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5 Public Health Response: Antivirals

5.1 Introduction

Antiviral drugs are essential components of a comprehensive pandemic response. There is evidence that, when given rapidly (within 12 hours of onset of symptoms) they can reduce infectivity and, when given within 48 hours of onset of symptoms, they are effective in treating seasonal influenza. They are also effective in preventing it. Pending the availability of virus-specific vaccines, antivirals will be the only influenza-specific medical intervention available for use in a pandemic. It is hoped that the effectiveness of antivirals against seasonal influenza will also apply to pandemic influenza. However, many countries have no or very limited supplies. There is a global shortage of antivirals, and it takes several years to construct new production facilities and significantly increase production capacity. Only those countries with stockpiles of antivirals drugs will have them in the event of a pandemic. Each country also has to consider which groups will have first call on scarce supplies. WHO has advised countries to set goals and priorities for the use of antivirals during a pandemic, which should reflect the particular circumstances of each country. **The Expert Group advises that the goals for Ireland for use of antiviral drugs should be, in order of priority:**

- **To prevent or reduce deaths and hospital admissions from influenza**
- **To prevent and reduce morbidity from influenza**
- **To maintain essential services**

This chapter outlines the drugs used in treatment and prophylaxis of influenza, their effectiveness, the potential uses of antivirals during a pandemic; recommendations on use of antivirals in Ireland during a pandemic; as well as outlining the other requirements needed for an effective public health antiviral treatment implementation strategy.

5.2 Types of antiviral agents

5.2.1 Neuraminidase inhibitors (Zanamivir and oseltamivir)

Zanamivir and oseltamivir are neuraminidase inhibitors (NAI), which interfere with replication of both influenza A and B viruses.

5.2.2 M2 Inhibitors (Amantadine and rimantadine)

These agents are inhibitors of the M2 ion channel protein contained within the influenza virus. They are effective against influenza A virus. Currently, only amantadine is licensed for use in Ireland, and only as prophylactic treatment against influenza A virus.

Up to date details, including the summary product characteristics (SPC) on these drugs are available at www.medicines.ie. A summary table of the properties of antiviral agents, extracted from a recent review on influenza antiviral medicinal products for potential use during a pandemic by the European Medicines Agency (EMEA, 2005) is presented in Appendix A.(1)

5.3 Review of effectiveness of antivirals in the treatment and prevention of influenza, antiviral resistance, and stability of oseltamivir

5.3.1 Neuraminidase inhibitors (NAI) in treatment

NAI treatment: Key points

Treatment with NAI (within 48 hours) for seasonal influenza leads to reduction of:

- 0.4 -1 days in duration of symptoms
- 25-43% of complications requiring antibiotics
- 55% in Lower Respiratory Tract Infections
- 34% in need for antibiotics
- 59% in hospitalisations
- 44% in otitis in children

A systematic review and meta-analysis of randomised controlled trials, based on studies published prior to December 2001, was carried out on the effectiveness of neuraminidase inhibitors in treatment and prevention of Influenza A and B.[2] It found that treating otherwise healthy adults and children with zanamivir and oseltamivir, when given within 48 hours of onset of symptoms, reduced the duration of symptoms in the intention to treat population by between 0.4 and 1.0 days, and provided a 29% to 43% relative reduction in the likelihood of complications requiring antibiotics. In high-risk populations, the results were less conclusive.

There is also evidence from a more recent study that oseltamivir treatment leads to a reduction in secondary lower respiratory tract complications (Lower Respiratory Tract Infections (LRTI), bronchitis, pneumonia) and hospitalisations.[3] Those receiving oseltamivir were 55% less likely than those on placebo to develop an influenza-related LRTI requiring antibiotic treatment. In patients with an increased risk of these complications, there was a 34% reduction in LRTIs requiring antibiotics and a 59% reduction in hospitalisation.

In children aged one year of age or older, oseltamivir treatment resolved illness 36 hours earlier than placebo, and it reduced the incidence of otitis by 44%.[4]

Oseltamivir was used to control the transmission of H7N7 in the outbreak of avian influenza in the Netherlands in 2003. All cases were treated, and prophylaxis (oseltamivir 75mg/day) was given to all people handling potentially infected poultry, to be continued for two days after their last exposure.[5] More recently, they have reported that oseltamivir was found to have a protective effect. It protected against conjunctivitis (OR=0.14; 95% CI 0.08-0.27) and against infection without specific symptoms (OR=0.47: 95% CI 0.25-0.88).[6]

Gani et al have modelled the effect of using antiviral stockpiles for treatment on hospitalisation with pandemic influenza.[7] A stockpile that covers 20-25% of the population would be sufficient to treat most of the clinical cases in the

first wave of infection and could lead to 50-77% reductions in hospitalisations. Treating all sick patients was the best strategy in reducing hospitalisations and transmission.

5.3.2 Neuraminidase inhibitors (NAI) as prophylaxis for seasonal influenza

NAI prophylaxis for seasonal influenza: Key points

Oseltamivir 75mg/d for 7-42 days as prophylaxis:

Reduces incidence of seasonal influenza by 81%

In children reduces incidence of febrile illness in contacts by 55%

Modelling studies show that:

Providing prophylaxis to 80% of population for 8 weeks contains an epidemic similar to the 1957/1958 pandemic, reducing the attack rate from 33% to 2%

Very early geographically targeted prophylaxis and social distancing could eliminate an emergent pandemic strain

Antiviral prophylaxis of household contacts reduces cumulative attack rates by one third and peak attack rates by 50%, but needs large stockpile to do this

Influenza antiviral agents can be used prophylactically as follows:

- To prevent infection given exposure,
- To reduce the probability of clinical illness given infection,
- To reduce the probability of transmission to others given infection.

In a 2005 review article which summarised the outcomes of studies on the use of oseltamivir in prophylaxis, the conclusions were that when oseltamivir was prescribed at a dose of 75mg/day once daily for 7-42 days, it reduced the incidence of laboratory confirmed clinical influenza by 81% [range 58%-92%]; reduced the proportion of patients shedding influenza virus; reduced the incidence of clinically diagnosed complications of influenza; did not prevent the formation of a specific antibody response to influenza infection; and did not result in the development of resistance.[8] There was no evidence that the protective efficacy of oseltamivir in adults and children >= 13 years was

altered by age, gender, geographic region, or the existence of pre-existing co-morbidity.

In 2004, Hayden et al determined the efficacy of post exposure prophylaxis (PEP) and treatment of ill index cases with oseltamivir in an attempt to prevent influenza transmission in households.[9] In this study, involving 277 households with 298 index cases, and 812 contacts aged >= one year, contacts were randomised by household to receive treatment for five days if illness developed, or PEP for 10 days. The number of households with at least one contact developing laboratory confirmed influenza was measured. They found that PEP with oseltamivir was 58.5% more effective in reducing secondary cases of influenza illness in households, and 68% more effective in individuals, compared with treating index cases alone. PEP must be initiated early however for optimal protection. They also investigated the efficacy of oseltamivir prophylaxis in children aged 1-12 years old. The overall incidence of influenza was three times higher in those paediatric contacts managed expectantly over those given PEP (24%-8%). PEP reduced the incidence of febrile influenza illness by 55% among paediatric contacts. The number of households given prophylaxis (number needed to treat) to prevent one household reporting a secondary case was six. Among individual contacts, the number needed to treat to prevent one secondary case was 11.

Longini et al investigated the use of targeted antiviral prophylaxis as a method for controlling pandemic influenza.[10] They modelled an influenza pandemic for an agent similar to influenza A virus (H2N2) that caused the Asian influenza pandemic of 1957-1958. In the absence of intervention, the model predicted an influenza illness attack rate of 33% of the population and an influenza death rate of 0.58 deaths /1000 persons. With the use of targeted antiviral prophylaxis, if 80% of the persons maintained prophylaxis for up to eight weeks, the epidemic could be contained, and the model predicted a reduction to an illness attack rate of 2% (95% CI: 0.2,16) and a death rate of 0.04/1000 persons (95% CI 0.0003, 0.25). If you extrapolate their data to the US population, this would require 1.9 billion doses of antiviral agent. This is equivalent to 27 million doses in the Irish population. These figures seem

unrealistically large, and the authors acknowledged this. They stated that using a targeted antiviral strategy using whatever stocks are available would save many lives and constitute the most prudent use of influenza antiviral agents. They also acknowledged that a successful strategy would require the identification of the index cases in households, preschools, schools, and other institutional settings. It would also be effective for healthcare personnel, other essential workers and first responders. They concluded that targeted antiviral prophylaxis has potential as an effective measure for containing influenza until adequate quantities of vaccine are available.

In 2005 Ferguson et al reported on strategies for containing an emerging influenza pandemic in Southeast Asia using targeted mass prophylactic use of antiviral drugs as a containment strategy.(11) A combination of geographically targeted prophylaxis and social distancing measures could eliminate an emergent pandemic strain, provided the reproductive number (average number of secondary cases generated by a typical primary case) is less than 1.8. The effectiveness of this strategy was critically dependent on rapid early identification of the original cluster of cases, rapid sensitive case detection, and ability to deliver drugs to the target groups rapidly, i.e. within 48 hours. Since publication of this article, WHO has developed a pandemic influenza draft protocol for rapid response and containment.(12)

In 2006, Ferguson, Cummings et al further investigated the use of various strategies, including antivirals for mitigating an influenza pandemic.(13) Using an individual based simulation model of pandemic transmission for the UK and the US, they found that treatment of clinical cases can reduce transmission, but only if antivirals are given within a day of symptoms starting. Antiviral prophylaxis of household members when a case is identified in a household is effective in reducing cumulative attack rates by at least one third and peak attack rates by a half, but requires an antiviral stockpile large enough to treat 46% or 57% of the population, at Ro of 1.7 and 2.0 respectively. In addition if classmates or close work colleagues of a clinical case are targeted for antiviral prophylaxis, this also has a dramatic impact on

attack rates but this requires stockpiles of 72% or 102% of the population size for Ro of 1.7 and 2.0 respectively.

5.3.3 NAI: Antiviral Resistance

Up to the 2007/2008 flu season, the frequency of resistance emergence was low during treatment with NA inhibitors. Resistance to zanamivir has been observed only in an immunocompromised host to date.[14] With oseltamivir, less than one per cent of immunocompetent adults and from 8 to 18% of infected children shed resistant viruses during or immediately after treatment.[15] Until the 2007/2008 season, these resistant variants mainly showed decreased virulence and infectivity.

In late January 2008 antiviral drug susceptibility surveillance of seasonal influenza viruses in Europe (the EU-EEA-EFTA countries) revealed that some of the A (H1N1) viruses circulating this season (winter 2007-8) were resistant to the antiviral drug oseltamivir through mutation at position 274 in the viral neuraminidase gene.[16] Analysis of 2499 A/H1N1 viruses from 24 European (European Union, EEA/EFTA) countries isolated between November 2007 and early April (data archived on April 23rd) showed that 577 were resistant to oseltamivir, but retained sensitivity to zanamivir and amantadine. The proportion of A(H1N1) viruses that are oseltamivir resistant varied significantly across Europe. The highest proportion of resistant viruses to date have been in Norway where 168 (67%) of the 252 samples are resistant to oseltamivir, whereas no resistant viruses have been detected in five of the 24 countries. In Ireland, 9.1% are resistant. There is also evidence of similarly resistant viruses in North America and the Far East.

There is no evidence that the appearance of these new viruses is related to use of oseltamivir. The 07/08 winter season is the first time there has been widespread and sustained transmission of such viruses in the community. Similar viruses have been seen before, but usually following treatment. Such viruses previously have not been able to readily transmit and have rapidly disappeared. At this stage the significance of these findings remains

uncertain. The emergence of drug resistance in the context of limited drug use is unexpected, and the extent of future circulation is difficult to predict.

In 2005, Mai Le et al reported isolation of drug resistant H5N1 virus from a Vietnamese girl.[17] This 15-year-old girl was treated with a prophylactic dose for three days, and then subsequently was given a therapeutic dose for seven days. She recovered. She had not had any direct contact with poultry, but had cared for her brother who had documented H5N1 infection. Although the virus was resistant to oseltamivir, it was sensitive to zanamivir. Since that report, there have been two additional cases reported where H5N1 virus, which is resistant to oseltamivir, was isolated.[18] In these patients, the viruses were isolated during or shortly after a course of oseltamivir at therapeutic doses. Both of these patients died. The authors stated that at least in some patients with A(H5N1) infection, treatment with recommended doses of oseltamivir incompletely suppresses viral replication, and that this can allow the infection to proceed, but also provides opportunities for drug resistance to develop.

Ferguson et al have modelled the potential spread of drug resistant influenza infections during community-based use of antivirals.[19] Looking at different scenarios of usage of oseltamivir, ranging from treatment of 6% of symptomatic infections, to treatment of 40% of symptomatic infections and PEP following 5% of exposure events, they found that the currently isolated strains of influenza exhibiting resistance are unlikely to be transmitted in a frequency that would significantly interfere with the efficacy of even high levels of drug usage. However, this work pre-dated the emergence of resistance of A(H5N1) to oseltamivir in the 2007/2008 season.

The potential human-to-human transmissibility of these variants is a major public health concern. If the A(H1N1) resistance to oseltamivir seen in the 2007/2008 season persists, it could affect our ability to use antiviral drugs during a pandemic, if this resistance were present also in the pandemic strain.

5.3.4 M2 inhibitors (amantadines) in treatment

In 2004, a Cochrane review of the effectiveness and safety of amantadine and rimantadine in healthy adults was carried out. All controlled trials registered up to September 2003 were included. Amantadine prevented 25% of influenza like illness (ILI) cases (95% confidence interval (CI) 13% to 36%), and 61% of influenza A cases (95% CI 35% to 76%). Amantadine reduced duration of fever by one day (95% CI 0.7 to 1.3). Rimantadine demonstrated comparable effectiveness, but there were fewer trials and the results for prevention were not statistically significant. Both amantadine and rimantadine induced significant gastrointestinal adverse effects. Adverse effects of the central nervous system and study withdrawals were significantly more common with amantadine than rimantadine. They concluded that amantadine and rimantadine have comparable effectiveness in the prevention and treatment of influenza A in healthy adults, although rimantadine causes fewer adverse effects than amantadine.

Several placebo controlled prospective studies, during the 1968 H3N2 pandemic and 1977 H1N1 pandemic reappearance, showed that amantadine and rimantadine provided therapeutic benefit in uncomplicated illness in previously healthy adults with reductions in fever, symptom severity and time to resuming normal activities.[20;21] No prospective trials to date have documented reductions in complications, antibiotic use or hospitalisations.[22]

5.3.5 M2 inhibitors (amantadines) as prophylaxis

Placebo controlled, prospective studies of seasonal prophylaxis with amantadine and rimantadine during the 1968 H3N2 pandemic and the 1977 H1N1 reappearance established that these agents are effective for chemoprophylaxis in naïve adult populations. The level of protection against illness averages approximately 60-70%, slightly lower than that achieved with inter-pandemic influenza.[20] However one study during the 1968 pandemic of short-term (10 days) post exposure amantadine prophylaxis in families, along with treatment of the index case, found low protective efficacy against illness (6%) and none against infection.[23] This may have been due to emergence of resistant variants, though this was not studied at the time.

5.3.6 M2 inhibitors: Antiviral Resistance

As the amantadines block the M2 ion channel protein, single nucleotide changes in any one of several sites within the transmembrane region of M2 can lead to high-level antiviral resistance. These variants are resistant to all M2 inhibitors, but seem to retain full virulence, infectivity and ability to transmit.[9] M2 inhibitors emerge rapidly when these drugs are used for treatment, and roughly 30% of treated children or adults will shed resistant variants from two to five days after initiation of treatment. In immunocompromised patients, this frequency is higher. In addition, in nursing home populations, resistant variants have caused failures of chemoprophylaxis and severe illness. Stilianakis et al developed a model for the emergence of drug resistant influenza viruses in a closed population single wave epidemic.[24] This model, based on treatment with amantadine and rimantadine, predicted that chemoprophylaxis of susceptibles (without treatment of symptomatic cases) led to lower levels of infection and that the emergence of drug resistance would be low. If treatment was combined with chemoprophylaxis, there was a similar effect on the number of infections and low likelihood of emergence of resistant variants. Treatment alone of symptomatic persons did not slow the epidemic and had a variable risk of developing drug resistance. However this model assumed that variant viruses were less transmissible than wild type viruses, and if this is not the case, then prophylaxis failures are expected to be common due to resistant virus. Ferguson et al, when modelling the potential spread of drug-resistant influenza stated that because amantadine resistance mutations in the M2 virus protein are not associated with a detectable loss in viral function, and that transmissibility, experimental infectivity and pathogenesis of resistant mutants are comparable to wild type, their analysis predicts that widespread use of amantadines for the treatment of symptomatic influenza could result in substantial transmission of resistant virus.[19] Recently H5N1 isolates recovered from children and adults in Viet Nam and Thailand have been resistant to M2 inhibitors.[22]

5.3.7 Oseltamivir----- side effects

Hypersensitivity to oseltamivir is listed as a contraindication. Side effects of oseltamivir are listed in appendix A, with nausea and vomiting the most commonly reported.

More recently there have been reports mostly from Japan of neuropsychiatric events including delirium, convulsions, and encephalitis mainly in children and adolescents who were taking oseltamivir. Japan has the highest usage of oseltamivir worldwide.[25] In March 2007, Tokyo's Ministry of Health and Welfare instructed the Japanese distributor of oseltamivir to include a warning not to give the drug to patients aged between 10 and 19, after reports that at least 18 Japanese children taking Tamiflu have died as a result of irrational behaviour. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) reviewed these reports. The relative contribution of the drug to these events is unknown. The EMEA's Committee for Medicinal Products for Human Use (CHMP) reviewed adverse drug reactions to the drug in 2005 and in 2007.[26;27] In 2007, it recommended an update of the product information to inform healthcare professionals and patients about neuro-psychiatric side effects. The recommended wording for patients is that "Convulsion, depressed level of consciousness, abnormal behaviour, hallucinations and delirium have been reported during Tamiflu administration, leading in rare cases to accidental injury. Patients, especially children and adolescents, should be closely monitored and their healthcare professional should be contacted immediately if the patient shows any signs of unusual behaviour". The current package leaflet[28] states the following for adults and adolescents "Influenza can be associated with a variety of neurologic and behavioural symptoms which can include events such as hallucinations, delirium, and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease. During Tamiflu treatment, events like convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares) have been reported, in a very few cases resulting in accidental injury, in some instances with fatal outcome. These events were reported primarily among children and adolescents and

often had an abrupt onset and rapid resolution. The contribution of Tamiflu to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Tamiflu."

5.3.8 Oseltamivir in pregnancy and for those <1 year of age

On 7th May, 2009, following a review of all the available evidence by the CHMP of the EMEA, that seems to show that no new safety risks to the foetus are connected to the use of oseltamivir in pregnant women, the CHMP concluded that overall the data suggest that the benefit of using oseltamivir in pregnant or breastfeeding women outweighs the risk in the context of novel influenza A (H1N1) in a pandemic situation.[29] (For seasonal influenza epidemics oseltamivir should not be used during pregnancy/breast feeding unless the potential benefit to the mother justifies the potential risk to the foetus/nursing infant.[1;29])

The CHMP of the EMEA acknowledged that limited data are available supporting the use of oseltamivir in children below 1 year of age. However considering the urgent need for recommendations to treat this population, in case of pandemic influenza being declared by WHO in the context of the novel influenza A (H1N1) outbreak, the CHMP recommends <u>treating</u> children below 1 year of age with oseltamivir.[29] The appropriate dosage to treat children below 1 year of age is 2-3mg/kg twice daily during 5 days. The paediatric suspension or dilution of the capsules of Tamiflu can be used to prepare the dose in children below 1 year of age. Children below 1 year of age should be treated under medical supervision. However in case of pandemic influenza, this recommendation could potentially place huge burden on hospital resources and therefore, the CHMP strongly recommends that at least children below 3 months of age are treated under medical supervision in hospital. The post-exposure prophylaxis of children below 1 year of age should be very carefully considered by prescribers. If it is decided to prescribe oseltamivir to prevent influenza for children below 1 year of age who have been exposed to the virus, the appropriate dose should be 2-3mg/kg once a day during 10 days. (For seasonal influenza oseltamivir is only indicated for children aged one year and older.)

5.3.9 Zanamivir in pregnancy

Zanamivir (Relenza) has in animal studies been shown to cross the placenta and to be secreted in breast milk. The non-clinical data are not indicative of any relevant cause for concerns regarding the safe use of zanamivir at recommended doses. The CHMP of the EMEA states that taken together the overall data suggest that the benefit of using zanamivir in pregnant or breastfeeding women outweighs the risk in the context of a novel influenza A (H1N1) in a pandemic situation.[29] (For seasonal influenza epidemics zanamivir should not be used during pregnancy unless the expected benefit to the mother is thought to outweigh any possible risk to the foetus and is not recommended in mothers who are breast feeding.[1;29])

5.3.10 Oseltamivir stability

Due to the public health emergency linked to the current risk of pandemic influenza (as a result of the recent outbreak of the novel influenza virus A (H1N1)), and based on data made available regarding the stability of oseltamivir 30mg, 45mg and 75mg capsules for an additional period of 2 years, the CHMP of the EMEA recommends that boxes of Tamiflu capsules should not be discarded where the expiry date has already passed.[29] For these batches an updated expiry date should be determined by adding a further period of 2 years to the stated expiry date. The conditions of storage play a role in the stability of medicinal products. It is of great importance that these boxes have always been kept and remain stored below 25^{o}C.

5.4 Expert Group recommendations on use of antivirals in the pandemic alert period and during a pandemic

5.4.1 Phases 2-5 (Present Position)

Oseltamivir has been used to treat avian influenza cases in Thailand, Viet Nam,Turkey and other affected countries, and to prevent infection in close contacts. The drug has also being given prophylactically to health care workers, family members and close contacts of cases. WHO has recently

published evidence based Rapid Advice Guidelines on the pharmacological management of humans infected with avian influenza A (H5N1) virus.[30] **The Expert Group advises that Ireland follows the WHO recommendations for treatment of cases as described below:**

Where neuraminidase inhibitors are available:

- **Clinicians should administer oseltamivir treatment (strong recommendation); zanamivir might be used as an alternative (weak recommendation). The quality of evidence if considered on a continuum is lower for the use of zanamivir compared to oseltamivir.**
- **Clinicians should not administer amantadine or rimantadine alone as a first-line treatment (strong recommendation).**

Recommendations regarding the use of antivirals for prophylaxis in contacts of human cases are detailed in the avian influenza Chapter 11.

If an outbreak of highly pathogenic avian influenza occurs in birds in Ireland, **the Expert Group advises that antivirals should be used in the prevention and control of avian influenza in occupational groups and other contacts exposed to dead or diseased birds. Antivirals should be used for personal protection of these workers and also to protect against transmission.** This is detailed further in Chapter 11 and Supplement 11.

Pandemic period

Antivirals may be used for treatment or prophylaxis of influenza. In a pandemic situation antivirals will **primarily** be used for treatment of influenza cases. Antivirals will have great importance as the only influenza-specific medical intervention for reducing morbidity and mortality. It is recognised that pandemic planning is a dynamic process. As the definition of risk is likely to change over time, recommendations for use of antivirals must be kept under review. In particular, the Expert Group will need to review the epidemiological data before final recommendations are decided in the setting of an imminent

pandemic, and during its course. The decision making process will be guided by relevant expert advice from the European Commission and the World Health Organization.

Antivirals will only be used in a community once the pandemic virus is detected in the community. The initial antiviral drug of choice for use will be oseltamivir. If however, evidence emerges that resistance is developing to oseltamivir and/or the clinical attack rate is very high, zanamivir will then be used. If the attack rate is very high, then it might be best to use zanamivir in those age groups where administration of the inhaled drug would not pose a problem, such as workers, including healthcare workers, and in the community rather than the hospital setting. Detailed guidance on indications for use will be developed if this situation arises, based on experience of treatment of the pandemic virus at the time.

5.4.2 Antiviral use in Ireland at the start of a pandemic

Antivirals have a role in trying to contain infection or slow transmission at a stage when isolated cases or small outbreaks are occurring, and when transmission is not occurring efficiently. **The Expert Group advises that at the start of the pandemic when isolated cases or small outbreaks are occurring, influenza cases should be treated with antivirals, and that contact tracing and short-term post-exposure prophylaxis to prevent infection developing in close contacts including family members and health care workers be carried out**. See treatment algorithms (Appendix B and C).

5.4.3 Antiviral use in Ireland during the pandemic

In the event of a pandemic, and a clinical attack rate of 25%, as per the HPA empirical model recommended for use in Ireland, it is likely that there will be sufficient quantities of antiviral drugs to be able to treat all early symptomatic cases. Antivirals should only be used where there is surveillance evidence or laboratory confirmation of influenza in the community/region.

If however the clinical attack rate is high (50% as per the worst case scenario outlined in Chapter 3) it will be necessary to prioritise or target specific groups for treatment. In advance of a pandemic, based on current knowledge of risk of mortality and morbidity due to influenza, the following priorities have been identified. **This is subject to change, once the epidemiology of the pandemic strain is known.**

Expert Group advice on priority groups for antiviral treatment during an influenza pandemic – *if stockpiled supplies are not sufficient to treat all symptomatic persons*

Group 1: Treatment of persons hospitalised for influenza (if hospitalised within 48 hours of onset of symptoms). To be consistent with the goal of reducing morbidity and mortality and considering the optimal use of antiviral drugs in relation to onset of illness, those who are hospitalised within the first 48 hours of onset of illness should be highest priority for treatment. Treatment with oseltamivir may be considered in those who are hospitalised more than 48 hours after onset of symptoms, although its effectiveness in this situation is not established.

Group 2: Treatment of ill health care and emergency services workers. Considering the essential role that health care workers and emergency service workers will have in the pandemic response, influenza infection in these groups, identified within the first 48 hours of onset of illness, should be high priority for treatment.

Group 3: Treatment of ill high risk persons* in the community. Persons with underlying heart and lung conditions or those who are immunocompromised, and who present for medical care within 48 hours of onset of symptoms, will also be considered high priority for treatment since they are at high risk of complications.

***NOTE: during a pandemic the definition of high risk persons may change based on epidemiological evidence.*

This categorisation is based partly on the priority groups outlined in the Canadian Pandemic Plan (February 2004) and reflects general guidance from the World Health Organisation.[31]

5.5 Planning requirements for an effective antiviral strategy

Identifying the antivirals to be stockpiled, the goals and the priority groups are only part of an effective antiviral strategy. For an effective antiviral strategy, a secure supply, with a well planned distribution and monitoring system, and the ability to target priority groups (if necessary) will be essential. In addition, it will require the availability of diagnostic tests (particularly in the early stages), and clinical case definitions to distinguish influenza from other respiratory symptoms, as well as enhanced surveillance to identify changes in the epidemiology of the virus, emergence of resistance to antivirals, and for drug related adverse events. Also, there is a requirement to develop clinical guidelines on their appropriate use, and study protocols to assess the effectiveness in treatment and prophylaxis, as well as effective materials for communication with the public and health care workers on antivirals.

The Expert Group advises that it is critical that sufficient attention is given to the significant logistical problems that will arise in achieving timely and appropriate distribution and delivery of antiviral drugs, and that sufficient resources are put into planning a robust capacity to deliver antiviral drugs as needed as quickly as possible.

5.5.1 Decision on stockpiling of antivirals

In February 2005, the National Pandemic Influenza Expert Group reviewed recommendations for the use of antivirals in line with international guidance.

Based on this assessment, it advised that pandemic planning be based on the assumption that the virus most likely to cause an influenza pandemic will be an avian influenza virus or avian influenza derived.

It also advised that oseltamivir should be stockpiled in view of its effectiveness against avian/avian-related influenza. The possibility of recommending the

use of amantadine in future if the evidence on the potential pandemic virus changes has not been ruled out.

The Expert Group also advised that a supply of the Active Pharmaceutical Ingredient (API), oseltamivir phosphate powder, should be purchased to treat young children between the ages of one and five years. Arrangements have been put in place so that API powder will be converted to paediatric capsules, which will be used for all children aged one to 11 years of age.

Following consideration of the expert advice, Ms Mary Harney T.D, then Tánaiste and Minister for Health and Children decided that one million treatment packs of Oseltamivir (Tamiflu) should be stockpiled. This quantity is sufficient to treat 25% of the population and is in line with international trends. 63kg of the API has also been purchased.

Subsequently, the Expert Group reviewed recommendations with regard to stockpiling of zanamivir (Relenza) in addition to oseltamivir. This was in light of a case report of suspected resistance to oseltamivir, detailed earlier in this chapter. The Expert Group advised that it would be prudent to stockpile a second antiviral agent that would allow for treatment of 20% of the population. The Minister for Health and Children accepted this advice.

Zanamivir has been shown to be effective against seasonal influenza. This antiviral agent could be used if resistance to oseltamivir developed in significant numbers of cases. However it cannot be used in young children and in some adults, due to the drug's method of administration (inhalation).

706,000 packs of zanamivir (Relenza) have now been ordered. This is sufficient to cover 20% of the population over the age of seven. This stockpile is now complete.

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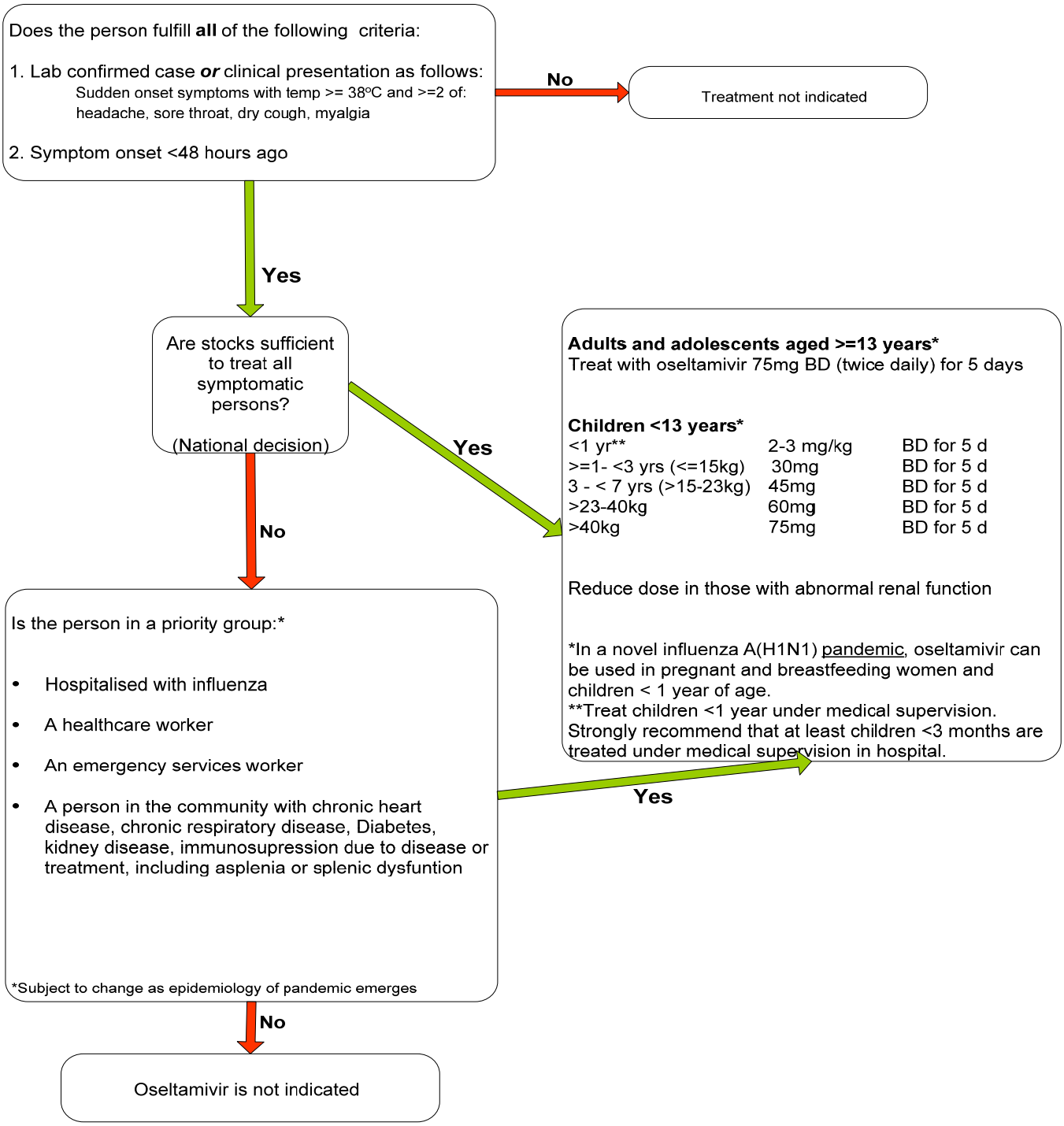
Appendix A Properties of the relevant influenza antiviral medicinal products
(taken from the EMEA report entitled Updated review of influenza antiviral medicinal products for potential use during pandemic[1])

Property	Amantadine	Oseltamivir	Zanamivir
Mode of action	M2 ion channels blockade	Neuraminidase inhibition	Neuraminidase inhibition
Adverse effects	Common-uncommon: CNS effects, nausea, vomiting, palpitation Rare. Cardiac arrhythmias, seizures	Common: Nausea, vomiting, headache Rare to very rare: hypersensitivity skin reactions hepatitis, elevated liver enzymes, neuro-psychiatric events	Very rare: bronchospasm, allergic-type reaction, dyspnoea, throat tightness or constriction and rash, urticaria
Warnings (some variation at the member state level)	Prostatic hypertrophy Narrow angle glaucoma Agitation and confusion History of seizure, psychosis or delirium Severe hepatic or renal dysfunction	Hypersensitivity reactions Observation of oseltamivir-treated children	Bronchospasm and/or decline in respiratory function
Use during pregnancy*	Not recommended	Only if the risk of infection exceeds the risk to the foetus*	Only if the risk of infection exceeds the risk to the foetus*
Use in children*	Very limited data	Used in children from one year of age Not recommended for children < 12 Mo.* Studies are ongoing to establish posology and safety in these children.	Limited data on children Not suitable for children <5 years
Contraindications (some variation at the member state level)	Hypersensitivity to the product Severe renal failure History of convulsions History of gastric ulcerations Severe heart disease	Hypersensitivity to the product	Hypersensitivity to the product
Drug-drug interactions	Anticholinergic agents Several medicinal products affecting CNS Combination diuretics Quinine, quinidine	Not known	Not known
Effect: treatment prophylaxis	Modest Good initially, may be lost due to resistance	Modest Good	Modest Good
Route of administration	Oral	Oral	Inhalation with a device
Site of action	Systemic	Systemic	Respiratory tract
Effect on past pandemic strains	Yes (*in vitro and in vivo*)	Yes (*in vitro*)	Yes (*in vitro*)
Effect on H5N1 "bird flu"strains	Questionable	Yes (*in vitro*, experimentally *in vivo*)	Yes (*in vitro,* experimentally *in vivo*)
Resistance	Common during treatment Primary resistance by many H5N1 strains	Rare (except in treatment of children)	Very rare
Formulations	Tablets	Capsules, powder for solution, extemporaneous formulations	Powder for inhalation

*On the 7th May 2009 the CHMP of the EMEA recommended that, in the case of a pandemic influenza declared by the WHO in the context of the novel influenza A (H1N1) outbreak, oseltamivir and zanamivir can be used in women who are pregnant or breastfeeding and oseltamivir can be used in children <1 year of age (see sections 5.3.8 - 5.3.9).[29]

Appendix B Oseltamivir treatment algorithm for pandemic influenza



Appendix C Algorithm for public health doctors prescribing oseltamivir as prophylaxis for human contacts of novel influenza

Please see www.hpsc.ie for most up to date version.

Post-exposure Prophylaxis (PEP) for close contacts of probable[1] or confirmed[2] human case(s) of Influenza A(H1N1) in WHO Pandemic Alert Phase 5

PEP for close contacts of probable and confirmed cases is a control measure to be applied before there is a wide spread sustained transmission within Ireland. Therefore this policy may be modified if the situation changes.

Post exposure prophylaxis is indicated for close contacts that were exposed to a probable or confirmed case during the period when the case was symptomatic and for 24 hours before onset of symptoms AND the contact's last exposure occurred no more than 7 days previously.
Any probable or confirmed human case of Influenza A(H1N1) should be notified to the local DPH as soon as possible.

Category of Contact		Actions
1	Household members of a case	YES → *Voluntary Quarantine of Contact

THEN

Quarantine Unnecessary

2	Roommates of cases in hospitals or institutions e.g. nursing homes	Yes →
3	People occupying the same room with a case (<1metre) for at least 4 hours	Yes →
4	Contact with fomites contaminated with respiratory secretions (e.g. touching used tissues or hands of infectious person)	Yes →
5	Travellers by plane sitting in the same row or in the 2 rows ahead or behind on flight of ≥ 4 hours of a symptomatic (sneezing and coughing) case OR persons caring for such a passenger	Yes →
6	Health or social care workers who provided direct clinical/personal care or who or who examined a symptomatic patient without wearing appropriate PPE**	Yes →
7	All others not classified as contacts	→ Information leaflets may be helpful but no other action is required.

- Start Antiviral PEP[3] as soon as possible unless more than 7 days have elapsed since last exposure. Post exposure prophylaxis should be taken for 10 days.[3]
- Provide information leaflets
- Coordinate active follow up for 7 days after last exposure to the case.[4]
- Taking serology may be relevant in certain circumstances in order to better understand transmission. In these circumstances paired samples should be taken (first sample when identified as a contact and second sample 14 days later).
- Contacts who work on pig farms should remain off work for 7 days as soon as diagnosis is suspected
- **If contacts are in a school, contact HPSC directly**

If a contact becomes unwell, they should contact local DPH and s/he should liaise with HPSC

***Duration of Voluntary Quarantine:**
Should last 7 days from last unprotected contact
****Appropriate PPE is:**
Routine care: (including taking nasal and throat swabs for viral testing) Surgical mask, Plastic Apron, Gloves (and goggles if risk of splashing/spraying)
Aerosolising generating procedures: FFP2 or FFP3 respirator mask, goggles, long-sleeved gown and gloves.

Footnotes:
1. Probable case: Any person meeting the clinical and epidemiological criteria AND with a positive test for influenza A (see Algorithm for the management of persons with acute febrile respiratory illness).
2. Confirmed case: Any person with laboratory confirmation of influenza A(H1N1).
3. Refer to relevant dosing schedule for antiviral prophylaxis in Advice of the Pandemic Influenza Expert Group
4. Active follow up: contacts to self-monitor for symptoms for 7 days, check temp twice daily. Staff from local office of Director of Public Health will make contact daily to ensure asymptomatic.

In case of uncertainty, discuss with your Director of Public Health

Adapted from material provided by HPA London