised staff and children in a closed institutional setting with high-risk pediatric residents (e.g., extended-care facilities)
- As a supplement to immunisation among high-risk children
- Post-exposure prophylaxis in a family setting
- High-risk children and their family members and close contacts, as well as healthcare workers, when circulating strains of influenza virus in the community are not matched with vaccine strains
- Ages between 6 and 24 months (no antiviral agent is currently approved for infants younger than 12 months)
- Asthma or other chronic pulmonary diseases such as cystic fibrosis
- Haemodynamically significant cardiac disease
- Immunosuppressive disorders or therapy
- HIV infection
- Sickle cell anaemia and other haemoglobinopathies
- Diseases requiring long-term aspirin therapy, such as rheumatoid arthritis or Kawasaki disease
- Chronic renal dysfunction
- Chronic metabolic disease such as diabetes mellitus
- Neuromuscular disorders, seizure disorders, or cognitive dysfunction that may compromise the handling of respiratory secretions

Pharmacies in the pandemic

Pharmacists and pharmacy owners need not just to plan but to act now to be able to operate effectively throughout the autumn period and up to the end of the year. To operate effectively, all of the team, those with responsibility for medicines and those responsible for other goods and services, full-time and part-time, need to be informed, equipped and motivated. This is an opportunity to manage a series of changes in the pharmacy that could produce a lasting alteration in the way in which patient and staff interactions occur. In particular, superintendent pharmacists need to consider how the procedures and tasks relevant to the management of the pharmacy, to medicines acquisition, storage, supply, documentation, recall, disposal and stock control, as well as patient care procedures will be managed in the event that a pharmacist, pharmaceutical assistant or pharmacy technician is unavailable and to what extent training of suitable staff in some of these skills is appropriate and feasible. A discussion needs to take place to determine how the pharmacy is to be organised while the staff are being informed about the pandemic and being trained to carry out the tasks and roles that they have been allocated. Crucial to the success of communications skills training in these circumstances will be how well the rationale for the actions and messages is understood, since once people appreciate that there is a reason, and that it has been arrived at through careful thought, they will not only accept the consequences but take responsibility for their role and the effectiveness of the team. The agenda topics for this discussion should include:

- Communication message: tone and content – knowledgeable, calm, reassuring
- Communication skills: face-to-face, telephone, public, parents and children, prescribers
- Advice about antivirals: frequently asked questions, referral criteria
- Advice about medicines for symptomatic relief: responding to symptoms, suitable products, responding to product requests

- Referral procedures for: those with symptoms that may need assessment, those whose circumstances may make them vulnerable
- Hand hygiene and cough etiquette: for everyone, every morning, afternoon and evening
- Possible setting aside of consultation area as the 'respiratory symptoms area' during the pandemic – the clearing out of extraneous items and arrangements for its regular cleaning with an appropriate disinfectant

There are many challenges in this: the message is clouded by the sheer volume of material and diversity of media sources delivering different stories and 'angles' on the issues. The provenance of the information is the crucial guarantee of the quality of the content and of the appropriateness of the tone. The websites of the PSI and the IPU, the National Plan and the documents and links to other organisations available from the Health Protection Surveillance Centre are the most reliable sources and are the basis of the advice offered here.

A pandemic in abstract is a distant and unthreatening phenomenon. As it affects those around us, it becomes an emotive and worrying reality. This is why staff need to understand and to be convinced that the right information and procedures will, ultimately, produce the best outcome. For example, an important message for staff today is, "Antivirals will not be used for everyone because it does not make sense to use them in that way – most cases will be mild – and the stock must be managed so that antivirals will be available for use by those at risk of complications in the later stages of the pandemic."

Compliance with antivirals

As is the case with other medicines, when antiviral drugs are used for treatment, compliance tends to be high, the main problem is making sure that patients finish the course of drug. When they are used for prophylaxis however, compliance is less and is more variable. The benefits of treatment, when they may be noticeable and what side effects are likely and how to deal with them, are the principal points that need to be made. The recommendations about which adults should receive oseltamivir for treatment and for prophylaxis at this stage of the pandemic clearly target those with severe symptoms and those at risk of serious illness or complications; patients in these groups can be reassured that the benefits outweigh the risks. Patients who feel confident that they have been told why they need a medicine and what to expect from it will also feel secure about making the decision whether or not to take the medicine. Even if they decide not to take the medicine they should be advised about warning signs, so they can seek help if necessary, and they should be told that they can get further advice if they want it.

Treatment of children should focus on those with severe symptoms and those at risk of complications. Although the recent Cochrane Review was able to consider the most common complication, otitis media, and to assess the reduction of episodes of asthma exacerbations, there are other complications and other chronic respiratory conditions that could not be addressed in the review. Two UK studies from the early stages of this pandemic provide some ideas about children's and parent's experiences and attitudes.

In a group of 95 school children, 41 in Primary School and 54 in Secondary School, just over 40% reported a GIT adr (nausea, stomach pain) and 18% a neuropsychiatric adr (sleeping problems).[1] Less than half of those primary school children (48%) who started oseltamivir prophylaxis, while three quarters (76%) of secondary school children completed the course. Comments from parents clearly indicated that they were sceptical of the need for prophylaxis in asymptomatic children and its scientific basis, that prophylaxis would not provide long-lasting benefit or immunity and that more information about side effects should be provided so that they, the parents, could make a fully informed choice about whether or not to use the drug.

A study in the first secondary school in the UK to be closed when a case of Pandemic (H1N1) 2009 occurred, found that compliance with the full course was high (77%), while 91% of pupils took at least seven days. Half experienced side effects, particularly nausea, headaches and stomach-ache while fewer reported tiredness and difficulty in concentrating.

It is clear from these two reports that insufficient information about side effects, even the most common and noticeable, nausea, was provided. Younger children were less likely to be given oseltamivir as prophylaxis and recent media stories will increased parent's feeling of uncertainty. In the first of the studies, apart from scepticism about the official recommendations, parents were also influenced by two other factors: (i) changing advice from the health authorities – this was viewed as evidence of unreliability of official scientific evidence and (ii) advice from healthcare professionals that was in conflict with the official recommendations – in particular private physicians.

In advising people about non-prescription medicines, the familiarity of these products and of the symptoms can lead to complacency. A high fever can produce effects that worry young, inexperienced parents, and may lead them or their relatives in the context of the pandemic to take risks that they are unaware of. Discussing with staff that people will need reassuring of the effectiveness of antipyretics, that it is not necessary to keep dosing a child until their temperature is back to 37°C, that aspirin should not be used because of the risk of Reye's syndrome, will help them to have the confidence to deliver these messages appropriately. Similarly, the use recommendations of medicines for coughs and colds in young children (from 2–6 years of age in particular) have changed, and these should be revisited as the labelling of some products has been revised.

Smoking damages the respiratory tract and predisposes a person to respiratory infections. Even though smokers view smoking as one of their consolations in life, they need to be told that in an influenza pandemic it increases their risk of serious infection and of complications. Furthermore, it is essential to reinforce with all smokers that passive smoking increases the risks to other people in a pandemic, especially children and those with respiratory conditions. Communicating both of these messages is an opportunity to ask a smoker if they are ready to quit and to counsel them about smoking cessation – and pharmacy staff should be the first to think about this.

The whys and wherefores of referral, of the person or of their question, within the pharmacy as much as to a GP or hospital, must be clearly worked out and communicated. Patients and the public should be told that they are being referred because it is appropriate, otherwise they may conclude it is because of the ignorance of the staff or the unwillingness of the staff member to help.

Pharmacies, through their close contact with the local community and through their Patient Medication Records, have the ability to identify and approach people who are likely to have to stay at home and may have no-one to help them get their medicines, food or other important supplies. Simply checking that these people, or their neighbours, have made arrangements or have thought about the issue may help, because once significant numbers of people are affected, there will more urgent work and less time for the rest to devote to this.

Similarly, it should be possible to identify patients who may be at risk and to check whether they have made arrangements, or wish to make arrangements and to discuss some of these situations with their GP practice. Some, despite their obvious need, will not want 'to bother' anyone.

Hand and Respiratory Hygiene

- Wash your hands with soap and water thoroughly and frequently. Alcohol-based hand cleaners are also effective if washing facilities are not available.
- Avoid unnecessary close contact with people who have influenza or have symptoms such as coughing, sneezing, fever or shivering.
- Avoid touching your eyes, nose or mouth.
- Cover your nose and mouth with disposable tissues when sneezing, coughing, wiping and blowing your nose.
- Dispose of used tissues in the nearest waste bin.
- Wash your hands after coughing and sneezing.
- It is important to ensure that all household surfaces that are touched by hands are kept clean, especially bedside tables, surfaces in bathrooms and kitchens and children's toys. Such surfaces should be wiped regularly with a household disinfectant according to directions on the product label.

Apart from the clinical issues, the pharmacy must be able to operate as a business. Forfás has produced a useful guide to Business Continuity Planning (http://www.forfas.ie/media/forfas070228_business_continuity.pdf) including a checklist, with four headings: Planning Activities, Business Issues to Address, Measures to Underpin Continuity and Responding to Workplace Risks, that should form the basis of any pharmacy's strategy. It is necessary to try to envisage who will work and what they can do when a staff member is ill, or one of their children is ill, or the children's crèche or school closes down because of illness. These periods of absence will be

measured in units of a week since that will be the recommendation. It is vital that in areas with widely dispersed pharmacies, if one or more has to close, contingency plans can be made, now, for a rota system, or a process for the referral of vulnerable patients, to cope with that eventuality, and consider who else among the area's health service providers should be informed. Finally, when the arrangements have been agreed, they should be published to the patients and local communities affected.

Pandemic-specific issues

The first tranche of oseltamivir from the national stockpile has been distributed to community and hospital pharmacies to coincide with a change in strategy. The initial approach in any epidemic is to try to contain the infection by identifying cases using specific diagnostic tests, treating cases and tracing contacts and if necessary prophylaxis of contacts. This can be effective in small localised groups but once the infection is sufficiently widespread to make this approach unfeasible then mitigation (also referred to as treatment in some sources here and overseas – it is probably a more easily understood term) is the next strategy. Treatment involves identifying cases according to clinical symptoms and treating as warranted, and identifying those at risk. For these cases the national stock is to be used and is provided free of charge to patients. This stock should be identified and a copy of the prescription sent to the HSE to enable tracking of the pandemic through antiviral drug use. Those not at risk but experiencing influenza-type symptoms should be told to stay at home since social distancing, as it is called, can limit the spread of infection.

Parallel-imported product cannot be used in place of the national stockpile and will not be reimbursed by the PCRS.

The national stockpile should not be diverted for non-approved use. In Norway and the US there has been evidence of personal stockpiling for prophylaxis, particularly by private prescribers and their patients. Any stockpiling diminishes the availability of drug for cases in need. Prescribers have been asked to resist demand for antivirals to have as personal stock from people without risk factors, but anecdotal and press reports suggest that it is a significant issue in private practice.

In addition, the recent letter from the HSE to clinicians noted that "anecdotal comments from GPs and pharmacists would suggest that there is a pressure from the public to obtain antiviral drugs for those going on holidays or for those with minor illness. This is inappropriate and needs to be resisted. Antiviral drugs are a valuable resource and need to be used judiciously so as to avoid the development of resistance and to ensure that those who need them can avail of them".

The decision to prescribe is always based upon the balance of the risks of the infection, the benefits and risks of the treatment and the specific needs and wants of the patient. Inevitably therefore, each decision is different because each patient is unique. However, the guidelines in the National Plan are an accepted consensus view.

What is complicating this pandemic is the fact that, although they have been available for some time, oseltamivir and zanamivir have never been used on this scale in so many diverse at-risk groups before. The relative mildness of the presentation of the infection in most patients lessens the potential benefits and proportionately increases the potential seriousness of the side effects of the drugs. This has become particularly evident for the option treating of children with oseltamivir. The apparent absence of benefit, particularly in a reduction otitis media in children above 5 years of age, will cause parents and prescribers to reconsider their position.

Adverse drug events can be reported to the Irish Medicines Board online or by fax. It is important that pharmacists understand that, in reporting a suspected event, they are not required to present clear evidence that the drug is directly responsible and nor should they be concerned that the event may be reported by two different healthcare professionals, leading to double counting. The Irish Medicines Board collates all of the reports it receives and assesses them. They will be able to eliminate any duplicates and ultimately, from their country-wide view, they will judge the nature and strength of the relationship between the drug and the event. The Irish Medicines Board issued a special advisory notice about reporting suspected adverse effects of antiviral medicines on May 15th of this year.

Suspected adverse effects of oseltamivir in patients with influenza are neuropsychiatric or neurological events, such as convulsions and delirium, hallucinations and abnormal behaviour. These have been reported mainly in paediatric and adolescent patients, sometimes serious or fatal injuries were associated with the events. These serious effects are thought to be rare, whereas disturbed sleep, bad dreams and difficulty concentrating are more common. Initial anecdotal reports and the small surveys of school children in the UK confirm that these effects occur and, although transient, they are unsettling. Seasonal influenza is also associated with encephalitis or encephalopathy and Reye's syndrome (this can also occur in the absence of aspirin) in children. Four cases of neurological complications, including seizures in two of the cases, have been described in the USA in patients with confirmed Pandemic (H1N1) 2009 infection. The duration of the neurological symptoms ranged from one to seven days; all four cases recovered without any consequences and all four received oseltamivir without any apparent effect. It is hard to distinguish between the events linked to the drug, those linked to the illness and those linked to the combination of drug and illness, particularly since there are no easily discernible risk factors.

As with all chemotherapeutic drugs, there is concern that Pandemic (H1N1) 2009 could become resistant to the antiviral drugs used against it. In the past, a number of different influenza strains have demonstrated resistance to amantidine and this has been one of the reasons for its very limited use.

Oseltamivir and zanamivir target the neuraminidase enzyme of the virus. However, they bind to it in different ways. Zanamivir binds directly to the active site of the enzyme without any alteration in the site's topography, while oseltamivir requires a shape change in the site before it can bind. To date, oseltamivir resistance seems to have occurred more frequently. However, it also seems to have occurred without the use of the drug, in other words, it arose spontaneously. Nevertheless, reports, particularly for the US, seem to indicate that the resistant virus is not associated with greater pathogenicity. It had been assumed that, since the neuramidase is essential to the virus's ability to spread to other cells, any change in its structure that conferred resistance would also probably reduce infectivity, but this may not be the case with some variants. Nevertheless, many countries have been typing and testing Pandemic (H1N1) 2009 virus samples from patients and so far no pattern of resistance and/or increased pathogenicity has been detected. It may be that extensive drug use does not promote resistance for this class of drugs, but that much of the resistance arises spontaneously, since it has been recorded in the absence of drug use, and decays spontaneously.

Vaccination

As soon as it is feasible, vaccination will begin. In patients with COPD influenza vaccination reduces 'flare-ups' of the disease according to a Cochrane Review. In patients with Cystic Fibrosis, vaccination results in an immune response but there is no direct evidence to show that it protects against influenza infection or prevents lung damage. An immune response to vaccination occurs in children with cancer although it is poorer than that in healthy children but there have been no studies that examined the clinical efficacy of vaccination in this group of patients. In all of these groups, apart from some instances of local, injection site reactions, vaccination was not associated with any severe adverse reactions. Vaccination against influenza is very effective in elderly patients despite their reduced immune response, hence the need for adjuvants. In this group it reduces mortality from all causes by around 70% and complications (exacerbations of lung disease, pneumonia, heart failure, angina and myocardial infarction) by around 50%. In patients with cardiovascular disease it helps prevent heart failure, brain infarction, recurrent myocardial infarction and primary cardiac arrest and in patients with diabetes mellitus it reduces hospital admission because of loss of diabetes control by approximately 79%.

Pregnant women are also candidates for vaccination since this will pass on immunity to the newborn, an immunity that will last until the infant is around 6 months old, after which, they become candidates for vaccination themselves. Parents and carers (such as those in crèches) of young children also pose less of a risk to the children (as transmitter of infection) once vaccinated. Similarly, vaccination of the staff of residential homes for the elderly and chronically ill, significantly reduces the chances of influenza in those facilities. It is worth remembering that a person without significant symptoms and signs can still transmit the infection to a vulnerable patient, hence the need for everyone who has contact with patients to improve and maintain their hand hygiene procedures.

The government has placed purchase orders for enough vaccine for the population, at an estimated cost of €80m. There are several companies producing vaccines and, as a result of the deficiencies in vaccine production facilities identified by previous pandemics, there is greater capacity and new methods of production have meant that faster production is possible. However, the virus still has to be clinically evaluated in trials and these are underway at the moment. Concern has been expressed by some that speeding up the process of vaccine assessment by the European Medicines Agency and other medicines regulators could lead to exposing the

population to unreasonable risks, particularly since the virus produces a mild infection in most people. However, the agencies involved are confident that their procedures are thorough and that unnecessary risks are not being taken.

Since this is an influenza virus, the formulations will be very similar to those used each year for the seasonal influenza vaccines and the details of these preparations for the purpose of authorisation are well known. As the WHO have stated; "In early June, WHO held a consultation of experts which reviewed the safety of adjuvants, or substances added to vaccines to make them more effective; no significant safety concerns were identified." Vaccine safety will be carefully monitored through post-marketing surveillance. It remains to be seen whether one dose or two of the vaccine will be required and it is likely that it will be delivered in multi-dose vials, raising anxieties that inefficient usage could lead to significant wastage. Additional clinical trials in children are likely to be conducted, especially as they are the group most susceptible to infection.

Vaccines are very often produced using eggs and the final formulation usually contains ovalbumin. Some patients are allergic to egg proteins and in the past have been excluded from vaccination. Since some of the vaccines that are being evaluated in clinical trials have been produced by new techniques using cells, they may have little or no ovalbumin in their formulations. Additional information on the constituents of the formulation of the vaccine purchased by the Irish Government will be available in the autumn. However, the British Society for Allergy and Clinical Immunology (BSACI) has suggested an approach to patients dependent upon the seriousness of their allergy, as shown below;

1 Patients with a relatively minor egg allergy who are able to tolerate foods containing moderate amounts of cooked egg or who only develop local symptoms after consuming a reasonable quantity of either lightly cooked or raw egg (such as a teaspoon of scrambled egg) should be vaccinated at the GP surgery with the usual precautions in place.
2 Patients with more severe egg allergy who have positive skin tests or RASTs to egg and with symptoms on exposure to small amounts of egg or a history of severe swelling or systemic features such as respiratory compromise or generalized urticaria should be referred to an allergy clinic for further assessment and vaccination if this is deemed appropriate.
3 Patients with poorly controlled asthma should also be referred to an allergy clinic regardless of the severity of the egg allergy.

In the US, an expert panel (Advisory Committee on Immunization Practices) has already decided which categories of patients should be given first priority in any vaccination programme (Box 4).

Table 4: Advisory Committee on Immunization Practices recommendations on patient groups to receive the new Pandemic (H1N1) 2009 vaccine

- **Pregnant women**, because they are at higher risk of complications and can potentially provide protection to infants who cannot be vaccinated
- **Household contacts and caregivers for children younger than 6 months of age**, because younger infants are at higher risk of influenza-related complications and cannot be vaccinated. Vaccination of those in close contact with infants less than 6 months old might help protect infants by 'cocooning' them from the virus
- **Healthcare and emergency medical services personnel**, because infections among healthcare workers have been reported and this can be a potential source of infection for vulnerable patients. Also, increased absenteeism in this population could reduce healthcare system capacity
- **All people from 6 months through 24 years of age**
  - ~ **Children from 6 months through 18 years of age**, because we have seen many cases of novel H1N1 influenza in children and they are in close contact with each other in school and day care settings, which increases the likelihood of disease spread, and
  - ~ **Young adults 19 through 24 years of age**, because we have seen many cases of novel H1N1 influenza in these healthy young adults and they often live, work, and study in close proximity, and they are a frequently mobile population
- **Persons aged 25 through 64 years who have health conditions associated with higher risk of medical complications from influenza.**

Future developments

The National Plan for Pandemic Influenza, drawn up in 2007, has provided the framework for the government's actions in the face of this pandemic. It represents a logical response in an age of rapid intercontinental travel and in a population with a high proportion of patients with chronic disease living in the community. Similar plans have been developed elsewhere and are being modified to meet the challenges posed by Pandemic (H1N1) 2009.

When the main evening television news programme can lead with the story that one visiting student is being kept in isolation in a summer school in UCD, it still suggests a lack of perspective among some of the media. However, the 'clinical attack rate', the proportion of people being infected each week, is around 35–40 per 100,000 which is much lower than the 120 per 100,000 that was recorded last year for seasonal influenza.

Nevertheless, Pandemic (H1N1) 2009 still remains a readily communicable disease with properties that have come as a surprise. It has continued to spread during the summer months whereas seasonal influenza does not. Some cases do not exhibit a high fever. It continues to infect the young much more frequently than the 'old' suggesting that an even milder form may have circulated before but was not detected but has left those over 45 with substantial immunity. Evidence from Australia seems to bear this out but also to confirm that recent vaccination against seasonal influenza offers no protection against the pandemic virus. Pregnancy confers susceptibility, not just for the illness but potentially for a more severe form. Predictably, patients with one or more chronic illness, immunosuppression, obesity or poor liver function are vulnerable to complications. Although hospitalisation for the complications of influenza is usually high, the pattern of mortality is not likely to be the same. Children, especially young children and infants are probably less at risk of dying than older people who are hospitalised – this is probably because they are more likely to have a co-morbidity. At the moment, only patients with one or more risk factors need to see their GP, the rest are being, and will continue to be, advised to stay at home and self medicate and self care. This will enable GPs to provide adequate monitoring and care for those with risk factors and to continue to provide care for patients with other conditions, since all of the usual acute and chronic episodes and illnesses will continue to occur.

Pharmacy for its part must be, and be seen to be, professional and reliable in its response. In many instances, pharmacists and pharmacy staff will listen and will provide reassurance. Outside Primary Care, few health service managers and providers fully appreciate the value of reassurance in patient care. In a pandemic, reassurance, from someone the patient knows, will be even more valuable than in non-pandemic times.

Seasonal influenza will also emerge in the autumn and its pathogenicity and its response to its vaccine is unknowable. Whether seasonal influenza and the pandemic strain will interact, and if they do, what form this interaction may take cannot be predicted. If the seasonal influenza infects mostly older people and the pandemic strain mostly younger people, their combined attack rates will undoubtedly stretch the health service's capacity to respond. Certainly, the necessity of having to vaccinate against two influenzas will place a considerable strain on the Health Service. The initiative of the IPU in arranging for training for pharmacists in vaccination procedures is a welcome development and has been supported by the HSE since those in Public Health have also thought of the possible scenarios described above. In addition, vaccination against pneumonia in vulnerable patients will be promoted although there is some debate about which vaccine provides the most benefit.

Pharmacy is helping, and must help, respond to this situation. Pandemic (H1N1) 2009 still has the potential to infect a substantial proportion of the population and in subsequent waves of infection to change into a more pathogenic virus. The Expert Pharmacy Advisory Task Force (see Background) was formed to help link the profession and its practitioners with the Health Service. Primary Care in this country remains poorly resourced and fragmented and it is around medicines use that this fragmentation is most evident. The National Pandemic Expert Group has elected to deal with the structures and bodies in Primary Care as they are presently constituted since the burden of the infection is not disrupting services – the infection is classed a 'moderate' by the World Health Organisation. This means that some of the communication from the HSPC for example, in its tone and content, still reflects a subordinate role for the pharmacist, rather than that of a front line communicator and service provider. This is not that different to many other countries and is perhaps

not surprising, since in an uncertain situation people tend to be overly cautious.

This looks like it will be a long lasting pandemic. It is difficult to predict whether the virus will change much as it infects new hosts in the population and it is difficult to know how it will react to the widespread use of antivirals and how effective the vaccine will be.

However, it is a mistake to think of each of the antiviral measures as a separate tool. The drugs, the vaccine, the hand hygiene, the cough etiquette and the social distancing are a combined force, they should be thought of as such by pharmacists and used as such. Now and until the pandemic has passed, hand hygiene and cough etiquette and social distancing must be practised and antivirals and the vaccine will be added to these as appropriate.

We must expect that the virus will spread, that people will become ill, that some will become more seriously ill than anyone could have foreseen and that there will be disruption to the normal life of the local community. But if all is done that can be done and should be done, then no more illness, suffering and dislocation will occur than is unavoidable.

Pandemic (H1N1) 2009 is a world-wide infection. What other countries do, and how successful their strategies are, will materially alter the extent to which future waves of infection affect the population of Ireland. The authorities in Mexico showed great capability given that the first cases occurred in Mexico City with a population of around 20 million and large areas of high population density. What happens in the UK has an impact here, not just because of the sheer numbers of Irish people living there and travelling back and forth each day, but also because of the ubiquitous transnational media that are continuously available. The WHO has been helping low income countries with their planning and trying to obtain donations of antivirals and vaccine. Sanofi-Aventis, one of the vaccine producers, has pledged 100 million doses. Pandemics should serve as a reminder that health is global issue and that infectious disease affects us all, so everyone must help their neighbour as well as themselves.