ECDC INTERIM **GUIDANCE**

Public health use of influenza antivirals during influenza pandemics

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This paper has been considerably strengthened in development by many constructive comments from and through members of ECDC's Advisory Forum on an earlier draft, as well as specialists inside and outside ECDC who were asked to comment in general or on particular issues. Comments were received on a late draft from the two major manufacturers of neuraminidase inhibitors. ECDC is grateful to all those who have contributed to date.

This is interim guidance and ECDC would very much welcome comments and contributions to this document with the expectation that it will probably need to be updated as the 2009–10 pandemic develops. These comments should be sent to influenza@ecdc.europa.eu marked 'Interim antiviral guidance'.

This interim guidance was updated (pages 1 and 8) on 18 August 2009 following the results of further studies on the use of antiviral prophylaxis.

Stockholm, June 2009

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Abbreviations

ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area (EU-27 plus Iceland, Liechtenstein and Norway)
EISS	European influenza surveillance scheme
EMEA	European Medicines Agency
EU	European Union
EWRS	Early Warning and Response System
NIC	National influenza centres
NIs	Neuraminidase inhobitors
NISN	Neuraminidase Inhibitor Susceptibility Network
US CDC	United States' Centres for Disease Control and Prevention
VIRGIL	European surveillance network for vigilance against viral resistance
WHO	World Health Organization

Executive summary

This background paper is intended as a resource for those in the European Union and EEA/EFTA area who are developing policies and practices concerning the use of influenza antivirals, especially in relation to influenza pandemics. The paper is based on scientific evidence, WHO guidance, expert opinions including those from ECDC's Advisory Forum and recommendations in European national pandemic preparedness plans. It focuses on options for the use of antiviral drugs in the context of an influenza pandemic.

The available evidence on antiviral effectiveness either for treatment or prophylaxis and consequent public health use during a pandemic, derives from studies conducted during seasonal influenza seasons among well adults and, to a lesser extent, in one of the higher-risk groups (older people) and some older children.

This evidence indicates that certain antiviral drugs, particularly the neuraminidase inhibitors (oseltamivir and zanamivir), offer some treatment benefits by reducing the duration of illness from influenza usually by 1–2 days and also reducing complications and the need for antibiotics in infected individuals. This effect is limited by the need for the drugs to be given early (within 48 hours of the start of symptoms). There is also some weak evidence from observational studies that the drugs might reduce morbidity and even mortality in sicker patients even if given later than the 48 hours. Minor side effects are frequently reported, especially nausea and even sometimes vomiting with the oral preparation (oseltamivir) which is why the manufacturer recommends taking the medication with a meal.

Trials in healthy adults suggest infection can be prevented with prophylaxis treatment with a 70% to 90% effectiveness rate provided the drug is taken as prescribed. The evidence for the public health benefits for higher-risk groups and settings is less strong but there does seem to be some reduction of infection, for example, in outbreaks of seasonal influenza in closed setting such as nursing homes. This suggests that such drugs can have an impact on the level of viral transmission and help to prevent infection.

Very occasionally, influenza viruses that have primary resistance to one or more antiviral drugs can arise naturally as result of genetic mutation and natural viral reassortment. This happened during the 2007–08 season in Europe when an influenza virus emerged that was resistant to oseltamivir. This was not related to antiviral use and this possibility should not influence default policies on the use of antivirals during a pandemic. However, the possibility of a fit novel virus that is resistant to antiviral treatment is a real concern, and it may require rapid changes of antiviral policies especially for prophylaxis should a fit resistant virus appear during a pandemic. This must not be confused with secondary antiviral resistance which emerges much more commonly when using antivirals. It usually results in a virus that is unable to transmit from person to person and is therefore not an issue of public health concern.

There are a range of different strategies for use of antivirals and these depend on the overall public health goals that authorities wish to attain, the availability of antivirals, and other practical considerations. These goals can include treatment of sicker people, treatment or protection of people at higher risk, treatment of all cases, reducing the level of transmission, or protecting healthcare and other essential workers. ECDC has suggested a hierarchy of priorities.

During pandemics, because of the high numbers and potential severity of infection, there are substantial practical challenges to meet the potential need for antiviral drugs, both for treatment of infected people and prevention of infection (prophylaxis). Many countries have developed stockpiles of antiviral drugs specifically for use during a pandemic. Currently the antiviral stockpiles in European countries seem to vary from coverage of a few per cent of the population to more than 50% of the population. However, even with stockpiles in place it is almost inevitable that demand for antiviral drugs will outweigh supply in a pandemic. Because of this, it is important that advanced strategic and logistical planning is carried out to optimise the usefulness of existing stockpiles. **An important general principle is that having stockpiles is of limited use without the agreed objectives, protocols, administration and delivery systems to go with them.**

Thus clear objective setting as part of pandemic planning activities will be crucial to maximise the benefit from antiviral stockpiles. This planning should take into account the total volume and availability of antivirals, the underlying epidemiology (predicted attack rates, etc.), size and duration of the outbreak and size of population groups. Modelling can also provide an important tool to extrapolate the effects of various antiviral strategies in a pandemic but such modelling is not straightforward. Based on the available evidence ECDC suggests the following prioritisation strategy for antiviral use:

1 **People with more severe disease.** The first priority is to treat people with more severe influenza illness even if they are beyond the 48 hour 'window' following the start of symptoms when it is considered that

antivirals are effective. However, for these patients it is even more important that there are adequate supplies of appropriate antibiotics available to treat secondary infections, and other essential drugs.

2 **People most at risk of severe disease.** Among these, priority could be given to those most at risk of developing severe disease. For seasonal influenza these are those for whom seasonal influenza vaccination is recommended: older people, those with pre-existing chronic conditions, and healthcare workers with direct patient contact. However, this may need to be modified during a pandemic to reflect those most at risk from the pandemic strain[*]. When both pandemic and seasonal viruses are circulating the seasonal and pandemic higher-risk groups will need to be combined. Some countries may want to consider giving prophylaxis in households containing people at higher risk though this would be a complicated policy to implement.

3 **All people just starting an illness.** After the more severe cases antivirals could be prioritised for people just starting their illness (within 48 hours of the first symptoms) because that is when these drugs are most effective.

4 **Use for prophylaxis.** Countries with larger stocks of antivirals can consider giving them also for prophylaxis. Candidate groups are: close contacts of cases, family contacts, and key workers for business continuity purposes. Home stockpiles are not recommended as supplies are limited though inevitably some people can be expected to request these from their doctors as they did with bird flu.

5 **Healthcare workers** with direct patient contact are a special case. They need to have reasonable protection with personal protective equipment. Should they become sick they need to receive antivirals promptly and to stay home from work. Countries with larger stocks may consider prophylaxis for certain groups of these workers.

Even greater challenges are posed by the organisational aspects of antiviral delivery. Namely the evidence indicating that antiviral treatment may only deliver its limited benefits if it is given within the first 48 hours following the start of symptoms. This will be particularly critical during a pandemic. Hence, for antivirals to be effective in treating infection, resources should also be put in place to develop protocols and systems to ensure their rapid delivery and administration.

The work that ECDC and the WHO European Regional Office have done with Member States indicates that the following operational issues in the delivery and management of national antiviral and other strategic stockpiles need careful consideration ahead of a pandemic:

1 In the initiation phase of a pandemic a decision needs to be made as to whether the severity of infection at the individual patient level is sufficient to offer antivirals to all those with symptoms or even to attempt delaying or containment. The issue of mitigation versus delaying is discussed in another ECDC document.[†]

2 Ensuring that there are always antivirals available for clinicians to treat those who are most ill.

3 Being able to deliver antiviral agents to people who need them most in a timely manner because to be effective they have to be given within 48 hours of symptoms beginning.

4 Identifying the key groups that should receive antivirals as a priority, based on pre-agreed criteria (a default position).

5 Being able to change priorities if it seems those most at risk are not those predicted from the experience with seasonal influenza.

6 Ensuring that the areas first affected do not exhaust national supplies and being able to move resources around the country.

7 Having a position on citizens seeking to have individual stockpiles and companies seeking to protect their staff.

8 Monitoring for antiviral resistance, especially primary resistance and being able to change national treatment strategies if it looks like supplies will be exhausted or antiviral resistance emerges (especially if the drugs are being used for prophylaxis).

9 Not burdening stressed primary care services by making them distribute antivirals to mildly or moderately unwell people when they are hard pressed dealing with sicker people. This also avoids possibly infected persons crowding together for antivirals (e.g. in queues or waiting rooms) and so further spreading infection.

10 Ensuring that other key pharmaceuticals are in good supply especially, but not only, appropriate antibiotics.

11 Being able to monitor compliance especially among the mildly unwell and those receiving prophylaxis.

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[*] Updated information on basic epidemiology of A(H1N1)v, and associated risk groups can be found in the regularly revised 'ECDC Risk Assessment - Human cases of influenza A(H1N1)v': http://www.ecdc.europa.eu/en/Health_topics/Novel_influenza_virus/2009_Outbreak/Risk_assessment.aspx

[†] See ECDC Interim Guidance: Mitigation and delaying (or 'containment') strategies as the new influenza A(H1N1) virus comes into Europe. 6 June 2009.

12 Anticipating milder common side effects of oseltamivir, notably some nausea, and being aware that there may be reports of less frequent but more severe side effects.
13 Having training materials and approaches to facilitate the use of zanamivir inhalers, especially among those who may find them difficult to use.
14 Considering approaches for special groups such as pregnant women and young children.
15 Having robust, reliable, tested communication strategies for professionals and the public concerning all the above as part of more general communications during a pandemic.

In addition, ECDC suggests that there are some practical systems that can operate at an EU level:

16 Member States reporting through the EWRS on their default policy positions and then on significant changes.
17 Having systems that are able to pick up reports and rumours of adverse events and having a mechanism with EMEA and ECDC for responding to these when they inevitably emerge.
18 With ECDC, the Community Network Reference Laboratory and WHO monitoring for the emergence of resistance to antivirals.
19 Anticipating the inevitable appearance of direct internet selling from unregulated sources of antivirals and other medication.

The work indicates a number of research and development priorities including a need to determine whether or not antivirals are of benefit when given outside the 48 hour 'window', especially in treating the more severely ill. An additional priority is having systems in place in the Member States that can determine in real time whether antivirals are actually effective against any pandemic virus; and systems for the early detection of true treatment and prophylaxis failures, which may be an indication of the emergence of resistance.

Background

During the pandemic preparedness self-assessments undertaken by ECDC and WHO with European Union (EU) and European Economic Area (EEA) Member States it has become apparent that policies and practices concerning the use of antiviral drugs differ considerably across Europe. There is broad consensus over their use for suspected and actual human cases of avian influenza (essentially following WHO guidelines and ECDC guidance). However, there are considerable differences over both the recommended use of these drugs for seasonal influenza and their planned use during a pandemic[1-3]. Some Member States have been examining the evidence base and developing policy on the use of antivirals for one or all three of the forms of influenza (avian, human seasonal and human pandemic)[4-6]. Most EU countries report that they have acquired stockpiles of antivirals (mostly of oseltamivir) since 2005[7]. However, the size of these stockpiles vary from a few per cent of the population to over 50%. In the self-assessments it was often particularly unclear as to the objectives these are intended to meet. More recently a number of countries have started working through the considerable operational difficulties that arise concerning how to manage and deliver the stockpiles in a timely manner during a pandemic. A number of the self-assessment reports have included a request that ECDC should prepare guidance on pandemic use in their *recommendations for future action*. This paper provides scientific advice and policy options in the area of antiviral use in the EU during an influenza pandemic.

1 Purpose and audience

1.1 Purpose

The purpose of this paper is to provide a guidance based on scientific evidence, expert opinions and on what is recommended in the various national pandemic preparedness plans in EU countries, on which, when and how influenza antivirals should be used, and on the appropriate prioritisation strategies to be employed during any influenza pandemic.

The paper is not intended to act as a clinical guide. Production of such treatment guidance is outside ECDC's essentially public health remit and competence.[*] Further, there are already a number of published clinical guidelines[8-10] [11] [12]. However, some important remarks have to be made in this paper concerning clinical use since antivirals can be given simultaneously for both clinical and public health purposes. For example, when used for treating individual patients antivirals can also have public health benefits by reducing the risk of onward transmission. When applied to numbers of people for treatment or prophylaxis the public health gain could be considerable. Finally, consideration should be given to the public health implications of ensuring appropriate prescribing practices in order to limit the risk of emergence and spread of antiviral resistance.

1.2 Audience

The audience for this document is broad. The principal groups are those responsible for public health and policy development in the EU and EEA countries for which it is intended to act as a resource document. However, it is expected that elements of the paper will also be useful or of interest to those responsible for clinical care and the public more generally.

[*] The European Centre for Disease Prevention and Control (ECDC), is an EU public health agency . One of the main tasks of the Agency is to support EU public health decisions by providing high-level independent scientific advice in the field of infectious disease. More information on ECDC activities can be found at: http://ecdc.europa.eu/index.html

2 Uses of antivirals

Antivirals are a group of medicines intended for treating, or to a lesser extent preventing, viral infections affecting humans. Antivirals are distinct from *virucides* which deactivate viruses in the environment but which are often toxic to human hosts if taken internally. Antivirals work in a variety of ways at different stages on the viruses' life cycles[13, 14].

Various antivirals are available for treating or at least suppressing a number of viral infections that affect humans, including influenza. Influenza antivirals are considered especially important for groups such as older people, those with chronic illnesses and others who lack complete immune competence (e.g. those on immunosuppressants) and may not respond optimally to influenza vaccines[15]. Antivirals can offer particularly important benefits to these groups.

In some countries (notably Japan and to a lesser extent the United States) influenza antivirals have been used extensively for immunocompetent people with presumed seasonal influenza. This practice, policies and guidance vary considerably across Europe[2, 3] (See para 4.4).

Since 2005 there has been interest in the potential roles of antiviral therapy for 'bird flu' in humans; the novel avian influenzas (the family of influenza A(H5N1) viruses) which are highly pathogenic to humans[5, 16].

There has been greater interest in the potential use of antivirals during influenza pandemics[17, 18]. The rationale is that when a pandemic occurs, whatever its specific viral type, by definition many or most humans will lack immunity and it will take several months to develop and license specific vaccines. Moreover, even as specific vaccines are licensed in Europe, demand will initially greatly exceed supply, even in Europe,[*] creating a vaccine 'gap'. It is argued that antivirals could fill that gap and give clinicians and public health specialists a tool that can be used immediately to prevent or treat infection. Some modellers go further and argue that if enough antivirals could be made available it should be possible to treat many or most people with the infection, and to limit transmission of a pandemic strain[19].

The vaccine gap, the threat of a pandemic and the emergence of neuraminidase inhibitors as effective antiviral treatments with fewer side effects than the earlier adamantanes, led to the concept of stockpiling antivirals for use against an emerging or established pandemic.

Drug resistance tends to emerge in all classes of pathogens for which antimicrobials are available, including viruses. This is due to the natural emergence of drug-resistant pathogens that are then selected under the pressure of the antimicrobial treatment or prevail over the non-resistant predecessors through having another advantage. This is discussed in section 3.2: drug resistance, below, which includes special mention of the emergence during the 2007–08 influenza season of fit human influenza A(H1N1) viruses with primary oseltamivir resistancein Europe and then worldwide[20-25].

[*] The EU/EEA area has a greater concentration of influenza vaccine production capacity that any other global region. However, the capacity remains limited and its manufacturers will still not be able to produce enough pandemic vaccine for all those who would benefit from it in the first year of a pandemic. Also, under contractual agreements considerable volumes of pandemic vaccine will pass to countries outside of the EU/EEA.

3 Types of antivirals used against influenza

Currently there are two main classes of drugs used for influenza treatment and prophylaxis: the M2-inhibitors or adamantanes (amantidine and rimantidine) and the newer neuraminidase inhibitors (NIs) (oseltamivir and zanamivir). A few other drugs are reported to be in development but are not yet available, including novel NIs. In addition, research exploring the possibility of developing drugs against other anti-influenza targets (inhibitors of cell fusion, of RNA polymerase, etc.) is ongoing and new antiviral classes will probably become available in the future.[*] In December 2007, EMEA updated its review of the potential use of these medications during a pandemic and has updated that guidance since the emergence of the novel influenza A(H1N1)v in 2009[†] [26].

3.1 The M2-inhibitors

Note these are not recommended for use in the 2009–10 pandemic because the pandemic virus has had, from the start, markers of resistance to these drugs.

Amantidine and the related drug rimantidine work by interfering with a viral protein known as M2 which is needed when the influenza viral particle is taken inside a human cell[27]. They are off-patent medications[‡] and relatively inexpensive compared with the neuraminidase inhibitors (See Table 1). Amantidine is readily available in Europe as the drug is used for other purposes and is manufactured by a number of companies.[§] Rimantidine is no longer generally available in Europe.

Effectiveness

Amantidine is a drug that has been used for many years so its clinical spectra of effectiveness against existing human influenza are reasonably well known, as are its side effects, which are significant (see 'drug toxicity', below)[5, 28]. However, as it was introduced before the era when classical clinical trials were required pre-introduction, there are limited good trial data. It was used during the 1968 pandemic and during the reappearance of H1N1 in the 1970s reportedly with some effect though we have not been able to identify references for this. It is considered to only work against type A influenza viruses, which are the only ones known to cause pandemics and the pathogenic avian influenzas.

Form and delivery

Amantidine is administered orally at a dose of 100mg once daily for five days. For prophylaxis the suggested regimen is also 100mg once daily for up to six weeks. The tablets are highly stable and remain effective even after extended storage.

Drug toxicity

There are significant drug toxicity issues with amantidine. Common side effects are on the central nervous system (the drug is also used for treatment of parkinsonism)[29]. At least one country in Europe officially does not recommend the use of the drug for influenza[30]. Because of toxicity issues the drug is not recommended for children under age 10 or pregnant women and is contraindicated in persons with histories of seizures, renal insufficiency or gastric ulceration.

Drug resistance

In recent years influenza A viruses have emerged that have primary resistance to amantidine. The cause, and specifically the relationship with use of the drug in humans and animals, is not clear[31]. **These two**

[*] It is also reported that other antivirals for treating influenza have been developed and are available in Russia and China. However, no data are available on the effectiveness of these (C Brown, CK Lee personal communication 2008).

[†] http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/28514809en.pdf

[‡] That is they are medicines that are now classed as *generics* following expiration of production patents held by the pharmaceutical companies that originally developed them. Hence they can be bought at low cost from a number of manufacturers.

[§] The prices are variable. In the commercial market an individual course costs about 3€ for a course http://www.bnf.org/bnf/bnf/current/3996.htm though considerably lower prices have been negotiated for bulk purchase

considerations (toxicity and drug resistance) have generally led to reluctance to use amantidine, especially where the neuraminidase inhibitors are available and affordable[11, 32].

Following the emergence of the novel influenza A (H1N1)v in 2009, WHO reported that the viruses obtained from the first human cases were sensitive to neuraminidase inhibitors (oseltamivir and zanamivir) but resistant to adamantanes (amantadine and remantadine)[*].

3.2 The neuraminidase inhibitors (zanamivir and oseltamivir)

These are a class of drugs that came into use in the 1990s. They work by binding to and blocking the activity of the viral protein neuraminidase and so preventing new viral particles from being released by infected cells[18]. Oseltamivir (company Roche, www.roche.com) is a prodrug that is converted in the liver into the active form (oseltamivir carboxylate). Zanamivir (company GlaxoSmithKline, www.GSK.com) is the active form of the drug. These medications were introduced in the 1990s and remain patent protected. They are much more expensive than the M2 inhibitors (see Table 1)**.**[†] Both medicines are licensed and available in all EU and EEA countries[‡].

Effectiveness

Randomised trials have found that these drugs have worked against both the human seasonal influenza types A & B, somewhat reducing the duration of simple disease in otherwise healthy adults. There is more effectiveness in prophylaxis with 70–90% effectiveness[33, 34]. However, in treatment the drugs seem to have to be given within 48 hours of the start of symptoms and the earlier the better. Even then the reduction in duration of disease is only in the order of one or two days; in the most comprehensive review to date it was noted that in randomised controlled trials against seasonal influenza, oseltamivir reduces the duration of symptoms by about 1.4 days for otherwise healthy adults, by 0.5 days for higher-risk groups and 1.5 days for older children. For zanamivir the results were 1.26 days, 1.99 days and 1.3 days for these same three groups[34]. In addition, neuraminidase inhibitors have been shown to reduce complications associated with influenza, including the need for antibiotics, and have also been shown to reduce viral shedding by infected individuals[11, 34]. What is less clear is whether or not the drugs have any effect in groups that would not normally be included in trials (young children, pregnant women and many people with other specific conditions). Another important question is the role of these treatments in more severe disease and when a person is beyond the 48-hour period. There are very few studies on this and they have, by necessity, to be observational. However, what evidence there is does suggest some benefit in terms of reduced mortality and many clinicians would expect to include antivirals in treatment [44]. Data on clinical effectiveness against avian influenzas, like A(H5N1), that affect humans is limited. However, WHO guidelines for the management of sporadic human infection with avian influenza include a strong recommendation that clinicians should administer oseltamivir (and to a lesser degree zanamivir) as soon as possible to patients confirmed or suspected as having H5N1, although the panel assembled by WHO noted that evidence on which to make such a recommendation was very limited[5, 32, 35].

Form and delivery

There are no parenteral (injectable) forms of either medicine at present[11]. Oseltamivir is delivered as oral capsules available as 30, 45 and 75 mg forms which can be given to both adults and children. Use in children under age one is not recommended by EMEA, although that advice was revised in 2009 following the emergence of A(H1N1)v for the specific situation of an influenza pandemic.[§] There is also a powder form available for children though it has an unpleasant taste. Dosages in children depend on the weight of the child. This is important as when a 'flat dose' (not adjusted for weight) was given to children in Japan it seemed there was sometimes under-dosage which seemed to facilitate the emergence of resistant viruses during therapy, though these resistant viruses did not have the ability to transmit from human to human[36]. For therapy in adults and adolescents (14

[*] World Health Organization. Use of antiviral drugs against influenza A(H1N1). http://www.who.int/csr/disease/swineflu/frequently_asked_questions/swineflu_faq_antivirals/en/index.html

[†] Prices differ for the powder (known as Active Produce Ingredient – AP1 which is available at about EUR 7 a course (EUR 7.70 in developed countries, EUR 7.00 for poorer countries. The easier-to-use capsules for pandemic use are EUR 15 and EUR 12, respectively, compared with the cost for seasonal flu which range between EUR 20 and EUR 51. http://www.roche.com/med_mbtamiflu05e.pdf

[‡] Oseltamivir is centrally authorised in the EU (i.e. by EMEA) while zanamivir is authorised in all 27 countries with the reference country being Sweden.

[§] http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/28514809en.pdf

years and over) the recommended dose is 75 mg twice daily for five days. Hence an adolescent or adult course consists of ten 75 mg capsules. Conveniently, a prophylactic course also consists of ten 75 mg tablets with one taken daily for ten days.

By contrast, zanamivir is administered via a breath-controlled drug delivery system. The patient inhales the powder drug directly to the lungs through a Diskhaler®. Each unit consists of 5 mg of the drug in discs which are delivered in collections of four discs. The Diskhaler® is a device often used for other inhaled medications such as bronchodilators for persons with asthma. Hence some population groups, including those with chronic respiratory disease (notably asthma) and at high risk from pandemic viruses are familiar with their use. The use of these inhalers has been examined in a number of studies. These have often found that training as well as written instructions are needed. This is especially the case with the older people, those unwell, and children though the problems can be overcome[37-39]. Because the Diskhaler® cannot be easily used by young children is not recommended in those under 5 years old. Some power is needed by the patient breathing in, and if the in-breath is not sufficient it may be that the amount of drug reaching in the lungs is significantly reduced[40]. However, evidence suggests that the very high dose delivered by the Diskhaler® to the lungs relative to the IC_{50} means that the drug is still likely to be effective when used sub-optimally[26].

Comparing the merits of inhaled zanamivir versus oral oseltamivir is a source of continuing discussion and it is significant that one of the largest EU technology assessments did not state any preference[30]. Inhaled zanamivir delivers active compound directly to the primary site of infection, and it is suggested that theoretically this may have some advantage as a prophylactic as it can immediately dampen viral replication in the respiratory tract without the need to absorb a prodrug and convert this into a systemic active compound. Conversely, because zanamivir has limited systemic action, it may be less effective in reducing viral replication in body compartments other than the lung, such us the blood (viraemia). The systemic replication of the pandemic strain seemed to play a relevant role in the clinical features of the 1918–20 pandemic and of the human H5N1 infections. In these cases an inhaled neuraminidase inhibitor may be less effective, particularly in the treatment of clinical cases[16].

For treatment, two inhalations of 5 mg are recommended twice daily for five days, i.e. a course consists of 20 inhalations. For prophylaxis the treatment consists of two 5 mg inhalations once daily for 10 days, i.e. again therapeutic and prophylactic courses consist of the same number of units. For zanamivir there is considered to be no requirement for adjustment for weight because of the high concentrations delivered to the lungs.

Drug supply

Manufactures of oseltamivir and to a lesser extent zanamivir have significantly scaled up their production capacity of NIs since 2005 to meet the increased global demand following the perceived increase in pandemic risk due to the spread of A(H5N1) avian influenza in bird populations. Prior to the emergence of the A(H1N1)v pandemic strain in 2009, supply had begun to exceed demand since the routine use of NI remained low, and global stockpiles were well established. The expanded production capacity would not be sustainable if the inter-pandemic period is long, although conversely in a pandemic, demand is expected to be huge and manufacturers may be unable to produce sufficient quantities to supply all demands, in spite of the large global production capacity.

With drugs having been bought in 2005 and 2006, attention is now turning to updating and extending the life of the existing stockpiles. This is not without complications; not least the question of who takes responsibility within the existing regulatory framework for the liability for the use of drugs beyond their shelf life. Recently, EMEA has recommended that the shelf life for oseltamivir should be extended from five to seven years in the event of a declared pandemic.[*]

Drug toxicity

To date, toxicity is unusual for the neuraminidase inhibitors; certainly it is less common than for the M2 inhibitors. There can be minor side effects, especially nausea and even sometimes vomiting for the oral preparation (oseltamivir) which is why the manufacturer recommends taking the medication with a meal[†] [61]. The use of NIs is not recommended for pregnant women or infants because of lack of human data[11]. Consequently EMEA only approved the use of oseltamivir for children over one year old, and recommends that the drug should only be used during pregnancy if the risk of infection exceeds the risk to the foetus[41]. However, following the emergence of A(H1N1)v in 2009, EMEA has issued revised guidance stating that in an officially declared influenza A(H1N1) pandemic, the benefits of the use of oseltamivir outweigh its risks in the treatment of children under the age of one, and that the benefits of using oseltamivir and zanamivir in pregnant or breastfeeding women outweigh the risks in the event of an influenza A(H1N1) pandemic.[*]

[*] http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/28497109en.pdf

[†] http://www.roche.com/tamiflu_pil_eu.pdf

There have been reports, mostly from Japan from post-marketing surveillance of oseltamivir, of acute delirium, accidental injuries and self-harm in adolescents, temporally associated with the administration of the drug. Oseltamivir is used more extensively in Japan than anywhere else in the world. Delirium is a known manifestation of severe influenza infection and it is not clear whether these conditions were any more common in those patients taking oseltamivir than those who were not[42, 43]. However, a product warning for both oseltamivir and zanamivir has been issued with advice to physicians to be alert for these conditions in people with suspected influenza.* Investigations in the United States and elsewhere have not reproduced the associations that were seen in Japan[44].

Drug resistance

According to global surveillance data collected by the Neuraminidase Inhibitor Susceptibility Network (NISN) between 1999 and 2002[45] and by the US CDC between 2004 and 2008[46], the prevalence of resistance to neuraminidase inhibitors in circulating influenza viruses was constantly below 1% and cross-resistance between oseltamivir and zanamivir was very uncommon. Although the worldwide use of neuraminidase inhibitors has been limited so far, these resistance data in addition to experimental studies in animals was taken to indicate that both zanamivir and oseltamivir have a high genetic barrier against drug resistance, i.e. that even under the pressure of drug treatment the emergence of drug resistance mutations was limited as compared with adamantanes. It was considered that if a person was infected with a susceptible virus it was unlikely that during treatment the virus would become resistant and render the drug ineffective. However, higher levels of secondary oseltamivir resistance were reported in children (up to 18%) and immunosuppressed individuals whilst on medication[36]. These findings were explained as being due to a higher rate of, and prolonged, viral replication in individuals immunologically naïve (children) or with compromised immunological response (immunosuppressed). It has also been attributed to suboptimal doses of oseltamivir used with children in Japan[11, 47]. Nonetheless this observation deserves attention because during a pandemic the level of observed antiviral drug resistance might be expected to be higher than for seasonal flu due to the immunological susceptibility of the population.

These considerations do not mean that influenza strains that are naturally resistant with primary resistance to oseltamivir could not emerge and become dominant strains. That is precisely what happened with the seasonal A(H1N1) influenza viruses in the northern hemisphere season 2007–08 with emergence of A(H1N1)H274Y[22, 23, 48].

Sequence analysis of neuraminidase (NA) and hemagglutinin (HA) genes from resistant viruses has allowed the identification of mutations associated with resistance[45]. Such mutations often lead to substitutions in the conserved residues in the NA enzyme active site with or without compensatory mutations on the HA glycoprotein[49]. This mutation reduces oseltamivir binding affinity at the active site, with the effect that the sensitivity of the drug is significantly decreased. Zanamivir binding is not inhibited by this mutation, and therefore viruses that carry the H274Y mutation remain sensitive to zanamivir. Until H274Y all of the mutations associated with resistance were associated with some level of reduced transmissibility (fitness) of the mutated viruses and this might partially explain the low prevalence of primary drug resistance in viruses isolated from clinical and animal model settings until 2007–08[4, 50, 51]. However, the recent mutations do not seem to severely or completely affect transmissibility as demonstrated by their detection in ill patients without known exposure to NA inhibitors[45] and in experimental studies in ferrets[52]. In all countries where surveillance has been possible, the A(H1N1)H274Y have come to dominate over other seasonal A(H1N1) viruses[22, 23]. In light of the emergence of oseltamivir-resistant strains, the US CDC issued Interim Recommendations which stated that (seasonal) influenza A(H1N1) virus infection should be treated with zanamivir, or a combination of oseltamivir and rimantadine is a more appropriate option than oseltamivir alone† This opinion is now under review following the emergence of the pandemic strain influenza A(H1N1)v.

In Europe, surveillance of the antiviral susceptibility of influenza viruses has been established since 2004 through the European Union-funded European Surveillance Network for Vigilance against Viral Resistance (VIRGIL), in collaboration with the European Influenza Surveillance Scheme (EISS), WHO and national influenza centres (NIC)[7], and it is now supported by ECDC through a project with the CNRL (Community Network of Reference Laboratories). Particular attention is being paid to looking for primary resistance and the occurrence of 'fit' transmissible viruses.

More details are available from the ECDC website, EISS website and the WHO website.

* http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/28514809en.pdf

† US Centers for Disease Control, Interim Recommendations for the Use of Influenza Antiviral Medications. Available at: http://www.cdc.gov/flu/professionals/antivirals/index.htm]

4 How antivirals are used against influenza

There are essentially three reasons for giving antivirals, though there is inevitably a degree of overlap between them.

4.1 Therapy

Giving antivirals to people who are ill (patients) with symptoms compatible with influenza. This is usually before test results are available as there is strong evidence showing that treatment can shorten the time until influenza symptoms are alleviated[53] and reduce mortality[54] when given within 48 hours of symptoms onset[9, 11]. Therefore most of these patients will have to be treated on the basis of their clinical symptoms and epidemiological information.[*] Treatment is mostly for the benefit of the patient with a view to making their infection milder (i.e. reducing clinical symptoms and duration of illness). Usually treatment regimes are for five days[11].

4.2 Prophylaxis

Giving antivirals to well people who are known or strongly suspected to have been exposed to another person with influenza. The prime purpose is to prevent the person from becoming infected with influenza or to make the infection milder[33]. This also includes giving antivirals to people who have a significant likelihood of being exposed (e.g. though their work or 'occupational exposure').[†] It is recommended that antiviral drugs are started as soon as exposure begins and continues for 7 to 10 days[11], at a lower dose than for therapy. Where there is continuing exposure then drugs may be recommended for continuous use for up to six weeks in adults[55]. Oseltamivir has been used as a prophylaxis for up to eight weeks for seasonal influenza, although there should be some caution over the use of antivirals beyond eight weeks. This limitation is because of a paucity of experience of longer use rather than because there are known dangers with prolonged use[5].

4.3 Public health use

There are four public health applications.[‡] [56]

Reduce ill health and mortality in closed settings

In outbreaks of seasonal influenza in closed settings the concerted and organised use of antivirals for treatment and/or prophylaxis can reduce ill health and mortality. This is already recommended in some countries when, for example, there is an outbreak among vulnerable elderly people in residential or care homes[57, 58]. In a number of EU countries small stocks of antivirals are kept for this purpose by public health authorities.

Prophylactic use in outbreaks of animal influenza

In outbreaks of animal influenza antivirals can be given to those who may have been exposed to the most pathogenic viruses such as avian influenza type A(H5N1)[32].

Mitigation

Antivrials can be used to treat all those with disease, sometimes making a distinction between those experiencing mild and more severe disease, or just those who are most vulnerable and likely to develop severe disease if infected (i.e. the higher-risk groups). This applies equally during either a pandemic or seasonal epidemics.

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[*] People having been in contact with a proven case or having an influenza-like illness in a time and place where this is known to have a high predictive value for influenza (i.e. someone with a particular symptom set is likely to have an influenza infection). This information is usually gathered from surveillance data with or without laboratory confirmation.

[†] Some people refer to this as *early treatment* on the grounds that post exposure the infection process may have started and the symptoms have not yet shown themselves. However, most people refer to both post-exposure application and ongoing application for exposed people as prophylaxis and the *early treatment* term is not used in this document.

[‡] An additional use is the unique circumstance of the first appearances of a new pandemic strain anywhere in the world.

Reduce transmission of the virus during pandemic

This is a hoped for secondary outcome of antiviral use either as therapy or prophylaxis, whereby the benefit extends beyond that to the individual receiving treatment[33, 59]. There are various suggestions as to how antivirals might be applied: just those with vulnerable contacts; all those with symptoms; members of their household; their work or school colleagues[19, 60]. A variant of this has been suggested; that is to use antivirals more extensively as prophylaxis when case finding and contact tracing in order to delay when cases first enter a country. There are significant limitations and demerits associated with this strategy and these are discussed in another ECDC document*.

4.4 Extent of current use of antivirals in Europe

This is a poorly researched field. However, it is highly relevant for a pandemic if clinicians are expected to suddenly use a drug to which they are not accustomed. Since the emergence of oseltamivir-resistant influenza A(H1N1) in early 2008, ECDC has been undertaking limited work to monitor drug sales and prescriptions[20] from 12 EU/EEA countries. These data show very few prescriptions in some countries but significant use in others (Figure 1)[3]. The determinants of these different levels of use are unclear though it is known that in some countries important factors are the existence of professional guidance that discourages use or the reluctance of major insurers to reimburse costs[61].

There was a surge in prescriptions in a number of countries in 2005 which has been widely interpreted as reflecting concern over the threat of avian influenza A(H5N1) ('bird flu') and home stockpiling. A similar phenomenon was observed in the United States following the emergence of A(H1N1)v.

* ECDC Interim Guidance: Mitigation and delaying (or 'containment') strategies as the new influenza A(H1N1) virus comes into Europe. 6 June 2009.

5 Evidence of effectiveness

Data on effectiveness are primarily focused on efficacy and safety[11, 18, 29]; there is a more limited set of analyses on cost effectiveness[30, 61]. These data are by necessity almost entirely derived from seasonal influenza since animal influenza cases in humans are too rare for trials and the last pandemic, in 1968–70, occurred well before neuraminidase inhibitors were available. In June 2009, data are not yet available for A(H1N1)v. There are few data for amantidine because it was introduced so long ago and has been much less used of late in Europe[6, 28]. When it was used during the 1968 pandemic it was considered effective. There are, however, more data becoming available for avian influenza A(H5N1) despite it being difficult to centralise the information. Such observational data as there are show some benefit from early treatment and WHO guidelines strongly recommend the use of NIs for prophylaxis in high risk populations exposed to A(H5N1)[5, 16].

5.1 Seasonal influenza

There is reasonable direct evidence that antivirals have some benefit in the treatment of moderate disease caused by seasonal influenza, particularly if the drug is administered early (in the first 48 hours following symptoms). Benefits include a modest reduction in the duration of symptoms and severity of illness, and a reduction in secondary complications following influenza infection in both adults[9, 34, 59, 62, 63] and children[26, 32, 64-66]. There is also a limited but increasing body of observational evidence that early or even late treatment with antivirals (mostly with oseltamivir) can also reduce the risk of severe disease or death in certain high risk populations, such as older people in long-term residential care homes[29], and among those who need to be hospitalised[54]. No trial data can be expected for these groups.

With regard to prophylaxis, accumulating evidence would also suggest that individuals who take NIs receive significant protection from seasonal influenza infection; both oseltamivir and zanamivir were 70–90% effective in preventing disease when used for prophylaxis[8, 9, 11, 33]. Hence it would appear that NIs are effective as a prophylaxis for seasonal influenza. A more specific public health benefit is that NIs reduce the level of viral shedding in those who are infected with influenza[59], so there is likely to be a reduction in the level of viral transmission to others[33]. However, it should be noted that latter observation is an inferred conclusion rather than one that has been rigorously investigated.

Japan has the greatest experience with use of antivirals against seasonal influenza. There, it is used especially to treat suspected influenza in children. Reviews of the publications related to use in Japan have not revealed much to add to current knowledge (Suzuki and Oshitani personal communication July 2007). Therefore, it is not possible to conclude that increased use of antivirals in Japan has led to a better control of influenza morbidity, mortality and transmission in comparison with other countries.

5.2 Pandemic influenza

The effectiveness of antivirals against a novel human influenza that will constitute a pandemic cannot be predicted. The emergence of transmissible oseltamivir-resistant A(H1N1) seasonal influenza provides a reminder that influenza viruses can also acquire resistance to the NIs, though the evidence to date is that this in not the case with A(H1N1)v[59, 66-71].

At present it seems both of the NIs (oseltamivir and zanamivir) can be expected to be effective. As of June 2009, the WHO and its laboratories in the Global Influenza Surveillance Network have reported that the novel influenza A(H1N1)v viruses obtained from the recent human cases were sensitive to neuraminidase inhibitors (oseltamivir and zanamivir) but resistant to adamantanes (amantadine and remantadine)[*]. But even that cannot be guaranteed to be sustained and it should be noted that this is based on the non-presence of markers of resistance. Clinical observations are awaited. However, the emergence of transmissible oseltamivir-resistant seasonal influenza creates a concern that a novel pandemic influenza virus might develop resistance to one or both drugs[11, 20-24].

It is important to emphasise that while the widespread use of NIs for prophylaxis or early treatment of human seasonal influenza is not recommended by some national authorities, a pandemic strain of influenza will justify a different approach and more use of antivirals. This is because a pandemic strain will be novel to many or most of

[*] See: WHO Interim Guidance on Antiviral Recommendations for Patients with Novel Influenza A(H1N1) Virus Infection and Their Close Contacts – 6 May 2009 (accessed 23 June): http://www.cdc.gov/h1n1flu/recommendations.htm

the population. It can also probably be more virulent than seasonal influenza to some, or at least higher-risk, groups[72] and an effective specific vaccine will not be available for some time after the start of the pandemic and even then in short supply. It is important to avoid a policy of denying antivirals to people at higher risk because of a fear of promoting antiviral resistance. It must be remembered that the emergence of A(H1N1)H274Y seemed to be unrelated to the use of antivirals. Different considerations apply once a resistant strain emerges, in which case *prophylactic* use of antivirals for which there is resistance may facilitate the dominance of the resistant strain.

A priority in a pandemic will be early and ongoing virological and clinical assessments of effectiveness of antivirals against the pandemic strain. There will also need to be careful monitoring for the emergence of pandemic strain viruses with genetic or clinical evidence of antiviral resistance.

5.3 Avian influenza

The evidence for effectiveness of antivirals against avian influenzas in humans, and specifically A(H5N1), is as yet only observational[5, 16]. To date, while they have shown markers of resistance to the adamantanes, very few of the A(H5N1) isolates have shown markers of oseltamivir resistance[5]. As is often the case with an emerging and severe infection there are as yet no trial data on the effectiveness of antivirals in treating or preventing human infection or disease with influenza A(H5N1) ('bird flu'). However, should infections become any more common, organising trials and better observations would be a priority and WHO and its partners have developed a network of clinicians for that purpose[73].

5.4 Antiviral resistance

There are broader considerations before any antimicrobial can be prescribed widely, including concerns that widespread use may facilitate the development or persistence of resistant strains. Such resistant viruses have been seen in some countries in relation to the adamantane class of antivirals. However, the primary observation is that the rise in resistance to adamantanes took place without specific drug pressure in humans and so the association of antiviral resistance with a successful human influenza virus may be accidental rather than due to human use[74]. It is thought by some (but not proven) that use of these drugs at least facilitated the development of resistant strains[47, 74, 75]. Irrespective of the cause, the effect is that the development of resistance quickly renders such drugs ineffective.

It is conceivable that incorrect or overuse of oseltamivir or zanamivir may allow drug-resistant strains to emerge[47]. Because of this, a number of authorities in countries where resistance is prevalent no longer recommend these drugs for routine therapy against seasonal influenza[76]. In some European countries, the possibility of the emergence of resistance has led to great reluctance to use the NIs against seasonal influenza in the community. This was a finding in a number of the national pandemic preparedness self-assessments undertaken with ECDC. An interesting observation from a recent Canadian study of people sick enough to be hospitalised with an infection who were found to have laboratory-confirmed influenza was that while most (90%) had been given antibiotics only about 30% had been treated with an antiviral. What is unclear from that study is why antivirals had not been given to these patients[54].

It is important to note that the most important oseltamivir-resistant influenza viruses that have emerged, A(H1N1)H247Y, did so naturally. There was no pressure through the use of antivirals. Modelling work suggests that use of antivirals for treatment would not necessarily facilitate the spread of a naturally emerging resistant pandemic strain because onward transmission would usually take place before treatment had started. However, prophylaxis could facilitate spread and domination of a resistant clade of a pandemic virus. Hence, there is a need to be able to switch prophylaxis strategies rapidly during a pandemic in Europe.

It has been suggested that as the active site in the viral protein targeted by the NIs is less prone to genetic variation, then influenza is also less prone to genetic changes that confer resistance to this class of drugs. For example, it is considered that this is the reason these drugs work across all the neuraminidase sub-types N1, N2, N3, etc.[11]. However, the identification in the 2007–08 season of transmissible human A(H1N1) influenza strains in Europe and elsewhere that are highly resistance to oseltamivir indicate that human influenzas can develop resistance to that drug[20, 21]. It is too early to understand the implications of this recent development for prescription strategies for NIs, and particularly oseltamivir, against seasonal influenza. The viruses have persisted, and indeed become proportionally more common in all countries where surveillance was undertaken as the 2007–08 and 20008–09 influenza seasons progressed[22-24]. However, it is not possible to predict whether such strains will come to predominate or vanish in future influenza seasons. Although there is no direct evidence that prescribing practices for oseltamivir have driven the development of resistant strains this finding makes a strong argument for not relying on any single antiviral and highlights the constant need for investment and development of new therapies[77].

6 Costs

Any public health analysis on a population scale has to consider resource issues because spending on, or investment in, antivirals will mean that human, financial and other resources cannot be used elsewhere. Antivirals are not cheap and one cost-benefit analysis concluded that compared with vaccination, which had a low or cost saving cost-effectiveness ratio, 'in the base case, the cost effectiveness of antivirals was relatively unfavourable'[23]. The adamantanes are less expensive than the NIs which cannot yet have generic equivalents (Table 1). However, the same report concluded that there were scenarios, such as the use of antiviral prophylaxis in residential care homes, or for higher-risk individuals where the use of antivirals as an additional strategy to vaccines and other measures could be considered to be cost effective against seasonal influenza[23]. Equally, the emerging findings from a Canadian study suggest that late use of antivirals in hospitals is effective in reducing deaths in patients sick enough to be hospitalised[35]. If confirmed in other studies, including in Europe, this is likely to make antiviral use cost effective in treating these few patients[54]. One estimate of the cost-effectiveness of pandemic influenza treatment in a single EU Member State has been published and that found that stockpiling antivirals would be a cost-effective option[78]. Economic analyses at an EU level could be done but because of the variation in healthcare at national level they are no substitute for country-level work.

Table 1 Relative prescription costs of influenza antivirals

Drug	Relative cost of single treatment course in euro (amantidine as base cost = EUR 3.18)*
Amantidine	1.00
Oseltamivir	6.80
Zanamivir	6.80

Several studies have been undertaken to look at the cost-effectiveness specifically of antiviral treatments[9, 79]. These broadly conclude that amantadine is the most cost-effective treatment, although given concerns about the M2 inhibitors' efficacy, toxicity and the emergence of resistant strains, this drug may not be used in many instances in Europe. For the NIs the available evidence generally suggests that zanamivir and oseltamivir have broadly comparable cost-effectiveness, with some minor variability depending on patient class, and whether the drug is being used for treatment or prophylaxis. Again an important caveat is that most cost-benefit analyses are written for a single Member State, with cost assumptions based on the healthcare systems and cost of the drugs in that country. Hence such analyses may not be broadly applicable. In addition, the exact clinical situation used to calculate cost-effectiveness does not lend itself easily to comparison given the large number of variables that are associated with each setting. The available cost-effectiveness data apply, by necessity, only to seasonal influenza; a pandemic is likely to be incomparable with data presented to date because the underlying biological parameters and drug effectiveness are likely to vary significantly from seasonal influenza.

* As cited in one national formulary website: http://www.bnf.org/bnf/ (from BNF edition 56). Note these cited costs are for a prescribed course of treatment. Cost may vary in different settings because of different procurement contracts and discount, and prices for bulk purchase are considerably lower.

7 When antivirals are used

7.1 Seasonal influenza

Clinicians may offer antivirals as treatment to patients they know or suspect have seasonal influenza. This is usually on the basis of individual doctor-patient relationships, although a few EU countries have more sophisticated central mechanisms for recommending when it is beneficial for doctors to offer certain medications and which risk groups should be considered[30]. The risk groups considered for antiviral treatment are usually those that are offered vaccination each autumn and include older people and those with chronic conditions, etc.[18, 29, 80]. Antivirals will also sometimes be offered as prophylaxis and some countries also have guidance for their prophylaxis and public health use during outbreaks, especially when vulnerable groups are affected, such as residential homes for older people, hospitals or other residential accommodation[57, 58, 80]. There is much variation in the use of antivirals against seasonal influenza across Europe with significant and systematic use in some countries but little use in most. A common concern expressed by physicians and policy makers to ECDC on pandemic preparedness self-assessment visits is that use of antivirals against seasonal influenza will promote antiviral resistance, thereby rendering the antivirals ineffective ahead of a pandemic[81]. Such concerns may be understandable, particularly given the recent identification of oseltamivir-resistant strains of seasonal influenza A(H1N1)[20, 21].

However, a pandemic will, by definition, be caused by a novel influenza strain, so prescribing policy against current circulating strains is unlikely to significantly impact on the development of a pandemic strain. Hence concerns over resistance in a pandemic ought not to preclude the proper use of antivirals during a normal influenza season. Also ECDC would observe that if clinicians have little experience with use of antivirals for seasonal influenza they may find it harder to use them when the next pandemic occurs; there will be limited experience either clinically or of rapidly prescribing large amounts of antivirals.

Scope for stockpiling for use during seasonal influenza outbreaks

Local public health departments in EU countries sometimes have small stocks of antivirals for public health use (e.g. when managing an outbreak in a nursing home for older people). There is no need for national stockpiles as requirements can be met through normal channels.

7.2 Avian influenza

As stated above, though data are limited, the WHO recommendation is to offer antivirals (usually oseltamivir) as treatment to a sick person that clinicians feel may be infected with influenza A(H5N1). The same recommendations would apply to anyone who is ill with symptoms compatible with any avian influenza infection and was thought to be infected with another avian influenza, a low pathogenic avian influenza causing symptoms, or an avian influenza of unknown pathogenicity. WHO has used a sophisticated expert group mechanism to prepare guidance on when to use antivirals against A(H5N1). The same guidance also applies to the use of antivirals for prophylaxis when people are considered to have been exposed[16].

The risk groups are anyone who would have been directly exposed, that is (using ECDC terminology) people living in close contact with domestic poultry (Group one) and people at occupational risk (Group two)[82]. ECDC's occupational guidance which recommended this has been in place since October 2006 and ECDC's broader general guidance develops this further in the Avian Influenza Portfolio[82]. ECDC has developed a tool kit which contains guidance on the handling of imported human cases[83]. ECDC's current guidance is compatible with that posted by WHO and the self-assessment visits find that the guidance has been adopted in most countries[35] [81].

Scope for stockpiling

Outbreaks of clinical human A(H5N1) cases have typically involved single or small clusters of people that have required therapy, with larger numbers, sometimes considerably larger, requiring prophylaxis.

The same principles apply when dealing with outbreaks in birds where people are exposed accidentally or though working in culling teams. Timely use of antivirals is considered vital for prevention and control even though the absolute risk of infection of an individual is very low indeed. The majority of EU countries have had animal cases of A(H5N1), and as a result have experience of deploying prophylactic antivirals for those that may have been exposed to the virus. Many EU countries therefore have a small 'stockpile' specifically available for this purpose or alternatively are able to rapidly mobilise enough antivirals from commercial pharmacy sources.

7.3 Pandemic influenza

How a pandemic virus will probably be similar to or may differ from seasonal influenza strains plus important areas of uncertainty*

This issue is discussed further in ECDC's guidance on Surveillance and Studies in a Pandemic.

Similarities

Pandemic strain will probably:

- transmit in the same way (by droplets, by direct human to human contact and by indirect contact through fomites);
- be susceptible to antiviral therapy if not naturally resistant to any or all of the available drugs[84].

Differences

Pandemic strain:

- will probably be more virulent (have a higher case-fatality rate);
- may affect different age and risk groups.

Major uncertainties

- The precise level of virulence.
- Whether or not there will be antiviral resistance and, if so, to which antivirals.
- The background level of population immunity and hence the age groups and risk groups that will be affected.
- The timing and magnitude of first and subsequent waves.

Since 2005, there has been considerable emphasis on antiviral supplies and the size of stockpiles in Member States. Published information gathered for one antiviral manufacturer indicates that the stated sizes of national stockpiles vary ten-fold across EU countries, though this is a constantly changing area[83]. Recently the European Commission has asked Member States to update their reports to the Directorate-General for Health and Consumers on their current stocks. Experience from the national self-assessments conducted with ECDC by national authorities suggests that in some countries emphasis is now moving onto delivery systems and exploring how distribution and management could work during a pandemic[81]. While the different sizes of national stockpiles in Europe and elsewhere can seem confusing they can be explained by the different objectives they are intended to meet. For example, a stockpile intended to ensure adequate treatment in secondary care (see below) can be quite modest compared with a stockpile needed to support family-based prophylaxis that can easily reach 100% of the population. Even with the same objectives different assumptions about the proportions of people presenting requiring antivirals that actually have the infection (most patients will be offered treated on the basis of symptoms and signs without test confirmation, depending on the availability of rapid diagnostic tests) can considerably change the calculated size of a stockpile.

Therapy: use in secondary (hospital) care

Though it is not at all clear that antivirals will help if given at a late stage of disease, most clinicians would wish to have antivirals available (and also appropriate antibiotics and other medicines) for treating patients sick enough to require hospitalisation. It would be a serious matter if hospital clinicians found they did not have enough medication to treat very sick people because national supplies were being used in primary care for prophylaxis and public health purposes. One danger in a pandemic situation is that authorities might distribute or use all their antiviral stocks before the end of the first pandemic wave and not have enough to offer to people who are seriously ill with pandemic influenza at the end of the first wave, or during a later second wave. Concern has been expressed in some EU countries that geographical areas within some countries affected late would be disadvantaged for this reason.

Therapy and prophylaxis in primary care and the community

During a pandemic many people will expect that they can have antivirals at least when they become sick with what they think is influenza. This is analogous to seasonal influenza except that more people will want them at the

* See: ECDC TECHNICAL REPORT: Surveillance and studies in a pandemic in Europe June 2009. http://www.ecdc.europa.eu/en/files/pdf/Health_topics/Surveillance_and_studies_in_a_pandemic_in_Europe.pdf

same time and demand will peak at a time when healthcare staff are also sick. However, with an infection that is only causing mild disease there may be less demand than anticipated. In that sense a good approach will be to focus on those who are most at risk of developing severe disease if they are infected. Common sense and local operational exercises in EU countries dictate that many primary care systems will find it very hard to assess, triage and dispense antivirals. A number of EU countries are working on this issue seriously and are coming up with both conventional and creative delivery mechanisms. This is important as without this work authorities could find themselves in the position that they are known to have a stockpile but are not able to deliver them. That is one reason why antiviral delivery is among ECDC local 'Acid Tests'[85]. A complicated scenario will emerge if there are co-circulating seasonal and pandemic strains, in which case primary care will need to consider both sets of risk groups – those for seasonal and pandemic influenza – as there will be no time to seek testing before starting treatment.

The situation becomes considerably more complicated for prophylaxis. The default potential risk groups for individual prophylaxis would be the same as for seasonal influenza.* However, there are three reasons for caution here. Firstly, pandemic viruses are novel and may effect sub-populations differently. Young adults were noticeably affected in the 1918–19 pandemic, but that was not the case in the later 20th century pandemics[86]. That is why it will be so crucial to undertake epidemiological fieldwork early in the pandemic, including in Europe. Secondly, the clinical disease is usually more severe than for seasonal influenza so a larger proportion of those infected could benefit from antivirals. Thirdly, during a pandemic, anxiety levels will be high and doctors will be under pressure to provide antivirals to more people than just those exposed to the virus.

Matters become much more complicated when prophylaxis for public health purposes is considered. There are important views put forward that to reduce further transmission when a clinical case is suspected, everyone in their household, workplace or classroom might be offered prophylaxis. These are just some of the enhanced measures suggested by modelling studies† [19, 60, 87]. Again there is little point in a country acquiring a stockpile for public health purposes without working through the complexities of the decisions on who to offer the antivirals to, and how the medicines will be delivered. A number of EU countries are now working on this topic though the issues are complex and they are finding that it is important to not only plan but also test plans to ensure that they are operational.

Home storage

Some members of the public have wished to have antiviral drugs at home in case of a pandemic and some physicians in Europe have prescribed these for this purpose. The international consensus is that this is undesirable on any scale[88]. The advantage is immediate availability to the public. The disadvantages include the fact that the demand could be bottomless, that all control of these supplies is lost and that use would become uncontrolled which could be dangerous to patients with a novel virus[11]. There is also some concern about generating drug-resistant viruses though, as has been stated, this concern may be excessive.

Scope for stockpiling

A simple public health guide following from the arguments above is summarised in section 7.3. One thing that is immediately obvious is that Member States would need to ensure that they at least have enough antivirals for hospital clinical care. Beyond that the size of the stockpile would depend on what each country feels it could deliver in primary care, either for treatment or for prophylaxis using enhanced measures. It can be very complicated at Member State level as some countries naturally delegated these responsibilities to lower administrative levels.

Further complications include the fact that alternative stocks may be in place for some sections of society; it is known for example that some large commercial companies are developing stockpiles for use by their employees. This raises issues of equity and ethics. On the one hand companies may reasonably feel they need to protect their employees and to ensure that they can continue to function corporately in a pandemic. On the other hand there are concerns that then certain members of society will receive antivirals on the basis of who they work for rather than need. Practical considerations concern what to do about casual and contract staff and whether to offer treatment to the families of staff.

* Given high attack rates and a severe clinical spectrum some critical non-healthcare sector staff (e.g. those concerned with food and fuel distribution) may be included in prophylaxis, which is not usually the case for seasonal influenza.

† It is important to point out here that this modelling work and conclusions drawn from it are constrained by the assumptions that they have to rely on.

7.4 ECDC advice on a hierarchy of use of antivirals

Member States, depending on the size of their stockpile, could consider the following hierarchical prioritisation strategy for antiviral use during a pandemic.

1 The first priority is to treat people with more severe influenza illness even if they are outside the 48 hour window. Although for these fewer patients it is even more important that there are adequate supplies of antibiotics available to treat secondary infections.
2 After the more severe cases, priority could be given to those most at risk for severe disease which are those for whom seasonal influenza vaccination is recommended: older people, those with pre-existing chronic conditions, and healthcare workers with direct patient contact. To these should be added those who are at higher risk from the pandemic strain*.
3 After that, antivirals could be given to people just starting their illness (within 48 hours of the first symptoms) because that is when these drugs are more effective.
4 Countries with larger stocks of antivirals can consider giving them as prophylaxis. Candidate groups are: close contacts of cases, family contacts, and key workers for business continuity purposes. Home stockpiles are not recommended as supplies are limited though inevitably some people can be expected to request these from their doctors as they did with bird flu.
5 Healthcare workers with direct patient contact represent a special case. They need to have reasonable protection with personal protective equipment. Should they become sick they need to receive antivirals promptly and to stay home from work. Countries with larger stocks may consider prophylaxis for certain groups of these workers.

Scientific evidence and European context supporting ECDC advice

In a pandemic situation, the numbers of infected persons and the potential severity of disease could be much greater than that observed during a normal influenza season. Therefore, issues around delivery and supplies of antivirals become critical. A pandemic virus is likely to behave differently from a seasonal influenza virus as described above (Boxed text). Although there are default assumptions such as that antivirals are as effective and safe with a pandemic strain as they are with seasonal influenza, these assumptions must be rapidly tested through observational data, preferably at an EU level.

* Updated information on basic epidemiology of A(H1N1)v and associated risk groups can be found in the regularly revised 'ECDC Risk Assessment - Human cases of influenza A(H1N1)v':
http://www.ecdc.europa.eu/en/Health_topics/Novel_influenza_virus/2009_Outbreak/Risk_assessment.aspx

8 Organisational and practical arrangements for delivering antivirals

The suggestions made in Section 7.4 have to be translated into practicalities and there are considerable difficulties around these. The work that ECDC and WHO have undertaken in this area during the self-assessment visits has revealed that the challenges are common to most or all countries. The first two of ECDC's Acid Tests[*] are:

1. Can local services robustly and effectively deliver antivirals to most of those that need them inside the time limit of 48 hours from start of symptoms?
2. Are there simple mechanisms for rapidly altering the indications for giving antivirals?

However, while there are advantages in sharing experiences and planning it is quite impossible to come up with common European solutions as these very much depend on how primary and secondary healthcare systems are organised in Member States.

8.1 Operational issues to consider in delivering and managing antiviral and other strategic stockpiles during a pandemic

The work that ECDC and WHO European Regional Office have undertaken with Member States indicates that the following operational issues need careful consideration in delivering and managing national antiviral and other strategic stockpiles ahead of a pandemic:

1 In the initiation phase of a pandemic a decision needs to be made as to whether the severity of infection at the individual patient level is sufficient to offer antivirals to all those with symptoms, or even to attempt delaying or containment. The issue of mitigation versus delaying is discussed in another ECDC document.[†]
2 Ensuring that there are always antivirals available for clinicians to treat those who are most ill.
3 Being able to deliver antiviral agents to people who need them most in a timely manner since to be effective they have to be given within 48 hours of symptoms beginning.
4 Prioritising key groups to receive antivirals depending on pre-agreed criteria (a default position).
5 Being able to change priorities if it seems those most at risk are not those predicted from the experience with seasonal influenza.
6 Ensuring that the areas first affected do not exhaust national supplies and being able to move resources around the country.
7 Having a position on citizens seeking to have individual stockpiles and companies seeking to protect their staff.
8 Monitoring for antiviral resistance, especially primary resistance and being able to change national treatment strategies if it looks like supplies will be exhausted or antiviral resistance emerges (especially if the drugs are being used for prophylaxis).
9 Not burdening stressed primary care services by making them distribute antivirals to mildly or moderately unwell people when they are hard pressed dealing with sicker people. This also avoids possibly infected persons crowding together for antivirals (e.g. in queues or waiting rooms) and so further spreading infection.
10 Ensuring that other key pharmaceuticals are in good supply especially, but not only, appropriate antibiotics.
11 Being able to monitor compliance especially among the mildly unwell and those receiving prophylaxis.
12 Anticipating milder common side effects of oseltamivir, notably some nausea, and being aware that there may be reports of less frequent but more severe side effects.
13 Having training materials and approaches to facilitate the use of zanamivir inhalers, especially among those who may find them difficult to use.
14 Considering approaches for special groups such as pregnant women and young children.

[*] ECDC 'Acid Tests' for helping assess, strengthen local preparedness for moderate or severe pandemics (updated February 2007) http://www.ecdc.europa.eu/en/Health_Topics/Pandemic_Influenza/Assessment_tools.aspx

[†] See ECDC Interim Guidance: Mitigation and delaying (or 'containment') strategies as the new influenza A(H1N1) virus comes into Europe. 6 June 2009.

15 Having robust, reliable, tested communication strategies for professionals and the public concerning all the above as part of more general communications during a pandemic.

In addition, ECDC suggests that there are some practical systems that can operate at an EU level:

16 Member States reporting through the EWRS on their default policy positions and then on significant changes.
17 Having systems that are able to pick up reports and rumours of adverse events and having a mechanism with EMEA and ECDC for responding to these when they inevitably emerge.
18 With ECDC, the Community Network Reference Laboratory and WHO monitoring for the emergence of resistance to antivirals.
19 Anticipating the inevitable appearance of direct internet selling from unregulated sources of antivirals and other medication.

Even these European level systems have to be considered by individual countries in the context of how their specific healthcare systems operate.

8.2 Scientific evidence and European context supporting this ECDC advice

An important and rather unique issue for antivirals is the need for speed of getting people started on drugs and the difficulties in managing a limited resource. All available data from seasonal influenza indicate that antivirals given early after the start of symptoms (within 24–48 hours) are far more effective in reducing levels of infection and alleviating symptoms than those given later. There cannot be any firm rules or time 'cut offs', although after 48 hours have elapsed following the development of symptoms, the benefits of any decision to prescribe are not so clear. From a clinical perspective, as the infection progresses, antiviral treatment may still offer some benefit to the individual, and may also reduce the level of virus shed and therefore reduce the possibility of influenza transmission to close contacts. Equally there are the recent observations on the benefits of late treatment in persons with more severe illness[29, 54]. Hence, if a patient remains sick from influenza and has not received any antivirals, clinicians may wish to prescribe antivirals no matter how long the course of the illness, usually along with a relevant antibiotic in case of concomitant bacterial infection[17]. This is particularly so if a patient is affected by more dangerous strains, including notably H5N1. However, these principles may have to be modified during a pandemic, when there is likely to be a scarcity of antivirals, and hence clinicians and authorities may have to make more pragmatic decisions on the use of limited resources. However, overall, the prescription policy can be summarised as 'the sooner antivirals can be administered after the development of symptoms, the better the outcome' [19]. The same principle applies to the use of NIs for prophylaxis though once the incubation period has been passed, if the person remains well it is likely that the individual is not infected and therefore prophylaxis would no longer be appropriate.

Given the importance of early treatment both for reducing clinical symptoms and interrupting chains of transmission, it is vital that thought is given to the logistical arrangements for antiviral delivery. This is the case for seasonal influenza and avian influenza, but is much more important to consider when developing strategies for pandemic influenza containment when it is likely that antiviral treatments will need to be delivered in large numbers within short time periods. There is also the further complication of needing to manage stocks so that they are not exhausted too early. It is therefore vital that strategies for antiviral stockpiles are considered in advance, and that they reflect the strategies for antiviral deployment in a pandemic situation. Such strategies must consider both the broad volume of antivirals that will be needed to fulfil a particular approach at a national level, and how the antiviral drugs will be made available when and where they are needed. An ECDC 'acid test' to help with planning is to consider how local services would robustly and effectively deliver antivirals to most of those that need them inside the time limit of 48 hours following the start of symptoms[85].

Hence an important general principle is that having stockpiles is of limited use without the agreed objectives, protocols, administration and delivery systems to go with them. This is a very complicated and difficult area for national authorities because of the need to manage limited stocks taking account of the progression of the pandemic, since it cannot be guaranteed that more supplies will become available from the manufacturer in the short term.

9 Possible impact on the environment

The potential impact on the environment from the sudden widespread use of antiviral drugs (for example at the start of a pandemic), particularly the ingested oseltamivir, has also recently been highlighted. The active substances in ingested antivirals are not easily broken down by water treatment processes, and although there is some evidence that microbiological activity can degrade the active product in the natural environment, it remains plausible that active metabolites may negatively impact on the biological activity in water treatment plants with subsequent consequences for the aquatic environment. Further, through direct leeching into the environment, they may drive the development of antiviral-resistant strains of influenza[89-91]. This is in addition to broader environmental concerns about active antiviral compounds entering the water supply and causing ecological harm[89, 92].

This is an area that should be considered for a pandemic, and further multidisciplinary research and assessment would be beneficial to better understand the potential environmental impact of wide-scale use of antivirals. However, the current evidence base on the risks presented by antivirals in the environment is unlikely to impact on planned prescribing practices in a pandemic situation.

10 Research and development priorities

Antivirals are a relatively new but important addition to the list of countermeasures against seasonal, avian and pandemic influenza. They are already making important contributions to the prevention and mitigation of the effects of seasonal influenza on patients in some EU countries. This is especially the case for those who are most vulnerable to the infection (older people and those with chronic illness). There may be scope for health gain by increased standardisation in approaches in this field across Europe. Antivirals will certainly save lives when the next pandemic comes, though their role may have been over-emphasised recently compared with other healthcare measures (antibiotics and supportive care), public health measures and vaccines. All three are essential in any comprehensive strategy.

Important research needs relate to the impact of antivirals in reducing the severe complications of seasonal influenza and specifically the question 'does early treatment or prophylaxis with antivirals reduce the risk of severe disease or death due to influenza?' This could be done in the immediate future through independent reviews of information from observational databases both within Europe and beyond, for example with researchers in Japan and North America. Antiviral resistance is already being monitored at the EU level and in most Member States supported by ECDC, CNRL and WHO. Since it should not be assumed that the effectiveness of antivirals will be the same against pandemic and seasonal influenza viruses it will be important to have plans in place for rapidly determining the effectiveness of the antivirals in a pandemic. That is, having systems in Member States that will determine in real time whether antivirals are actually effective against any pandemic virus and for the early detection of true treatment and prophylaxis failures.

Annex

Table

Table 2 Public health aspects of stockpiling influenza antivirals

Use	Local or national level	International level
Seasonal influenza		
Therapy	Commercial issue	Little rationale
Prophylaxis	Justified locally but small scale (application in nursing homes)	Little rationale
Avian influenza		
Therapy	Justified but modest scale	May be justified for accession, candidate and neighbouring states – modest scale
Prophylaxis	Justified but modest scale	May be justified for accession, candidate and neighbouring states – modest scale
Pandemic influenza		
Therapy: hospital care	Essential	No public health rationale
Therapy: primary care	Rational but needs an efficient and tested delivery system	Little rationale
Prophylaxis: reducing transmission	May be rational but needs an efficient and tested delivery system. Even then may be significant practical problems	Little rationale
Prophylaxis: early response and containment (first emergence of the strain anywhere in the world)	Best tackled internationally but vulnerable countries need to respond	Essential. Large scale There already are WHO stockpiles of about 5 million treatment courses
Prophylaxis: early response and containment (first appearance of the strain in a new country after pandemic has started)	Scientific opinion is that this would not work for MS. Perhaps some rationale for isolated communities that could isolate themselves and reduce travel to a minimum	No rationale
Personal/Family	Not recommended. Very difficult to mount consistent policies, impossible to know how much is available.	Not applicable
Employer (companies public or commercial providing antivirals for their employees)	Difficult to prevent but introduces major problems over equity and the same difficulties over application of rational policies as 'personal/family'. above.	Not applicable

Figures

Figure 1 Prescriptions of oseltamivir per 1 000 inhabitants in eight European countries, 2002–2007

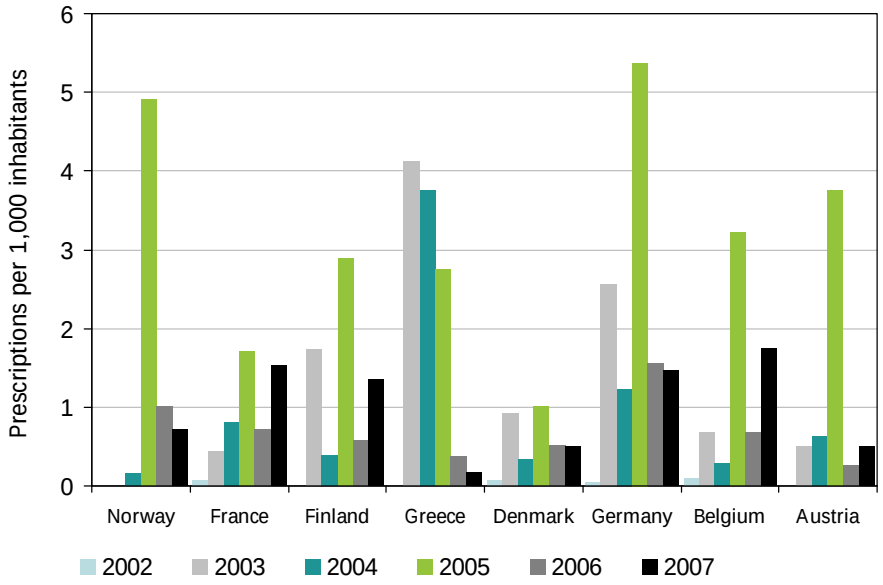
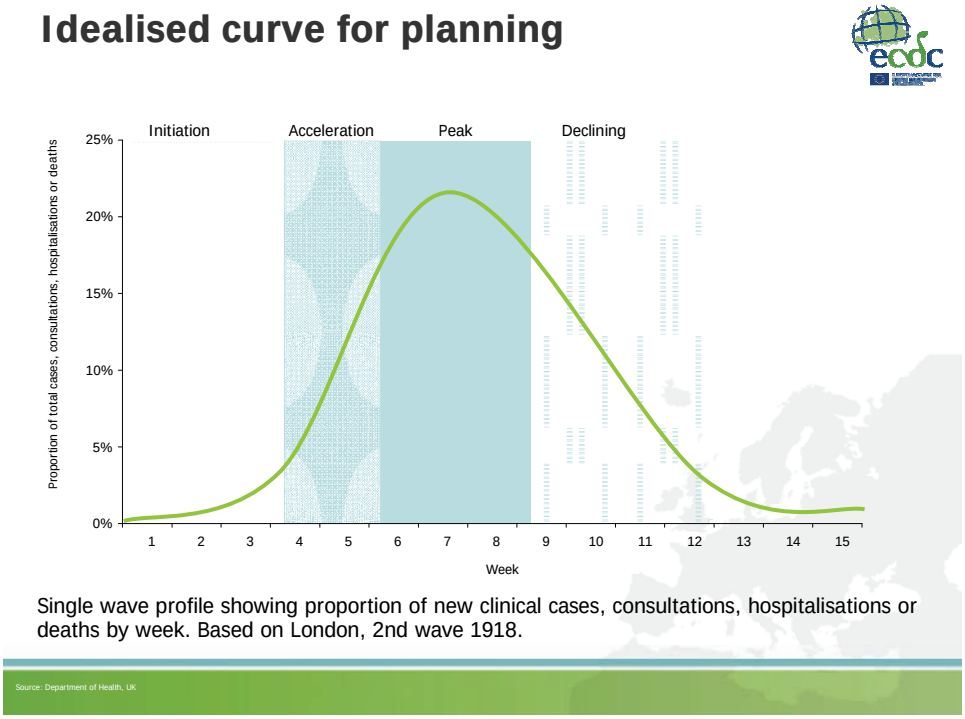
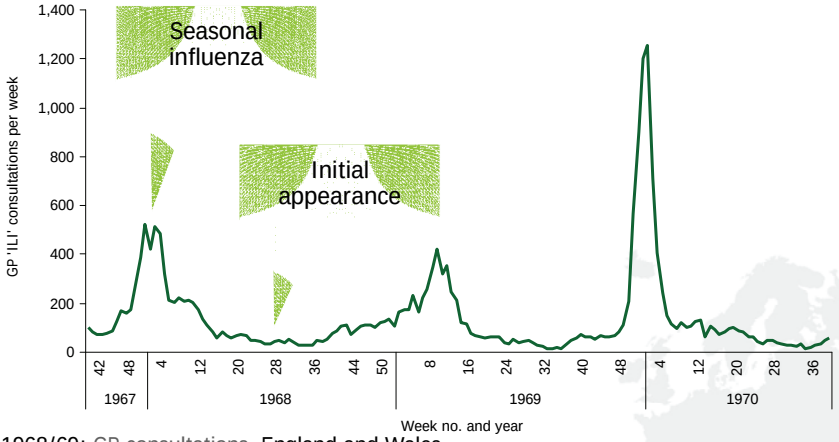


Figure 2 Idealised and reality curves for a pandemic*



* Figure 2 is taken from a downloadable presentational resource from ECDC: Likely evolution of the pandemic of the new influenza virus A(H1N1)v

1968/1969 pandemic: A(H3N2) — transmitted and affected all age groups



1968/69: GP consultations, England and Wales

Transmissibility: estimated Basic Reproductive Number (R_o)

R_o = 1.5-2.2 (World) Cooper et al (PLoS Med.2006)
R_o = 2.2 (UK) Gani et al (EID 2005)
R_o = 1.3-1.6 (UK) Hall et al (Epidemiol. Infect. 2006)

Courtesy of the Health Protection Agency, UK

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