DRAFT SCIENTIFIC ADVICE FOR CONSULTATION

ECDC PRELIMINARY SCIENTIFIC ADVICE

Expert Opinion on neuraminidase inhibitors for prevention and treatment of influenza

Review of recent systematic reviews and meta-analyses

ecdc
EUROPEAN CENTRE FOR
DISEASE PREVENTION
AND CONTROL

THIS DRAFT SCIENTIFIC ADVICE IS SUBJECT TO A PUBLIC CONSULTATION PROCESS. THE RESULT OF THAT PROCESS MAY LEAD TO CHANGES IN THE FINAL REPORT

Stockholm, February 2016

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Glossary

Accelerated failure-time model	A model for survival analysis that models the relation between exposure (or treatment) and survival time.
Advisory Forum	The Advisory Forum advises the Director of the Centre on the quality of the scientific work undertaken by ECDC. It is composed of senior representatives of national public health institutes and agencies, nominated by the Member States on the basis of their scientific competence, and a public health official from the European Commission.
Attack rate	A form of incidence that measures the proportion of persons in a population who experience an acute health event during a limited period (e.g. during an outbreak.).
Case-fatality ratio	The proportion of persons with a particular condition (e.g. patients) who die from that condition. The denominator is the number of persons with the condition; the numerator is the number of cause-specific deaths among those persons.
Contact	Exposure to a source of an infection; a person who has been exposed.
Effectiveness	The extent to which a specific intervention, procedure, regimen, or service, when deployed in the usual circumstances of living and practice, does what it is intended to do for a specified population. A measure of the extent to which an intervention or policy fulfils its objectives in practice. Estimates derived from observational studies.
Efficacy	The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions. If possible, the determination of efficacy should be based on the results of randomised controlled trials.
Epidemic	The occurrence of more cases of disease, injury, or other health condition than expected in a given area or among a specific group of persons during a particular period. Usually, the cases are presumed to have a common cause or to be related to one another.
Expert Opinion	A scientific view or comment of designated experts based on a review of scientific evidence and/or expert opinion (ECDC definition).
Exposure	Having come into contact with a cause of, or possessing a characteristic that is a determinant of, a particular health problem.
Hazard ratio	A theoretical measure of the probability of occurrence of an event per unit time at risk.
Health technology assessment	The systematic evaluation of properties, effects, and/or impacts of health care technology. Its main purpose is to inform technology-related policymaking in health care.
Immunocompromised patients	Patients with impaired immunity.
Incidence	A measure of the frequency with which new cases of illness, injury, or other health condition occurs among a population during a specified period.
Incubation period	The time interval from exposure to an infectious agent to the onset of symptoms of an infectious disease.
Index case	An index case is the case through which an outbreak was first discovered, i.e. the first patient to be observed by the health care system or by the health authorities.
Individual data	Values or observations from each record (also called raw data).
Infection control practices	Programmes to prevent nosocomial infections that are comprehensive and include surveillance and prevention activities as well as staff training.

Intensive care unit	An intensive care unit (ICU), also known as an intensive therapy unit or intensive treatment unit (ITU) or critical care unit (CCU), is a special department of a hospital or health care facility that provides intensive care medicine.
Intention to treat	A method of analysis for randomised trials in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment. In RCTs for neuraminidase inhibitor efficacy includes all ILI cases, including cases not confirmed in laboratory.
Intention to treat - infected	Analysis of only laboratory -confirmed, influenza-infected participants of influenza trials.
Isolation	The separation of infected persons to prevent transmission to susceptible ones. Isolation refers to separation of ill persons; quarantine refers to separation of potentially exposed but well persons.
Long-term care facility	Health care facility for inpatients that require a long term stay.
Morbidity	Disease; any departure, subjective or objective, from a state of physiological or psychological health and well-being.
Mortality rate	Proportion of deaths in a given population and during a given time.
Neuraminidase inhibitor	A class of drugs which block the neuraminidase enzyme preventing the reproduction of the influenza virus in the host cell.
Observational study	A study in which the investigator observes rather than influences exposure and disease among participants. Case-control and cohort studies are observational studies (see also study, experimental).
Odds ratio	An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure.
Outbreak	The occurrence of more cases of disease, injury, or other health condition than expected in a given area or among a specific group of persons during a particular period. Usually, the cases are presumed to have a common cause or to be related to one another.
Pandemic	An epidemic occurring over a widespread area (multiple countries or continents) and usually affecting a substantial proportion of the population.
Polymerase chain reaction	A laboratory technique used to make multiple copies of a segment of DNA. PCR is very precise and can be used to amplify, or copy, a specific DNA target from a mixture of DNA molecules.
Population	The total number of inhabitants of a geographic area or the total number of persons in a particular group (e.g. the number of persons engaged in a certain occupation).
Post-exposure prophylaxis	Any preventive medical treatment started immediately after exposure to a pathogen (such as a disease-causing virus), in order to prevent infection by the pathogen and the development of disease.
Poultry	Domesticated bird raised for food.
Public health	The science and art of preventing disease, prolonging life and promoting health through organised efforts and informed choices of society, organisations, public and private, communities and individuals.

Per protocol population	The per protocol population in randomised clinical trials is restricted to participants who fulfil the study protocol in terms of eligibility, interventions, and outcome assessment. The analysis of the per-protocol population restricts the comparison of treatments to the ideal patient, that is, those who adhered perfectly to the clinical trial instructions as stipulated in the protocol. This analysis is known as the per protocol analysis. A per-protocol analysis envisages determining the biological effect of a new drug. However, by restricting the analysis to this selected patient population, it does not show the actual impact of the drug when used in real life when patient groups are not studied in RCTs and not all will comply with treatment recommendations. Therefore it is common to analyse also the intention-to-treat (ITT) population including individuals regardless of whether or not they completed or received the treatment.
Randomised clinical trial/randomised controlled trial	A clinical trial in which persons are randomly assigned to exposure or treatment groups.
Re-assortment	A form of recombination in which two (or more) influenza viruses, of the same or different subtypes, co-infect a single cell and exchange RNA segments to form genetically novel viruses. The segmented genome of the influenza virus facilitates reassortment.
Relative risk	A general term for measures of association between exposure and outcome in epidemiological studies, including risk ratio, rate ratio.
Risk	The probability that an event will occur (e.g. that a person will be affected by, or die from, an illness, injury, or other health condition within a specified time or age span).
Risk assessment	The qualitative and quantitative estimation of the likelihood of adverse effect that may result from exposure to specified health hazards or from the absence of beneficial influences.
Risk factor	An aspect of personal behaviour or lifestyle, an environmental exposure, or a hereditary characteristic that is associated with an increase in the occurrence of a particular disease, injury, or other health condition.
Risk group	A group of persons whose risk for a particular disease, injury, or other health condition is greater than that of the rest of their community or population.
Safety population	In randomised clinical trials the population that was randomised to receive treatment and complied with at least one dose of the treatment under study
Scientific evidence	Information gathered from scientific research that can support or counter a hypothesis or theory.
Transmission	Any mode or mechanism by which an infectious agent is spread to a susceptible host.
Variable	Any characteristic or attribute that can be measured and can have different values.

Executive summary

The neuraminidase inhibitors oseltamivir and zanamivir, currently authorised in the European Union/European Economic Area (EU/EEA) for treatment and prophylaxis of influenza disease (including seasonal, pandemic and zoonotic influenza) have been the subject of debate concerning their effectiveness and safety, as well as the appropriateness of stockpiling these drugs for use in future influenza pandemics.

In 2013, the ECDC Advisory Forum requested an assessment of the evidence for use of antivirals in influenza outbreak settings, specifically during institutional outbreaks and new and emerging influenza virus outbreaks. In August 2014, the EU Health Security Committee requested a review of the evidence, and on 10–11 February 2015, an expert consultation with international public health experts was convened in Stockholm to review data presented in newly conducted systematic reviews/meta-analyses of clinical studies on influenza antivirals, and in order to develop an ECDC Expert Opinion.

Three new large systematic reviews and meta-analyses assessing efficacy, effectiveness and safety of two licensed neuraminidase inhibitors, oral oseltamivir and inhaled zanamivir, were reviewed: The 2014 Cochrane Collaboration report (Jefferson et al.), the 2015 MUGAS study (Dobson et al.) and the 2014 PRIDE study (Muthuri et al.). Additional reviews and studies were considered where appropriate.

The 2014 Jefferson et al. report describes a systematic review with meta-analyses of clinical study reports from published and unpublished randomised, placebo-controlled trials (RCTs) assessing treatment or prophylaxis with oseltamivir (20 trials) and zanamivir (26 trials) up to July 2013, most of which were conducted among otherwise healthy persons in the community with influenza-like illness during seasonal epidemics.

The Dobson et al. review reported a meta-analysis of individual patient data of 12 RCTs assessing treatment of adults with oseltamivir. Eleven of these trials were also included in the Cochrane report.

In the observational study by Muthuri et al. investigators assembled data directly from study sites, assessing the association between use of neuraminidase inhibitors and mortality in a meta-analysis of individual participant data from 29 234 patients (all ages). The data were collected in 78 study sites located in 38 countries with laboratory-confirmed or clinically diagnosed pandemic influenza A(H1N1)pdm09 infection admitted to hospital.

The reviews by Jefferson et al. and Dobson et al. conclude that, for adults, oseltamivir decreases the time to first alleviation of symptoms of influenza-like illness (ILI) by 16.8 hours (95% CI 8.4–25.1) and 17.8 hours (95% CI -27.1 to -9.3), respectively. The time to alleviation of all symptoms among the influenza-infected sub-population was decreased by 25.2 hours (95% CI 16.0–36.2) in the Dobson et al. analysis.

Additional analyses within the Jefferson et al. and Dobson et al. reviews documented a statistically significant reduction in patient-reported pneumonia, a reduction in lower respiratory tract infections and a decrease in hospital admissions following influenza diagnosis among oseltamivir-treated groups. The individual RCTs included in these meta-analyses were not, however, designed or powered to assess these severe clinical outcomes, thus limiting the quality of evidence on such outcomes.

Observational studies have also indicated reductions in severe outcomes (patients receiving intensive care or cases of death). In the pooled individual data from the observational studies from the three pandemic waves of the influenza A(H1N1)pdm09 in 2009–2011, analysed by Muthuri et al. decreased mortality was shown to be associated with the use of neuraminidase inhibitors among hospitalised patients (OR 0.81; 95% CI 0.70–0.93). However, in this analysis, the researchers were able to access data from only 20% of the global sites that were identified to have done clinical research among hospitalised influenza patients during the pandemic, thereby limiting the power of the analysis but also raising questions about generalisability and selection bias.

All three reviews point to the importance of initiating treatment early, ideally within 48 hours (within 36 hours in the case of zanamivir in children) of onset of symptoms. However, observational studies, including the analysis by Muthuri et al. indicate some mortality benefit for neuraminidase inhibitors (NAI) therapy started up to 4–5 days after symptom onset in hospitalised patients.

With regard to prophylaxis, the review by Jefferson et al. assessing pre- or post-exposure prophylactic oseltamivir observed a 3.05% reduction in absolute risk for laboratory-confirmed influenza A among groups receiving oseltamivir in four RCTs (RR 0.45; 95% CI 0.30–0.67). The trials were conducted in ambulatory community members and nursing home residents. Assessing efficacy in a household setting Jefferson et al. report an absolute risk reduction of symptomatic influenza of 13.6% (RR 0.20; 95% CI 0.09–0.44). Similarly, Okoli et al. reported an association in an RCT between reduction in laboratory-confirmed influenza A(H1N1) infection and prophylactic treatment with oseltamivir (OR 0.11; 95% CI 0.06–0.20), and in four observational studies of zanamivir (0.23; 05% CI 0.16–0.35) [1]. No studies focusing on prophylaxis offered to healthcare workers or animal industry workers during seasonal or avian influenza exposure were identified.

The most commonly reported adverse effect was an increased risk of nausea and vomiting; Jefferson et al. reported the risk in adults receiving oseltamivir for vomiting (RR 2.43; CI 95% 1.75–3.38) and children (1.70; 95% CI 1.23–2.35), and Dobson et al. in adults (RR 2.43; 95% CI 1.83–3.23).

Limitations were identified for all three systematic reviews and meta-analyses. The evidence on severe clinical endpoints provided by the two RCT reviews are limited by the very low frequency of these events in the outpatient populations under study, and the fact that the original trials were not designed to assess rare and severe outcomes. The observational studies are limited by low numbers of severe endpoints (hospitalisation, intensive care and mortality), the inherent problems of confounders, and lack of standardised study protocols.

While the reviews considered for this Expert Opinion add to the evidence on the beneficial and adverse impacts of neuraminidase inhibitors, it is clear that further studies are needed to strengthen the evidence base overall, in particular for severe clinical end points and for individual risk groups (e.g. patients with asthma, chronic obstructive pulmonary disease (COPD), cardiovascular disease, or diabetes). This Expert Opinion provides an overview of ongoing efforts to strengthen the evidence base for current NAIs and possible new influenza antivirals. Research and development work is underway on new NAI formulations, several new antivirals, and various combination therapies with current and new antiviral drugs.

This ECDC Expert Opinion confirms earlier assessments by ECDC and national authorities that there is no significant new evidence from RCTs to support any changes to the approved indications and recommended use of neuraminidase inhibitors in EU/EEA Member States. Recommendations to treat patients with severe influenza, or those at high risk of the complications of influenza, and provide prophylaxis to the most vulnerable and their families are based on the evidence from RCTs of a significant protective effect of antivirals against influenza, evidence from observational studies of protection against severe endpoints, extrapolation from studies suggesting suppression of virus excretion and a generally benign safety profile. These national recommendations are further supported by this review. This position is consistent with guidance from the World Health Organization (WHO) and many national public health organisations in Europe, North America, Southeast Asia, Australia, Japan and New Zealand.

Available evidence provides support for the use of NAIs as prophylaxis and treatment and thus they can be considered a reasonable public health measure during seasonal influenza outbreaks, pandemics and zoonotic outbreaks caused by susceptible influenza virus strains. With respect to stockpiling of NAIs, evidence reviewed by the expert group support the practice to stockpile NAIs as part of country preparedness plans. However, this Expert Opinion did not consider other relevant issues such as cost-effectiveness, opportunity costs, strategies for protection of vulnerable subgroups or essential services, public perception of risks and benefits of the threat and the intervention, the methods available for a timely delivery of interventions, political and ethical issues. EU/EEA governments will have to take difficult policy decisions on preparedness plans based on incomplete evidence on upcoming threats and possible interventions to protect their populations, bearing in mind that the evidence base for NAIs should be strengthened and research focusing on new influenza antivirals should be supported to facilitate these decisions.

Background

Seasonal influenza causes illness in 5–10% of the European population each year. Individuals of all age groups are affected, but rates of illness are highest among young children. During most influenza seasons, rates of serious illness and death are highest among children <2 years, individuals >65 years, and individuals at increased risk for complications from influenza due to chronic illnesses. Studies conducted during the 2009 influenza A(H1N1) pandemic indicate that morbidly obese persons (BMI ≥40) and pregnant women are also at greater risk for developing severe influenza disease. In addition, there are certain occupational groups at increased risk of acquiring zoonotic influenza, e.g. poultry and swine industry workers.

Severe influenza disease may evolve following seasonal, zoonotic or pandemic influenza, and is often associated with high viral load. An acute influenza infection may be complicated by otitis media, sinusitis, viral and bacterial pneumonia, acute lung injury, myocarditis, pericarditis, septicaemia, encephalitis, and/or death. In addition, influenza disease may trigger worsening of chronic medical conditions present before acquiring the influenza infection, especially underlying cardiopulmonary conditions and diabetes, and increase the risk of complications such as cardiovascular events like myocardial infarction and stroke.

Influenza viruses constantly change through two main mechanisms:

- antigenic drift which is characterised by point mutations leading to minor and gradual antigenic changes in the surface haemagglutinin (HA) and neuraminidase (NA) proteins
- antigenic shift caused by reassortment between human, avian and swine viruses and characterised by major antigenic changes in which a new HA with or without a new NA subtype is introduced into the human population.

These changes, particularly those resulting from antigenic shift, can result in influenza strains that are immunologically distinct from the previously circulating strains, resulting in high infection rates in the immunologically naïve population, and may lead to the emergence of novel geographically localised influenza epidemics or pandemics (see Table 1).

Table 1. Emergence of novel localised influenza infections/epidemics and pandemics in the 20th and 21st centuries*

Emergence (year)	Influenza subtype	Estimated global mortality
2014	A(H7N9)avian	>180 persons
2009	A(H1N1)pdm09	123 000–203 000 (in 2009)
2003	A(H7N7)avian	1 person
1997	A(H5N1)avian	>400 persons
1977	A(H1N1)	unknown
1976	A(H1N1)swine	1 person
1968	A(H3N2)	1 million
1957	A(H2N2)	1.5million
1918	A(H1N1)	>50million

Excluding sporadic cases of zoonotic influenza by H3N2v, H5N8, H9N2, H10N8

Due to the constant change of influenza viruses, susceptibility to antiviral drugs can change over time. Since there is geographic and seasonal variability of viral resistance and rapid changes may occur, viral susceptibility is continuously monitored in nine sentinel EU/EEA Member States (Austria, Finland, Germany, Ireland, Netherlands, Norway, Portugal, Spain, Sweden and the UK).

Four licensed influenza antiviral agents are available in the European Union/European Economic Area (EU/EEA): amantadine, rimantadine, zanamivir and oseltamivir. However, currently circulating seasonal influenza A viruses are resistant (>99%) to the two first antiviral agents; amantadine and rimantadine, which are included in a class of drugs known as influenza NAI and are active against both influenza A and B viruses.

In general, influenza viruses have been susceptible to the two NAIs available for treatment in the EU/EEA over the past ten years. However, during the 2007–2008 influenza season, an oseltamivir-resistant influenza A(H1N1) strain emerged in Europe [2] and was later detected throughout the world. This virus strain remained susceptible to zanamivir [3]. Fortunately, this resistant strain has not circulated worldwide since the 2009 influenza A(H1N1) pandemic virus became dominant. Based on an analysis of 11 387 influenza viruses circulating globally in 2012–2013, the proportion of A(H1N1)pdm09, A(H3N2), B/Victoria- or B/Yamagata-lineage viruses with reduced or highly reduced susceptibility was low (1%, 0.4%, 1% and 0.3%, respectively) to one or more of the NAIs tested (oseltamivir, zanamivir, peramivir and laninamivir) [4]. Even in parts of Asia, e.g. Japan, where use of antivirals has been significantly greater than in the EU/EEA Member States, the level of antiviral resistance is low. The neuraminidase inhibitors peramivir and laninamivir are licensed in some non EU/EEA countries; and peramivir is also licensed for use in USA and Japan, and laninamivir in Japan.

Although influenza vaccination is viewed as the primary tool for the prevention of seasonal influenza disease, influenza antivirals are authorised in the European Union/European Economic Area (EU/EEA) for treatment and prophylaxis of influenza disease (including seasonal, pandemic and zoonotic influenza). All EU Member States recommend NAIs, in combination with clinical supportive care, for treatment of severe, complicated or progressive illness, or for patients at high risk of complications, irrespective of vaccination status. Furthermore, influenza antivirals are being used for treatment and prophylaxis of severe influenza disease caused by zoonotic influenza strains, especially if no vaccines are available [5].

The use of oral inhalation powder zanamivir (Relenza) has been authorised through the mutual recognition procedure since 1999 in all EU/EEA Member States except Cyprus. Current European Medicines Agency/Committee for Medicinal Products for Human Use (EMA/CHMP) opinion is also permissive to the use of zanamivir as an intravenous infusion solution formulation for compassionate use programmes in the EU/EEA [6].

Use of oral oseltamivir (Tamiflu) has been centrally authorised by the European Commission since 2002 and available in all EU Member States [7]. Further, the first generic oseltamivir (Ebilfumin) was approved in 2014 via the centralised procedure[8,9]. For recommended dosage and schedule see Table 2.

Table 2. **Recommended dosage and schedule of neuraminidase inhibitors for treatment and chemoprophylaxis in the EU/EEA**

Antiviral⌡	Indication	Age recommendations (years)					
		0–1	1–6	7–9	10–12	13–64	≥65
Oseltamivir* [7] [9]	Treatment of influenza A and B§	Dose dependent on weight of child‡	Dose dependent on weight of child	Dose dependent on weight of child	Dose dependent on weight of child, if >40 kg = adult dose	75 mg twice daily	75 mg twice daily
	Prophylaxis of influenza A and B§	Dose dependent on weight of child‡	Dose dependent on weight of child	Dose dependent on weight of child	Dose dependent on weight of child, if >40 kg = adult dose	75 mg once daily	75 mg once daily
Zanamivir**[10,11]	Treatment of influenza A and B	Not approved	Not approved for age 1–4 ≥ 5 years of age 10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
	Prophylaxis of influenza A and B	Not approved	Not approved for age 1–4 ≥ 5 years of age 10 mg (2 inhalations) once daily.	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily

⌡Treatment should be initiated as soon as possible, preferably within 48 hours (oseltamivir- all age groups and zanamivir – adults), or 36 hours (zanamivir for children) from onset of symptoms. *
Available in 30 mg, 45 mg and 75 mg tablets. An oral solution containing 6 mg/ml is available for individuals unable to take tablets. Note that dose reductions are indicated in setting of renal insufficiency.
**Available as oral inhalation 5 mg/dose.
§Treatment of suspected or confirmed influenza should be offered for 5 days or longer in severely ill, while duration of prophylaxis depends on setting and objective.

National recommendations regarding influenza antiviral use are available in 24 EU/EEA Member States. These policies generally recommend use of antivirals for patients with severe or progressive influenza requiring hospitalisation. EU/EEA Member States recommend NAI use as treatment (14 Member States) or prophylaxis (9 Member States) for residents of nursing homes or other long-term care facilities at risk of severe disease. A minority of EU/EEA Member States recommend use as treatment or prophylaxis for outpatients who may have a higher risk of severe outcomes of influenza (young children, elderly or individuals of any age with underlying chronic illnesses) [12].

The European Surveillance of Antimicrobial Consumption Network (ESAC) collects information on use of neuraminidase inhibitors in EU/EEA Member States. Based on data from the network, significant variation in actual use of NAIs in different Member States can be observed (Figure 1).

Figure 1. Consumption of neuraminidase inhibitors (ATC group J05AH) in the community and hospital sector in Europe, by country (reporting year 2014).
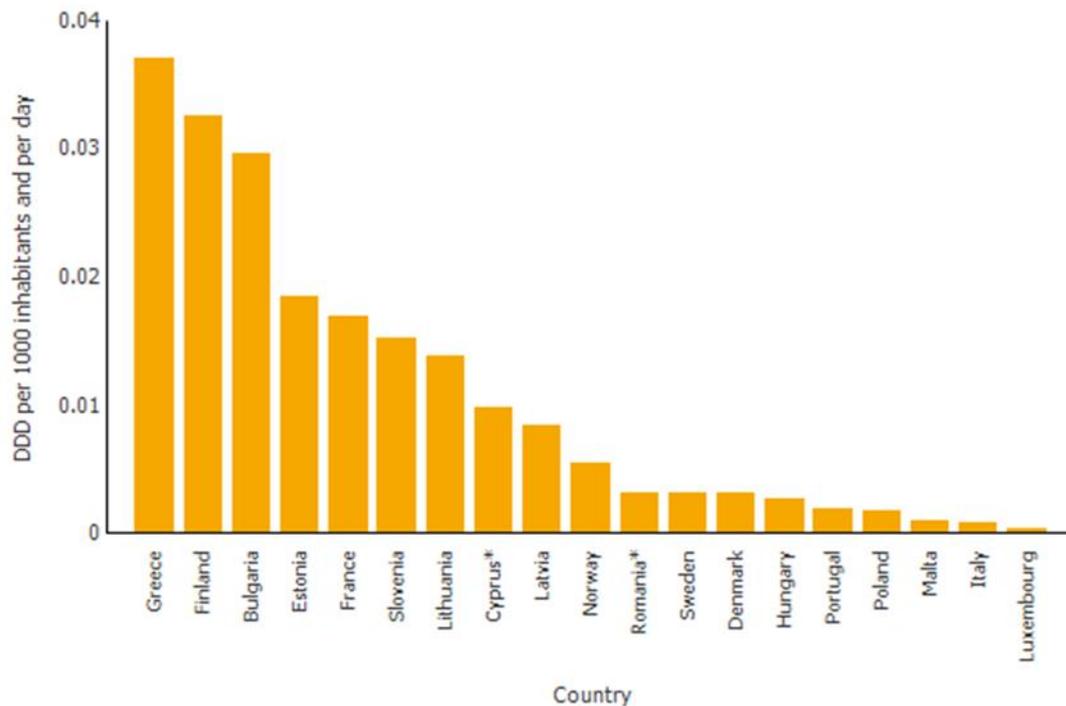
*Country provided only total care data

Hungary and Luxembourg reported data to ECDC only for consumption in the community sector.

The data indicate that neuraminidase inhibitors are used infrequently as a medical and public health countermeasure in many EU/EEA Member States. The underutilisation may be explained by the difficulty of a timely enough confirmation of an influenza diagnosis, as well as the limitations of the scientific evidence base on published efficacy and effectiveness.

Many EU/EEA Member States maintain a stockpile of influenza antivirals as capsules or powder for use during influenza pandemics [13]. The rationale for this is based on the possibility of supply problems during a future pandemic and the need to protect the population or vulnerable population sub-groups, maintain essential services, or both during a pandemic. During the 2009 pandemic only some of the stockpiles were released for use in Europe, as the normal pharmaceutical supply chains worked sufficiently to cover the demand. The potency and stability of these drugs when maintained as emergency stockpiles is being tested regularly to ensure adequate and retained potency over the years.

Request for ECDC Expert Opinion

Neuraminidase inhibitors have been subject to debate concerning their safety, efficacy and effectiveness for treatment and prevention of seasonal influenza infections and its complications, as well as concerning the appropriateness of stockpiling these drugs for use in the next influenza pandemic.

In 2013, the ECDC Advisory Forum requested an assessment of the evidence for use of antivirals in influenza outbreak settings, specifically during institutional outbreaks and new and emerging influenza virus outbreaks. In August 2014 the EU Health Security Committee requested a review of the evidence for stockpiling as part of pandemic preparedness. Given the recent publication of new systematic reviews of safety and efficacy assessed in randomised clinical trials, and effectiveness assessed in observational studies, ECDC convened a public health expert group to review the new evidence with the aim to develop an ECDC Expert Opinion.

Methods

A consultation with European and international public health experts was convened to review data presented in newly conducted systematic reviews and meta-analyses regarding influenza antivirals, in order to develop an ECDC Expert Opinion.

The objectives for the expert consultation were to:

- review the new evidence base on safety, efficacy and effectiveness of influenza antivirals in the treatment and prophylaxis of influenza
- consider the implications of the findings of the review for recommendations on the use of influenza antivirals, including stockpiling by EU/EEA Member States in pandemics
- identify remaining gaps in the current knowledge base
- provide recommendations for further public health research to strengthen the current evidence.

Three large systematic reviews and meta-analyses assessing safety, efficacy and effectiveness of the two licensed neuraminidase inhibitors oral oseltamivir and inhaled zanamivir were reviewed;

- The 2014 Cochrane report, by Jefferson et al. published on 10 April 2014 [14]. This report was summarised in two peer-reviewed articles:
  - Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments published by Jefferson et al. April 9 [15].
  - Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments published by Heneghan et al. April 9 [16].
- The 2015 MUGAS review: Oseltamivir treatment for influenza in adults: a meta-analysis of individual patient-level data from randomised controlled trials published by Dobson et al. on January 30 2015 [17].
- The 2014 PRIDE study: Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data published by Muthuri et al. on 19 March 2014 [18].

Background documents, including links to the three meta-analyses, were distributed to experts in advance of the meeting.

The experts reviewed the three systematic reviews and associated meta-analyses and identified additional studies to be included in the ECDC Expert Opinion for areas which were not sufficiently covered by these.

The expert group consisted of ECDC Advisory Forum members, researchers, European public health experts, European regulatory experts and experts from North American public health organisations. (For a list of the experts please see the Acknowledgements.) All experts were informed that the views they expressed would be understood to reflect their personal opinions, and not the official opinions of their institutions or employers.

The expert group was selected based on the following criteria:

- experience in evaluating scientific evidence addressing antiviral safety, efficacy and effectiveness
- experience in issuing national recommendations for antiviral use.

To ensure transparency regarding the independence of experts and the resulting Expert Opinion, ECDC required all participants to submit a general Annual Declaration of Interest as well as a Specific Declaration of Interest for this expert group. All declarations were received prior to the meeting and reviewed by the Acting Head of the Influenza and other Respiratory Viruses Disease Programme and the ECDC Compliance Officer. Additionally, time was set aside at the beginning of the meeting for the experts to orally declare any additional interests not covered by the Declaration of Interest forms or provide additional information about their already declared interests. No additional oral declarations were made from the experts, and this was noted in the meeting minutes.

Dr Hayden had declared, in writing, interests that could potentially cause a conflict of interest. These interests were considered to be of diverse nature and did not outweigh the benefits his experience could bring to the discussion. This existence of a potential conflict was disclosed to the meeting participants orally at the beginning of the proceedings. In addition, professors Monto and Nguyen-Van-Tam declared interests in writing; however, as they had been invited only to present their own studies and respond to clarifying questions, and did not participate in the drafting of the opinion on the second day of the meeting, these declared interests were considered not an issue.

Before the meeting, ECDC also consulted the Advisory Forum members from the European countries with representatives in the expert group, to determine if there were any additional concerns around the selected group of experts. No objections on the composition of the expert group were raised by Advisory Forum members.

248 Lead researchers of the Cochrane review, the MUGAS review, and the PRIDE study were invited to present their
249 findings. On the first day of the meeting, Prof. Arnold Monto presented the MUGAS study results, and Prof.
250 Jonathan Nguyen-Van-Tam presented the PRIDE study results. The Cochrane group declined the invitation to
251 present their review. The Cochrane results were therefore presented by ECDC staff at the meeting. Following
252 respective presentation and a subsequent question and answer session, the researchers responsible for the
253 systematic reviews to be evaluated left the expert meeting.

254 In advance of the expert meeting, draft position statements were prepared by ECDC for consideration and
255 discussion by the expert group. Minutes were taken of the discussion on the content of the Expert Opinion. ECDC
256 experts then drafted the Expert Opinion, which was sent to the expert group for review. The final draft was shared
257 with the ECDC Advisory Forum and is being made available for public consultation.

258 The final document will include a section on the outcome of the public consultation, summarising in general terms
259 the main issues arising from the consultation and how they are addressed in the document. Additionally, all
260 submitted contributions from the public consultation will be published separately in order to share the results of the
261 consultation in a transparent way.

Results and discussion

General characteristics of the systematic reviews and meta-analyses reviewed by ECDC expert group

Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children – Jefferson et al. 2014

In 2014, Jefferson et al. published a meta-analysis of study-level data gathered from reports of published and unpublished randomised, placebo-controlled trials and regulatory comments and presented the results in the Intervention Review 'Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (Review)' [14-16]. This is the fifth and most extensive review of NAIs by the Cochrane group.

The review team identified study reports through trial registries, electronic databases and regulatory archives and corresponded with manufacturers to identify all randomised, placebo-controlled trials on adults and children with confirmed or suspected exposure to naturally circulating influenza. Many study reports had, until then, been confidential and available only to respective manufacturer and reviewing regulators. For inclusion, studies were evaluated for quality using CONSORT criteria, and risk of bias in each analyses was quantified using a Cochrane 'risk of bias' tool.

Data from 46 clinical trial study reports were analysed for time to first alleviation of symptoms, influenza outcomes, complications, hospitalisations and adverse events in the intention-to-treat (ITT) population. The analysis included 20 studies which assess oseltamivir with 9 623 participants, and 26 studies which assess zanamivir with 14 628 participants. Treatment effects of oseltamivir and zanamivir among influenza-infected, but otherwise healthy adults were studied in 11 RCTs and 14 RCTs respectively, and healthy children were studied in five and two RCTs respectively. Prophylaxis was assessed in five and ten RCTs that were included, respectively, for oseltamivir and zanamivir. The sample size ranged from 26 to 1406 participants per RCT. Some of the trial results were originally analysed together, hence there were eight analyses from the oseltamivir RCTs available for the meta-analyses.

Jefferson et al. conclude that their confidence in the trials is limited due to their assessment that many of the included studies have a high risk for selection bias, used non-identical presentation of placebo, had evidence of selective reporting for both oseltamivir and zanamivir studies, and finally the placebo interventions may have contained active substances. Primary and secondary outcomes used in the trials are presented in Table 3.

Table 3. **Primary and secondary outcomes used in the 2014 analyses by Jefferson et al.**

Primary outcome measures for treatment studies	1. Symptom relief 2. Hospitalisation and complications 3. Harms
Primary outcome measures for prophylaxis studies	1. Influenza (symptomatic and asymptomatic, always with laboratory confirmation) and influenza-like illness (ILI) 2. Hospitalisation and complications 3. Interruption of transmission (reduction of viral spread from index cases and prevention of onset of influenza in contacts) 4. Harms
Secondary outcome measures for treatment studies	1. Symptom relapse after finishing treatment 2. Drug resistance 3. Viral excretion 4. Mortality
Secondary outcome measures for prophylaxis studies	1. Drug resistance 2. Viral excretion 3. Mortality

The RCT analyses included mainly previously healthy individuals, excluding people with illnesses with significant impact on the immune system (such as malignancy or HIV infection). However, subjects with other pre-existing chronic conditions, such as asthmatic children, were included in these clinical trials. Results were presented only for the intention-to-treat or safety populations, which will include a large portion of subjects who have influenza-like-illness that is not caused by infection with influenza viruses. The authors propose that use of the ITT population is more appropriate for extrapolation to clinical practice and also because their 2012 review had reported a biased distribution of the influenza-infected individuals in treatment arms of the trials.

8

Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials – Dobson et al. 2015

In 2015, Dobson et al. published 'Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials' [17].

This report is a meta-analysis of individual adult patient data from twelve randomised placebo-controlled clinical trials with a total of 4 328 participants using the dose of 75 mg twice a day. They report data on an intention to treat population (ITT) as well as on an intention to treat (influenza) infected population (ITT-I).

In the ITT population, two thirds of the subjects had laboratory-confirmed influenza (66% in the oseltamivir arm, and 68% in the placebo arm). The primary outcome was time to alleviation of all symptoms assessed with the accelerated failure time method.

A comparison of clinical trials included in the analyses by Jefferson et al. and Dobson et al. are presented in Table 4. These meta-analyses included 11 RCT's in common. The Jefferson meta-analysis was based on the results of six individual RCTs, and two sets of combined results, one for two RCT's and one for three RCT's.

All were trials of oseltamivir as treatment of healthy adults, with Dobson et al. including one additional trial. Jefferson et al. also analysed results for zanamivir trials and for children. The methodology for the meta-analyses was similar, however Jefferson et al. focused on the intention-to-treat population (influenza-like-illness), while Dobson et al. focused on the intention-to-treat-infected population (laboratory-confirmed influenza).

Table 4. **Comparison of trials on treatment of adults included in the Jefferson et al. and Dobson et al. analyses**

Trial Number	Jefferson et al.	Dobson et al.
M76001	X	X
WV15670	X	X
WV15671	X	X
WV15707	X	X
WV15730	X	X
WV15812	X*	X*
WV15872		
WV15819	X**	X**
WV15876		
WV15978		
JV15823***		X
WV16277	X	X

*These trials were analysed together, hence the discrepancy between number of trials and analyses/studies in the main text.
** These trials were analysed together, hence the discrepancy between number of trials and analyses/studies in the main text.
***Trial excluded from Jefferson et al. analyses, because the full clinical study report was not available for assessment.

Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A (H1N1)pdm09 virus infection – Muthuri et al. 2014

In 2014, Muthuri et al. published 'Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A(H1N1)pdm09 virus infection: a meta-analysis of individual participant data' [18].

This study assembled published and unpublished clinical data from observational studies at 80 study centres worldwide on the association between use of neuraminidase inhibitors and mortality, for a meta-analysis of individual participant data from 29 234 patients (all ages) with laboratory-confirmed or clinically diagnosed *pandemic influenza* A(H1N1)pdm09 infection admitted to hospital in 78 study centres in 38 countries[i], between 2 January 2009 and 14 March 2011, including the third pandemic wave of cases.

Individual datasets were standardised before pooling for analysis and propensity scoring was used.

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[i] The centres were located in Austria, Argentina, Australia, Bangladesh, Brazil, Canada, China, Croatia, Denmark, Egypt, Finland, France, Germany, Greece, Hong Kong, India, Iran, Israel, Italy, Japan, Jordan, Lithuania, Mexico, Mongolia, Morocco, Netherlands, Norway, Poland, Saudi Arabia, Serbia, Singapore, Slovenia, South Africa, Spain, Switzerland, Turkey, United Kingdom, United States

331 The primary outcome was mortality, defined as death occurring during admission to hospital or individual study
332 follow-up period for the generalised linear mixed regression models, and as death occurring within 30 days of
333 illness onset in the Cox regression models.

334 The use of neuraminidase inhibitors was defined and compared in the following manner:

335 • neuraminidase inhibitor (at any time) versus none
336 • early neuraminidase inhibitor treatment (starting ≤2 days from onset of symptoms) versus later (starting
337 >2 days from onset of symptoms)
338 • early neuraminidase inhibitor treatment versus none
339 • later neuraminidase inhibitor treatment versus none.

340 Adjustments were done for propensity score for the likelihood of neuraminidase inhibitor treatment, and for
341 corticosteroid and antibiotic treatment.

Additional publications reviewed

343 The following reviews and studies were reviewed at the proposal of the invited experts:

344 • A systematic review of systematic reviews by Michiels et al. [19]
345 • A systematic review and meta-analysis of observational studies of severe outcomes and mortality among
346 hospitalised patients by Muthuri et al. [20]
347 • Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation by Burch et al.
348 [21]
349 • A systematic review and meta-analysis of individual and household transmission studies by Okoli et al. [1]
350 • A systematic review of observational studies by Hsu et al. [22]
351 • Freemantle and Calvert reviewed nine post-marketing studies on oseltamivir [23]
352 • The 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature
353 (Mosby et al.) [24]
354 • Two randomised placebo-controlled studies conducted in children and adolescents, not included in the
355 Jefferson et al. analysis [25,26]
356 • One observational study among hospitalised children by Louie et al. [27]

Treatment of outpatients

Safety

The Expert Group concluded that on the basis of their review of the evidence presented, oseltamivir or zanamivir use was not associated with an increase in serious adverse events or events leading to withdrawal from treatment or prophylaxis among previously healthy adults or children [14,17].

Adults

Oseltamivir is associated with an increased absolute risk of 3.66% for nausea (RR 1.57; CI 1.14–2.15 in the Jefferson et al. analysis and RR 1.60; 95% CI 1.29–1.99 in the Dobson et al. analysis) and 4.56% for vomiting (RR 2.43; 95% CI 1.75–3.38 in the Jefferson et al. analysis, and RR 2.43; 95% CI 1.83–3.23 in the Dobson et al. analysis) among adults in the RCTs [14].

Cardiovascular events and gastrointestinal events can occur as both an adverse event from medication but also as complications or symptoms of influenza infection. In the Jefferson et al. analysis, oseltamivir use was associated with a decrease in 'cardiac body system adverse events' (RR 0.49; 95% CI 0.25–0.97) and a decrease in risk of diarrhoea (RR 0.67; 95% CI 0.46–0.98).

Zanamivir appears to be associated with a decreased risk of nausea and vomiting in adults, when used as treatment (RR 0.60; 95% CI 0.39-0.94) [14].

Children

In trials with children the risk of vomiting was increased when using oseltamivir, and the relative risk was of a similar magnitude as for the adults (RR 1.70; 95% CI 1.23–2.35) [14]. Significant effects of similar magnitude were also seen in the two RCTs not included in the Jefferson et al. or Dobson et al. analysis [25,26]. In another Cochrane review by Wang et al. published in 2012, vomiting was more commonly associated with oseltamivir (number needed to harm = 17; 95% CI 10–34) [28]. No similar effect was observed for zanamivir.

Efficacy

Results for treatment efficacy from the Jefferson et al. and Dobson et al. meta-analyses are collated in Table 6. Neuraminidase inhibitors treatment does not show any efficacy in those with ILI due to pathogens other than influenza virus (non-influenza ILI) [14].

Alleviation of symptoms

Adults

Jefferson et al. and Dobson et al. conclude that, for adults (ITT population), oseltamivir decreases the time to first alleviation of symptoms of influenza-like illness (ILI) by 16.8 hours (95% CI 8.4–25.1) and 17.8 hours (95% CI -27.1 to -9.3), respectively [14,17]. The time to alleviation of all symptoms among the influenza-infected (ITTI) sub-population was decreased by 25.2 hours (95% CI 16.0–36.2) in the Dobson et al. analysis. The effect of oseltamivir on symptom duration appears to be slightly attenuated among the elderly or patients with pre-existing chronic illnesses [17].

Zanamivir reduced time to first alleviation of ILI symptoms by 14.4 hours (95% CI 9.36–19.44) in adults [14].

Children

In one RCT, included by Jefferson et al. among previously healthy children given oseltamivir, symptom duration was decreased by 29 hours (95% CI 12–47) in the ITT population [14]; no effect was seen in the ITT population in the two RCTs that included asthmatic children. Subsequently published RCTs have found a 2.8 day (p<0.001) decrease in time to resolution of all symptoms among children younger than three years who received oseltamivir within 24 hours from onset of symptoms in the ITT-I population [26] and a one day (p=0.01) decrease in median duration of major symptoms among children and adolescents irrespective of the starting time of treatment [25]. In the latter trial, only results for ITT-I populations were reported, and the treatment and placebo arms had very different rates of influenza, which, according to the authors, gives cause for concern over the randomisation process.

In the Jefferson et al. review no significant effect of zanamivir use on symptom duration in children was seen: time to first alleviation of symptoms was 1.08 days lower in the zanamivir group (95% CI 2.32 lower to 0.15 days higher).

In another Cochrane review by Wang et al. published in 2012, oseltamivir reduced duration of illness in laboratory-confirmed influenza in children by a median of 36 hours (26%, p<0.001) [28]. Oseltamivir significantly reduced acute otitis media in children 1–5 years of age with laboratory-confirmed influenza (risk difference -0.14; 95% CI -0.24 to -0.04). In children with oseltamivir-resistant influenza, Laninamivir octanoate 20 mg reduced symptoms by 2.8 days (60%, p<0.001). Further, zanamivir reduced median duration of illness by 1.3 days (24%, p<0.001).

11

Risk groups

Burch et al. reviewed the evidence of efficacy of oseltamivir (six trials) and zanamivir (nine trials) in reducing symptom duration, time to returning to normal activity and adverse events among risk groups (children with co-morbid conditions, the elderly, or a population specifically described as at risk in separate trial or as part of a mixed-population trial (see Table 5) [29]. The authors observed an overall reduction in the median time to symptom alleviation in healthy adults by 0.57 days (95% CI -1.07 to -0.08; p=0.02; 2 701 individuals) with zanamivir, and 0.55 days (95% CI -0.96 to -0.14; p=0.008; 1 410 individuals) with oseltamivir. In those at risk, the median time to symptom alleviation was reduced by 0.98 days (95% CI -1.84 to -0.11; p=0.03; 1 252 individuals) with zanamivir, and 0.74 days (95% CI -1.51 to 0.02; p=0.06; 1 472 individuals) with oseltamivir. Oseltamivir use was not consistently associated with decrease in time to return to normal activity in the ITT or ITT-I populations. However, these results were sensitive to exclusion of one trial from the pooled analysis.

Zanamivir use was associated with a decrease in symptom duration but not with time to return to normal activity in both ITT and ITT-I populations.

Among the elderly (65 years or older), there was no evidence of efficacy of oseltamivir (three studies) and zanamivir (five studies) in reducing symptoms duration, time to return to normal activity and adverse events in the ITT or ITT-I populations except for time to return to normal activity in the oseltamivir trials (ITT): -98.07 hours (95% CI -170.98 to -25.16) [29].

The number of study subjects and events were small in these trials and sub-analyses of larger trials.

Lower respiratory tract disease or pneumonia

Although influenza, due to the large numbers affected each year, causes large numbers of pneumonia cases, pneumonia is still a relatively infrequent outcome of seasonal influenza infection among the general population. The study population sizes in the RCTs reviewed by Jefferson et al. and Dobson et al. were based on study designs not primarily aiming to assess the impact of treatment on the risk of pneumonia as an outcome in primary healthcare. Therefore the power to detect such associations in these trials is generally low. However, some of the RCTs were designed to prospectively collect data under blinded conditions on antibiotic use for clinically diagnosed lower and upper respiratory tract complications as a secondary outcome.

Adults

In the Cochrane analysis of the RCTs, oseltamivir use as treatment was associated with a 1% absolute rate reduction in pneumonia that was neither radiologically nor microbiologically confirmed (RR 0.55, 95% CI 0.33–0.90 [14], ITT population; and RR 0.40, 95% CI 0.19–0.84 [17], ITT-I population). Unfortunately, no radiological or microbiological diagnosis was documented for pneumonia in most of the original trials. The effect was similar, though no longer statistically significant, in a sub-analysis of the two studies with more specific data on pneumonia signs and symptoms recorded (RR 0.69; 95% CI 0.33–1.4) [14]. This finding is supported by the analysis by Dobson, et al. of lower respiratory tract complications (pneumonia, bronchitis or unspecified lower respiratory tract infections) leading to antibiotics 48 hours or more after randomisation in the studies [17]. The oseltamivir treated groups of adults with influenza (ITT-I population) had a 3.8% absolute rate reduction (RR 0.56; 95% CI 0.42–0.75) of such complications as compared to the placebo treated groups. However, this effect does not appear to be as large in a subgroup analysis of the high-risk groups (≥65 years; in chronic illness trial; or chronic obstructive airways disease at baseline; RR 0.70; 95% CI 0.49–0.98).

Adults using zanamivir have a 1.8% absolute risk reduction of bronchitis compared to those on placebo (RR 0.75; 95% CI 0.61–0.91). Zanamivir was not shown to be associated with decreases in unconfirmed or confirmed pneumonia in adults, although the number of events was very low in these studies [14] .

Children

In the three RCTs including children reviewed by the Jefferson et al. group, no statistically significant effect of oseltamivir on otitis media or bronchitis was seen, (RRs of 0.8 (95% CI 0.62–1.02) and 0.65 (95% CI 0.27–1.55), respectively) [14]. In one additional Cochrane review by Wang et al. published in 2012, pooling data from two RCTs by Heinonen et al. and clinical trial data (Roche, WV15758) resulted in statistically significant reductions in otitis media with oseltamivir treatment in children aged 1–5 years (RD -0.14, 95% CI -0.24 to -0.04) and 1-12 years (RD -0.09, 95% CI -0.16 to -0.03) [28].

In two RCTs, no effect of zanamivir on pneumonia or bronchitis was seen among children [14].

Table 5. Clinical groups deemed to be at risk of developing influenza-related complications [28]

Clinical risk category	Examples
Chronic respiratory disease, including asthma	• Chronic obstructive pulmonary disease, including chronic bronchitis and emphysema, and such conditions as bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia • Asthma requiring continuous or repeated use of inhaled or systemic steroids, or with previous exacerbations requiring hospital admission • Children who have previously been admitted to hospital for lower respiratory tract disease
Chronic heart disease	• Congenital heart disease • Hypertension with cardiac complications • Chronic heart failure • Individuals requiring regular medication and/or follow-up for ischaemic heart disease
Chronic renal disease	• Nephrotic syndrome • Chronic renal failure • Renal transplantation
Chronic liver disease	• Cirrhosis • Biliary atresia • Chronic hepatitis
Diabetes requiring insulin or oral hypoglycaemic drugs	• Type 1 diabetes • Type 2 diabetes requiring oral hypoglycaemic drugs
Immunosuppression	• Due to disease or treatment • Asplenia or splenic dysfunction • Human immunodeficiency virus (HIV) infection at all stages • Patients undergoing chemotherapy leading to immunosuppression • Individuals on or likely to be on systemic steroids for more than a month at a dose equivalent to prednisolone at ≥20 mg per day (any age), or for children less than 20 kg in weight a dose of ≥1 mg/kg per day • Some immunocompromised patients may have a suboptimal immunological response to the vaccine

Hospitalisations

Hospitalisation is a relatively uncommon outcome of seasonal influenza infection in the general population (<1% of influenza infected individuals), and the RCTs reviewed by Jefferson et al. and Dobson et al. were not designed to provide a robust assessment of the impact of treatment in outpatient settings on hospitalisation, although hospitalisations were recorded prospectively. Therefore the power to detect such potential effects in these studies is low.

In the Jefferson et al. analysis of the safety populations, no effect on hospital admissions was seen among adults or children (ITT population) [14]. In the Dobson et al. individual patient data meta-analysis from RCTs, laboratory-confirmed adult influenza patients treated with oseltamivir had a 1.1% absolute risk reduction (RR 0.37; 95% CI 0.17–0.81) in all-cause hospitalisations [17]. This effect is attenuated, and no longer significant (RR 0.61; 95% CI 0.36–1.03) in the intention-to-treat population.

No RCTs have adequately investigated the effect of inhaled zanamivir on hospitalisations.

Effectiveness

None of the systematic reviews, and meta-analyses reviewed above and during the expert consultation included earlier observational studies on treatment effectiveness in outpatients who had medically attended illness during the influenza season.

Risk groups or people with pre-existing medical conditions

Several observational studies on outpatients have been published, mainly including individuals with chronic conditions. For example, Orzeck et al. assessed effectiveness of oseltamivir in a retrospective cohort study in patients 18 years or over with diabetes (n=9 090) [30]. Clinical outcomes assessed were occurrence of pneumonia, other respiratory conditions, and otitis media within 14 days after onset of influenza. Patients receiving oseltamivir had a 17% reduction in the risk of respiratory illnesses (RR 0.83; 95% CI 0.73–0.93) and a 30% reduction in the risk of hospitalisation for any reason (RR 0.70; 95% CI 0.52–0.94). Casscells et al. also assessed oseltamivir treatment in patients 18 years or over with an already known cardiovascular disease [31]. The incidence of recurrent cardiovascular events within 30 days after the influenza diagnosis was significantly reduced (OR 0.42; 95% CI 0.35–0.50) in the treatment group. Further, the effect of oseltamivir treatment on the risk of stroke in patients 18 years or over after influenza infection was assessed by Madjid et al. in a retrospective cohort study [32]. Oseltamivir treatment was associated with a 28% overall reduction across age groups at risk of stroke/transient ischemic attack in the six months after a diagnosed influenza (HR 0.72; 95% CI 0.62–0.82), while a 51% reduction was seen among those 65 years of age or over one month after influenza.

Treatment of inpatients

Safety
No RCTs have been conducted to investigate the safety of treatment with oseltamivir or inhaled zanamivir in those hospitalised with laboratory-confirmed influenza.

Efficacy
No RCTs have been conducted to evaluate the effect of treatment of laboratory-confirmed influenza with oseltamivir or inhaled zanamivir on the outcomes, and death among hospitalised patients.

Effectiveness
The current evidence reviewed by the expert group included new data from a large meta-analysis of individual patient data from observational studies during the 2009–2010 influenza A H1N1 pandemic conducted by Muthuri et al. (2014) to assess the association between neuraminidase inhibitors and mortality in patients influenza A(H1N1)pdm09 virus infection. Further analyses are expected from this work by Muthuri et al. on effects on pneumonia and length of hospital stay.

Pneumonia
In a previous 2013 meta-analysis of observational studies made during or after the 2009 pandemic, Muthuri et al. reported that NAI treatment (mostly oseltamivir) was associated with an increased risk of pneumonia diagnosis (OR 2.29; 95% CI 1.16–4.53), most probably reflecting the increasing propensity to treat individuals with severe or rapidly worsening illness. Patients treated early (before 48 hours) had a lower risk of pneumonia when compared with patients treated late (OR; 0.35 95% CI 0.24–0.50). Patients treated early had a non-significantly lower risk of pneumonia than patients receiving no NAIs (OR 0.73; 95% CI 0.27–2.02).

Severe outcomes
In the previous meta-analyses by Muthuri et al. (2013) the evidence from observational studies on severe outcomes (patients hospitalised with influenza A(H1N1)pdm09 virus infection and receiving critical care or cases of death) was reviewed [20]. NAI treatment was associated with an increase of severe outcomes in a pooled analysis of 24 studies, when compared with no NAI treatment (OR 1.76; 95% CI 1.22–2.54). This observation again probably reflects the increased propensity to treat individuals with severe illness with NAIs. Early NAI treatment compared with late (24 studies) significantly reduced the likelihood of a severe outcome (OR 0.41; 95% CI 0.30-0.56), and pre-admission NAI use significantly reduced severe outcomes (OR 0.51; 95% CI 0.29–0.89).

Mortality
In the individual patient level meta-analysis done by Muthuri et al. (2014) in patients hospitalised with influenza A(H1N1)pdm09 virus infection, decreased mortality was associated with the use of NAIs among hospitalised patients (OR 0.81; 95% CI 0.70–0.93) [18]. Among adults, treatment was associated with a 25% reduction in likelihood of death, irrespective of the timing of treatment (OR 0.75; 95% CI 0.64–0.87); among children under the age of 16, a similar association was observed but the reduction was not significant (OR 0.82; 95% CI 0.58–1.17). Similar results were observed when restricting the analysis to adult critical care patients (OR 0.72; 95% CI 0.56-0.94) and pregnant women (OR 0.46; 95% CI 0.23–0.89). Late treatment (started after 48 hours of symptom onset) was associated with reduced risk of death only among adult critical care patients (OR 0.65; 95% CI 0.43-0.93).

For patients for whom exact timing of NAI treatment from symptom onset was available, when antiviral use was modelled as a time-dependent covariate to overcome potential immortal time bias (i.e. survivor bias), NAI treatment was significantly associated with decreased hazard rate of mortality within 30 days of illness onset (adjusted HR 0·51 [95% CI 0·45–0·58], p<0·0001) as compared with no antiviral treatment. Among treated cases, there was an increase in the hazard with each day's delay in initiation of treatment up to day five as compared with treatment initiated within two days of symptom onset (HR 1.23 [95% CI 1.18–1.28], p<0·0001 for the increasing HR with each day's delay). The unadjusted and adjusted survival curves comparing survival by time to treatment initiation are shown in Figure 2.

14

538   **Figure 2. Survival by time to treatment**[i]

Number at risk

Early NAI treatment (within 2 days)	5192	2414	1939	1843
Treated with NAI day 3	1477	689	492	460
Treated with NAI day 4	1012	567	322	282
Treated with NAI day 5	812	541	272	241
Treated with NAI after day 5	2298	1981	1009	735
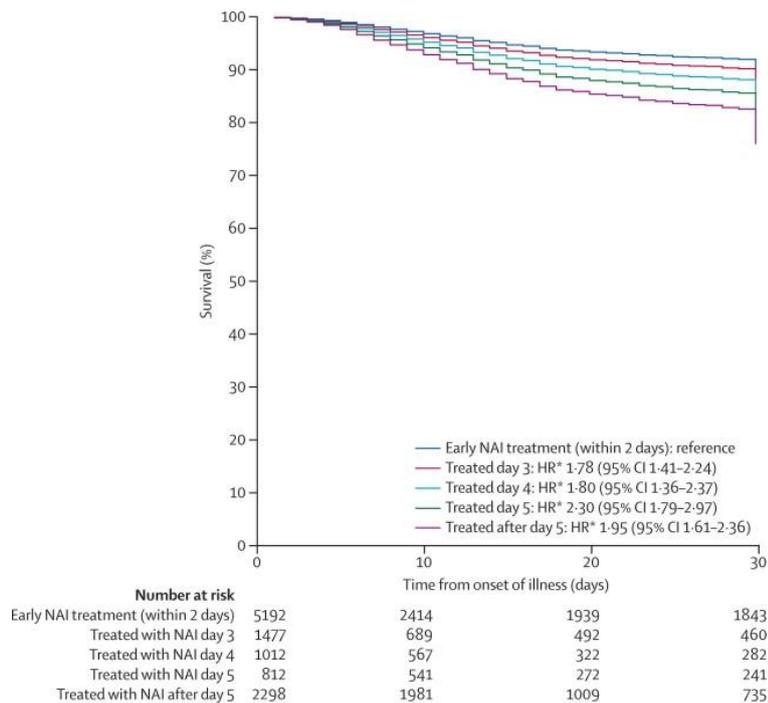
*HR=hazard ratio. NAI=neuraminidase inhibitor. *Cox regression shared frailty model (adjusted for treatment propensity and in hospital steroid or antibiotic use) [18].*

One observational study published in late 2013 on hospitalised children with laboratory-confirmed influenza infection analysed whether treatment with neuraminidase inhibitors improved survival of critically ill children aged 0–17 years [27]. In a multivariate model that included mechanical ventilation and other factors associated with disease severity, the estimated risk of death was reduced in NAI-treated individuals (OR 0.36; 95% CI 0.16–0.83) compared to patients without treatment. In addition, treatment within 48 hours from onset of symptoms was associated with improved survival (p=0.04).

Severe outcomes in pregnant women

Pregnancy is a known risk factor for severe influenza disease, as also noted for the 2009 influenza A(H1N1)pdm09 pandemic, and a systematic review published by Mosby et al in 2011 was drawn to the attention of the group by one of the experts [24]. This systematic review identified five observational studies, in which neuraminidase inhibitors administered within 48 hours from onset of symptoms compatible with influenza, conferred decreased risk of severe disease [24]. No meta-analysis was conducted, but in the identified studies Louie et al. in 2010 reported an increased risk of being admitted to the intensive care unit (ICU) or to die if treatment was initiated later than 48 hours from onset of symptoms (RR 4.3 95% CI 1.4–13.7) [33]. Creanga et al. reported 3.3% of pregnant women who received oseltamivir treatment within two days of symptom onset had severe illness compared with 21.4% and 44.4% pregnant women who started treatment three to four days and five days, respectively or more after symptom onset (P=.002 for trend) [34]. Siston et al. reported that pregnant women who had treatment initiated more than four days from onset of symptoms were more likely to be admitted to the ICU (RR 6.0 05% CI 3.5–10.6) [35].

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[i] Reprinted from The Lancet Vol 2 (5), Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TS, Al Mamun A, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. The Lancet Respiratory medicine. 395-404., 2014 May; with permission from Elsevier.

Post-exposure prophylaxis

Prophylaxis with NAIs can be provided pre- or post-exposure to influenza disease. If used post exposure, it needs to be administered early given the short incubation period (one to four days, average two days) for influenza infections. Post-exposure prophylaxis is typically used for a total of no more than 10 days after the most recent known exposure to a close contact with confirmed influenza.

Safety

Adults
Based on the Jefferson et al. report, in prophylaxis trials, in addition to nausea and vomiting, the analysis found that oseltamivir was associated with a 3.16% increased absolute risk of headaches (RR 1.18; 95% CI 1.05–1.33), and an increased risk in miscellaneous 'neurological events' (RR 1.21; 95% CI 1.03–1.42) [14].

In prophylaxis trials, zanamivir use was not associated with any increases in adverse events [14] .

Children
No significant overall drug-related or serious adverse effects could be found in pooled results from treatment and prophylaxis trials [19].

Efficacy
In another Cochrane review by Wang et al. published in 2012, prophylaxis with either zanamivir or oseltamivir were associated with an 8% (95% CI -0.12 to -0.05; p<0.001) absolute reduction in risk of developing influenza after the introduction of a case into a household [28].

Furthermore, based on a meta-analysis of RCTs and observational studies, a statistically significant negative association between individual pre- or post-exposure prophylactic use of oseltamivir and laboratory-confirmed influenza A(H1N1) infection compared to placebo was observed by Okoli et al. (OR 0.11; 95% CI 0.06–0.20) [1].

Household settings
The Jefferson et al. review refers to only one RCT assessing efficacy of oseltamivir as household prophylaxis. In this trial of 405 people, the absolute risk reduction of symptomatic influenza was 13.6%
(RR 0.20; 95% CI 0.09-0.44) among household members given oseltamivir as compared to household members given placebo. One open-label RCT, not included in the Jefferson et al. review found protective efficacy of 78.8% (95% CI 40.6–92.3) in households with an influenza-positive index case [1]. A meta-analysis of these two trials yields a pooled OR of 0.23 (95% CI 0.09–0.59).

In a meta-analysis of two RCTs studying zanamivir use as prophylaxis, Okoli et al. found an OR of 0.18 (95% CI 0.10–0.31) favouring zanamivir use [1].

Healthcare workers
No studies were identified assessing efficacy or effectiveness of NAIs among healthcare workers following either seasonal influenza or avian influenza exposure or during outbreaks.

Effectiveness

Individuals
Okoli et al. report a negative association between individual prophylactic use of zanamivir and risk of laboratory-confirmed influenza in four studies (OR 0.23; 95% CI 0.16–0.35) [1].

Household transmission
One observational study reviewed by Okoli et al. suggests a protective effect of 42% (95% CI 27–56) for households where the index case is treated with either oseltamivir or zanamivir [1].

Finally, in one observational study of 1 547 households, treatment of the index case showed 42% (95% CI 14-62%) protection against secondary cases in the household if the index case was treated within 24 to 48 hours of onset of symptoms [36].

Institutional settings or long-term care facilities
Michiels et al. reviewed one outbreak control study, which found no significant evidence of efficacy of zanamivir as prophylaxis in a long-term care facility for the elderly [19]. Gravenstein et al. found zanamivir more effective than rimantadine as prophylaxis in one RCT done among nursing home residents (n=482) over three seasons [37].

One study among school children found post-exposure prophylaxis with oseltamivir to be associated with an absolute risk reduction of 12.1% (efficacy 64%; 95% CI 16–85) [19].

Poultry and swine industry workers
No randomised placebo-controlled trials on poultry and swine industry workers were identified. An observational study in an outbreak setting during the 2003 influenza A(H7N7) outbreak in the Netherlands observed a protective effect of ≈79% (95% CI 40%–97%) of oseltamivir against influenza-associated conjunctivitis [38].

Pre-exposure and seasonal prophylaxis

Pre-exposure prophylaxis can be offered for a short period of time, if known exposure is expected; it can also be offered for a whole influenza season. There is no agreed definition and time period for prophylaxis during the influenza season. Regimens as long as 28 days for zanamivir, and 16 weeks for oseltamivir, have been studied and well tolerated [39]. Failure to complete prophylaxis may be greater in children because of nausea and stomach discomfort.

Safety

No increase in risk of severe adverse events were reported in five prophylaxis trials including 2 000 adults on oseltamivir prophylaxis, or in 10 trials including 2 301 adults on zanamivir prophylaxis [14].

Efficacy

Healthy adults

The analysis done by Jefferson et al. suggests seasonal prophylaxis with oseltamivir use is associated with an absolute risk reduction of 3.05% (RR 0.45; 95% CI 0.30–0.67) in the development of symptomatic influenza [14]. No statistically significant effect of oseltamivir was reported on rates of bronchitis (RR 0.75; 95% CI 0.56–1.01,) or hospitalisations (RR 0.92; 95% CI 0.57–1.50).

In the meta-analysis by Okoli et al. of the four RCTs studying the prophylactic efficacy of zanamivir against laboratory-confirmed seasonal influenza at the individual level, an OR of 0.23 (95% CI 0.16-0.35) was obtained.

In a randomised placebo-controlled trial in vaccinated frail older people, pre-exposure prophylaxis was tested in a once-daily dose of 75 mg oral oseltamivir for six weeks against laboratory-confirmed (virus-culture) clinical influenza [40]. Oseltamivir resulted in a 92% reduction in the incidence of laboratory-confirmed influenza compared to placebo (p=0.002).

Children

No trials or studies on seasonal prophylaxis among healthy children were identified in the reviews [1,15,19].

Immunocompromised individuals

A recently published randomised, double-blind, placebo-controlled trial also provides evidence to support the use of seasonal prophylaxis in transplant recipients. In this trial, kidney, liver, kidney-liver, and hematopoietic stem cell transplantation (HSCT) patients were given 12 weeks of oseltamivir 75 mg QD (or the renal function adjusted equivalent) or placebo[41] [42]. Although the trial failed to demonstrate superiority of the intervention for the primary endpoint, laboratory-documented symptomatic influenza infection, most patients with laboratory-proven influenza did not present with signs or symptoms of infection. There was a statistically significant reduction in the frequency of culture (0.4% versus 3.8%; 88% protective efficacy) or RT-PCR (1.7% versus 8.4%; 74.9% protective efficacy) proven influenza in favour of seasonal prophylaxis.

Effectiveness

Healthy adults

According to the review by Michiels et al. oseltamivir used as seasonal prophylaxis is associated with an absolute risk reduction of influenza infection by 3.6% (efficacy 76%; 95% CI 42–90) among healthy adults, and zanamivir is associated with an absolute risk reduction of 4.1% (efficacy 68%; 95% CI 37–83) [19].

Prophylactic zanamivir is associated with a 1.98% absolute risk reduction in symptomatic influenza (RR 0.39;95% CI 0.22–0.70) [14]. Prophylactic zanamivir use also reduces the absolute risk of pneumonia by 0.32% (RR 0.30; 95% CI 0.11–0.80) but does not appear to have a significant effect on the risk of bronchitis (RR 0.49; 95% CI 0.20–1.19).

Individuals at risk and elderly

Only one RCT was identified assessing the effect of oseltamivir and zanamivir in people at risk of severe influenza complications [19]. Seasonal oseltamivir use reduced the absolute risk of developing symptomatic influenza infections by 1.2% (efficacy 92%; 95% CI 37-99) among elderly at-risk subjects.

Seasonal zanamivir use was associated with an absolute risk reduction of 4.0% (efficacy 83%; 95% CI 56–93) among at-risk adults and children.

One outbreak study assessing effectiveness among elderly in long-term care found no evidence of effectiveness of zanamivir [19] .

Limitations in evidence base

Randomised, double-blinded placebo-controlled clinical trials are generally considered the gold standard for evidence when evaluating public health or medical interventions as this methodology, when appropriately implemented, reduces the risk of bias. Such studies are generally required for the approval of agents for the prophylaxis or treatment of influenza. Despite this, there are still often outstanding questions important to clinicians treating their patients, and for public health experts issuing recommendations on the use of antivirals, that have not been investigated in the formal pre-authorisation trials. In this situation, recommendations need to be based on extrapolation and supported by available data from observational studies, which may be the only data available. In this context it is notable that the Cochrane collaboration recently decided to create a working group to develop standards to assess observational studies in addition to randomised clinical trials. This will guide investigators of observational studies to ensure that study protocols are scientifically sound with appropriate endpoints and analysis plans.

The randomised placebo-controlled trials assessed for this Expert Opinion on use of neuraminidase inhibitors for treatment and prevention of influenza were neither designed nor statistically powered to provide evidence for the more infrequent severe clinical endpoints (e.g. hospitalisations, mortality). The pivotal trials on neuraminidase inhibitors were designed to provide the evidence necessary for registration, rather than to answer all questions relevant for clinical and public health use. In the randomised placebo-controlled trials, as has been noted in the review by the Expert group, study subjects were mainly recruited from the healthy general population suffering from medically attended influenza in the outpatient setting. When risk groups for influenza complications or more severe clinical endpoints were included, the number of subjects or events was low, and results obtained did not meet statistical significance. The Cochrane acute respiratory infections group led by Dr. Jefferson emphasises the value of randomised placebo-controlled trials which provide the strongest evidence of efficacy, and have further suggested that they should be the only evidence considered for decisions on the recommendations for use of neuraminidase inhibitors.

Only observational studies have been powered to make inferences on the effect of NAI treatment on mortality. Although observational studies are prone to bias and confounding, which cannot be conclusively controlled for through study design [43,44], much of the evidence on the effectiveness of neuraminidase inhibitors is provided by such studies.

Results from the randomised placebo-controlled trials and observational studies of the use of NAIs for treatment indicate that neuraminidase inhibitors must be administered early (<48 hours from onset of symptoms) to achieve the most clinical benefit. This time-dependency is observed in most of the studies reviewed, be it time to alleviation of symptoms, development of otitis media in children, or impact on mortality among hospitalised patients. However, some studies lack information on exact timing of initiation of treatment from onset of symptoms. This is suboptimal and may dilute the estimates considerably.

In certain settings, benefits have been observed, even if treatment started later than 48 hours after symptom onset. The observational study by Muthuri et al. in patients hospitalised with influenza A(H1N1)pdm09 virus infection suggests an effect on mortality, with treatment initiation up to five days after symptom onset [18]. However, in this analysis, the researchers were able to access data from only 20% of the global sites that were identified to have done clinical research among hospitalised influenza patients during the pandemic, thereby limiting the power of the analysis but also raising questions about generalisability and selection bias. Earlier observational studies in those hospitalised with proven seasonal, pandemic 2009 H1N1, or avian H5N1 influenza also indicate some reduction in mortality with oseltamivir treatment started within 4–5 days of symptom onset. Also, in the randomised placebo-controlled trial by Fry et al. a modest reduction in the duration of symptoms and virus shedding was observed in children less than 5 years old with uncomplicated influenza, even when treatment was initiated 48 hours or later from symptom onset [25].

In the review by Jefferson et al. efficacy is assessed in the intention to treat population, which comprises randomised patients that receive treatment (ILI patients), regardless of laboratory confirmation of influenza. The rationale for this approach is that results would be more relevant to common clinical practice of the mean presumptive treatment effect in suspect influenza cases presenting with ILI.

It is also the case that the proportion of ILI cases that have influenza infection will vary according to the epidemic context. The proportion of ILI cases confirmed with influenza varies over time during the seasonal or pandemic evolution, with the highest proportion confirmed positive during the peak of the outbreak. It is dependent on the overall level of population susceptibility, transmission patterns, and pathogenicity of the circulating virus. There are also many other pathogens that result in ILI, differing by season and age group, and NAI are presumed only to have effects in those infected with drug sensitive influenza. Several studies including the Dobson et al. re-analysis confirm that oseltamivir treatment does not provide benefit endpoints in ILI patients without laboratory-confirmed influenza virus infection. Dobson et al. primarily considered the effect in the laboratory-confirmed influenza infected population (ITT-I), in accordance with the original trial designs. Provided that there is no bias in case ascertainment, this analysis provides a more accurate assessment of efficacy in those patients that actually have disease due to influenza.

In the Dobson et al. analyses, the ITT-I population constituted 66% of the ITT group in the oseltamivir arm and 68% in the placebo arm. This is a very high proportion of confirmed influenza cases in an ILI trial group, even in strictly controlled trial settings, especially considering that the more sensitive RT-PCR confirmation was not available when the RCTs in question were conducted. It is unlikely that during normal influenza seasons and in normal conditions of use, such high proportions of influenza-positive cases would be seen outside community outbreaks.

The evidence for efficacy of neuraminidase inhibitors in children is limited. The meta-analysis by Jefferson et al. did include studies with children in outpatient care, but the numbers are small. Dobson et al. included data on only adults. Some further data is provided by Wang et al. reporting on six treatment trials involving more than 1 200 children with laboratory-confirmed influenza. Assessing the observational studies in children is also challenging.

The large Muthuri et al. study evaluating neuraminidase inhibitor effectiveness on mortality among hospitalised children found similar point estimates as in the studies of adults, but with large confidence intervals making the results non-significant. In principle, this suggests that at least a larger sample size is needed to reduce the uncertainty. On the other hand, one observational study by Louie et al. found a 2% absolute risk reduction in mortality in critically ill children (OR = 0.67; 95% CI: 0.34–1.36) [27].

The randomised placebo-controlled trials reviewed by Jefferson et al. and Dobson et al. assessed efficacy against different outcomes for seasonal influenza, mainly A(H3N2) virus, and do not cover novel zoonotic influenza infections. The observational study by Muthuri et al. included mainly infections with the pandemic influenza A(H1N1)pdm09 virus. Assuming neuraminidase inhibitor susceptibility is known through surveillance activities, the default assumption must be that the results of the Jefferson et al. and Dobson et al. reviews on antiviral efficacy can be extrapolated to novel zoonotic and pandemic scenarios, however the clinical benefit in these situations may vary considerably and will need to be assessed with each emerging influenza subtype and strain. Of note, in observational studies of severe avian H5N1, disease mortality benefit (observed to be 40% with treatment and 76% in the absence of treatment) have been reported if provided up to approximately one week following symptom onset [45,46]. However, when treating individuals infected with avian influenza A(H7N9) and A(H5N1), development of antiviral resistance against neuraminidase inhibitors has been observed in some cases. The antiviral arsenal therefore needs to be extended to more influenza antiviral products with differing mechanisms of action, and the possibility of combination therapies using several antivirals should be explored rapidly to increase preparedness to treat the severe cases of seasonal influenza, zoonotic influenza and potential pandemic viruses that may arise [47]. Due to the small numbers of infections with other zoonotic subtypes (H5N8, H5N6, H9N2, H10N8, etc.), and many other complicating factors, only case reports of individual patients are available as evidence for antiviral effectiveness against these infections.

Some countries in the EU/EEA follow a similar public health strategy as Japan to combine use of influenza vaccination before the start of the influenza season, and use of influenza antivirals when needed in risk groups including the large aging population. Currently, five neuraminidase inhibitors are approved for chemotherapy against influenza in Japan where the highest frequency of use in the world is reported; favipiravir, laninamivir, oseltamivir, peramivir, and zanamivir [48].

Remaining gaps in the current knowledge base

One of the areas that need further research is how the antiviral activity of neuraminidase inhibitors translates into clinical effectiveness in recognised risk groups for severe influenza disease, and particularly in terms of severe outcomes.

Efficacy and effectiveness against severe outcomes in previously healthy individuals

The limited available evidence for the treatment of previously healthy children and adults suffering from severe influenza-associated disease, including clinical outcomes such as unscheduled medical visits for complications, hospitalisations, need for intensive care and mortality, is discouraging. These outcomes represent the largest burden of the disease overall and the main burden on the healthcare systems during seasons predominated by more highly pathogenic viruses. Large prospective randomised placebo-controlled trials would be needed to detect the impact of such events in seasons other than the most severe (which cannot be predicted). As described above, funding of such trials with the current neuraminidase inhibitors authorised in the EU/EEA is unlikely in the future. Further, as neuraminidase inhibitors are recommended as the standard of care in many settings throughout the world, it is increasingly unlikely that placebo-controlled randomised studies will be planned. More well-designed prospective observational studies are therefore urgently needed. Funding for such observational trials is also an issue and needs more attention.

Efficacy and effectiveness in risk groups

The limited evidence available on the treatment or prophylaxis of risk groups with underlying chronic conditions is discouraging, as these are the groups who are known to develop severe disease and would most need to be protected from severe outcomes of influenza. It is unlikely that more RCTs will be conducted due to the expiry of patents for oseltamivir and zanamivir, and the unavailability of public funding for such studies. It is also unlikely that ethical boards would approve randomised placebo-controlled trials, given the existing evidence for efficacy. Well-designed prospective observational studies among specific risk groups would be a useful addition to the knowledge base. Funding for such observational trials is also an issue and needs more attention. These studies should include longer term follow-up in order to confirm reports on reduced late sequelae (MI, stroke) in oseltamivir-treated persons compared to no treatment.

Efficacy and effectiveness against emerging zoonotic and pandemic influenza strains.

The effectiveness of NAIs needs to be assessed through studies and surveillance against each emerging zoonotic and pandemic influenza strain, as the clinical benefit may vary considerably, depending, for example, on the virulence and clinical severity of the illness caused by that strain.

Options for recommendations in EU/EEA Member States

Influenza viruses transmitted to humans, whether seasonal, zoonotic or pandemic, may cause severe disease in large numbers of people and there is a clear need for effective treatment and prophylaxis. Available evidence from randomised placebo-controlled clinical trials and observational studies conducted to assess two neuraminidase inhibitors authorised in the EU/EEA, oseltamivir and zanamivir, were recently summarised in three new large systematic reviews that included a range of meta-analyses. Although the reviewed evidence provides limited new data (with the exception of trial data provided by the manufacturer of oseltamivir) in support of public health recommendations, the meta-analyses presented in these new reviews nonetheless strengthen the evidence base.

The two reviews assessing efficacy in randomised placebo-controlled clinical trials are consistent with results from observational studies indicating that neuraminidase inhibitors have clinical benefit and, to be most beneficial, must be administered early i.e. less than 48 hours from onset of symptoms [14,17]. This time-dependency is observed in most studies reviewed and conducted in previously healthy children and adults, be it time to alleviation of symptoms or development of otitis media in children. The time-dependency is a limitation in clinical settings where patient delay in seeking medical attention for an influenza infection and diagnostic delay may both be an issue. Further, the two reviews indicate a greater efficacy in individuals with laboratory-confirmed influenza than individuals with influenza-like illness. There is no evidence that NAIs affect the course of ILI due to pathogens other than influenza. Diagnostic methods, such as RT-PCR, that are becoming more readily available, may improve the feasibility of beginning antiviral treatment for influenza within 48 hours from symptom onset.

The efficacy observed when neuraminidase inhibitors were administered in randomised placebo-controlled clinical trials as prophylaxis, is more pronounced than the efficacy observed in treatment trials, and provide statistically significant support to prophylaxis regimens against seasonal, zoonotic or pandemic influenza caused by influenza strains susceptible to neuraminidase inhibitors.

The most severe clinical endpoint for public health recommendations and pandemic preparedness – mortality – is fortunately uncommon, and so has rarely been observed in the available RCTs, and has therefore only been assessed in observational studies, in particular during the 2009 influenza A(H1N1) pandemic. Consequently, such data must be assessed with caution, as there may be residual confounding. Although a statistically significant impact on mortality was observed among NAI treated hospitalised patients of all age groups, who were given treatment with NAIs up to five days following onset of symptoms, the survival rates were greater the earlier treatment was initiated. The observed time-dependency in the randomised placebo-controlled clinical trials was confirmed in the observational studies assessing mortality, although a longer time window for initiation of treatment to acquire clinical effect was observed suggesting it is worthwhile in the severely ill to initiate treatment, even if it was more than 48 hours from onset of symptoms. Initiation of treatment before laboratory confirmation of any suspected case of influenza causing severe disease is essential to increase clinical benefit.

The reviews and additional scientific literature contributed by the Expert Panel provide some conflicting evidence on whether the neuraminidase inhibitors provide reduction in development of lower respiratory infection in previously healthy adults and otitis media in children. Additional and larger randomised placebo-controlled trials using the sensitive diagnostic methods based on viral RNA amplification, which are now available in most hospital laboratories, could potentially address the current lack of information. However, no further placebo-controlled randomised clinical trials are likely to be conducted using the currently licensed neuraminidase inhibitors, since both products are authorised, and no further regulatory requirements are expected. Instead, further high-quality observational studies are more feasible. Observational studies conducted throughout the world to assess effectiveness for different circulating influenza viruses would strengthen the evidence base for individual risk groups. If done, they should preferably be conducted with standardised study protocols to increase comparability.

The reviews clearly demonstrate that the efficacy of current NAI is relatively limited, and highlight the urgent need for new influenza antivirals with greater efficacy. Several new antiviral products and strategies are currently being investigated.

Evaluation of safety in the reviews of the randomised placebo-controlled clinical trials emphasises that nausea and vomiting during treatment with neuraminidase inhibitors does occur. In the trials, however, treatment was rarely terminated due to these side effects and therefore was not considered by the expert panel to be a substantial clinical problem.

Based on a consensus opinion of the experts consulted, the options for treatment and prophylaxis for EU/EEA Member States to consider while updating the recommendations for influenza antivirals are summarised in Table 6. Although the available evidence of the current neuraminidase inhibitors is limited in scope (with regards to risk groups and severe outcomes), and the estimates of effectiveness are modest, the expert consensus was that it is sufficient to justify use of these medicines for providing protection against influenza disease, development and duration of symptoms, and probably progression to severe outcomes.

A majority of EU Member States provide national public health recommendations for use of neuraminidase inhibitors to treat cases of severe or progressive influenza. The new observational data on mortality reduction in those hospitalised with influenza A(H1N1)pdm09 virus infection is supportive of this position, as well as the position expressed by WHO [5] [49] [50]. The importance of further research to develop more effective influenza antivirals is emphasised, and any support and initiative in this area from EU/EEA Member States and the European Commission should be welcomed.

Many EU Member States have decided to stockpile neuraminidase inhibitors for use during pandemic scenarios or severe outbreaks of novel influenza strains. The systematic reviews of the randomised clinical trials provide evidence for use of neuraminidase inhibitors as pre- and post-prophylaxis, providing protection against seasonal influenza in randomised clinical trials. Vulnerable population groups known to be prone to severe influenza disease may benefit significantly from being offered prophylaxis in a new pandemic that is susceptible to the relevant drug. Some of these risk groups often respond poorly to vaccines, which further strengthens the rationale for the use of NAIs in this group.

Therefore, while recognising uncertainties resulting from the lack of randomised controlled trials to directly support the full range of treatment recommendations, as well as considering the benign side effects profile of the NAI, it is considered that sufficient evidence supports the use of NAIs as a public health measure during pandemics of susceptible influenza strains. This Expert Opinion did not consider other aspects such as; cost-effectiveness considerations, including opportunity cost; strategies for protection of vulnerable subgroups; essential services of society; public perception of the risks and benefits of the threat and intervention; and the methods available for a timely delivery of interventions, which are all relevant and necessary as an evidence base for decisions on stockpiling. EU/EEA governments will need to take difficult policy decisions on preparedness plans based on incomplete evidence on upcoming threats, and possible interventions to protect their populations, acknowledging that the evidence base for NAIs should be strengthened and research focusing on new influenza antivirals should be supported to facilitate these decisions.

Table 6. ECDC Expert Opinion on options for public health recommendations on treatment and prophylaxis of influenza with neuraminidase inhibitors

	Treatment of patients with medically attended influenza-like illness (ILI)*	Treatment of patients with laboratory-confirmed influenza	Pre- or post-exposure prophylaxis for asymptomatic individuals	Key evidence supporting the Expert Opinion on treatment and prophylaxis recommendations
OUTPATIENTS				
Healthy adults 18–65 years	Evidence available from RCTs or observational studies. **Expert Opinion:** Treatment during seasonal influenza epidemics should be recommended on an individual basis. Treatment during emerging influenza outbreaks and pandemics should be considered depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	Evidence available from RCTs or observational studies. **Expert Opinion:** Treatment during seasonal influenza epidemics should be recommended on an individual basis. Treatment during emerging influenza outbreaks and pandemics should be recommended depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	Evidence available from RCTs or observational studies. **Expert Opinion:** Prophylaxis during seasonal influenza epidemics should be considered on an individual basis, e.g. for household members of people in risk groups, especially for the unvaccinated and immunocompromised (congenital or acquired) who do not respond to vaccination. Particularly during years when low vaccine effectiveness is expected due to mismatch between vaccine strains and strains circulating in the populations. Effectiveness of prophylaxis is likely better than treatment. Prophylaxis for emerging influenza outbreaks and pandemics should be considered on an individual or population basis depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality. Effectiveness of prophylaxis is likely better than treatment.	Evidence from RCTs: **Treatment** Oseltamivir decreases time to first alleviation of symptoms of influenza-like illness (ILI) by 16.8 hours (95% CI 8.4–25.1) and 17.8 hours (95% CI -27.1 to -9.3), respectively in the ITT population in two separate systematic reviews of conducted *RTCs* [14,17]. Zanamivir decreases time to first alleviation of ILI symptoms by 14.4 hours (95% CI 9.4-19.4) as documented *in RCTs* [14]. Oseltamivir decreases time to alleviation of all symptoms among the influenza-infected (ITT-I) by 25.2 hours (95% CI 16.0–36.2) as documented in RCTs [17]. A lower risk of lower respiratory tract infections (risk ratio 0.56 (95% CI 0.42–0.75) in the oseltamivir-treated ITT-I population [17], and a lower risk in in the oseltamivir-treated ITT populations demonstrated in RCTs [14,17] A lower risk of all-cause hospitalisations among the oseltamivir-treated ITT-I populations (risk ratio 0.37 (0.17–0.81)) [17], while no similar effect was observed when assessing ITT populations demonstrated in RCT [14]. Evidence from observational studies: **Prophylaxis** A lower risk in developing laboratory-confirmed influenza illness among individuals offered oseltamivir as prophylaxis (risk ratio 0.45; 95% CI 0.3–0.7) demonstrated in RCTs [14], confirmed by a meta-analysis conducted by Okoli et al. and demonstrated in observational study [1].

	Treatment of patients with medically attended influenza-like illness (ILI)*	Treatment of patients with laboratory-confirmed influenza	Pre- or post-exposure prophylaxis for asymptomatic individuals	Key evidence supporting the Expert Opinion on treatment and prophylaxis recommendations
Healthy elderly - 65 years or older	Evidence is available from RCTs or observational studies. **Expert Opinion** Treatment during seasonal influenza epidemics should be recommended on an individual basis. Treatment during emerging influenza outbreaks and pandemics should be recommended on an individual or population basis depending upon risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	Evidence is available from RCTs or observational studies. **Expert Opinion** Treatment during seasonal influenza epidemics should be recommended on an individual basis. Treatment during emerging influenza outbreaks and pandemics should be recommended depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	Evidence is available from RCTs or observational studies. **Expert Opinion** Prophylaxis during seasonal influenza epidemics should be considered on an individual basis, e.g. household members in households with people in risk groups, especially unvaccinated and immunocompromised (congenital or acquired) who do not respond to vaccination, or if vaccine failure is expected due to mismatch between vaccine strains and strains circulating in the populations. Effectiveness of prophylaxis is likely better than treatment. Prophylaxis during emerging influenza outbreaks and pandemics should be considered on an individual basis or more generally dependent upon risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	Evidence from RCTs: **Treatment** No statistically significant reduction of time to alleviation of symptoms or return to normal activity in elderly, oseltamivir treated ITT-I populations (mean decrease 73 hours; 95% CI -151.2 to -3.8). In ITT populations the mean decrease in time to alleviation of all symptoms or time to return to normal activity was 98 hours (95% CI -170.9 to -25.2) demonstrated *in RCTs* [29]. No clear evidence was documented of differences between zanamivir and placebo for reduction time to alleviation of symptoms or return to normal activity in elderly in any population assessed demonstrated in RCTs [29] A lower risk of lower respiratory tract infections (risk ratio 0.77 (95% CI 0.49–0.98) in the oseltamivir-treated ITT-I population was observed in RCTs [17]. **Prophylaxis** Seasonal prophylaxis with oseltamivir reduced the absolute risk of developing symptomatic influenza infections by 1.2% (efficacy 92%; 95% CI 37–99) among elderly risk population demonstrated in RCTs[19]. No prophylactic effects were seen with zanamivir in one outbreak study demonstrated in RCTs [19].

	Treatment of patients with medically attended influenza-like illness (ILI)*	Treatment of patients with laboratory-confirmed influenza	Pre- or post-exposure prophylaxis for asymptomatic individuals	Key evidence supporting the Expert Opinion on treatment and prophylaxis recommendations
Risk group adults including immunocompromised and pregnant women – 18 years and older	Limited evidence is available from RCTs or observational studies. **Expert Opinion** Although limited evidence is available from clinical trials for treatment recommendations of this vulnerable group, treatment during seasonal influenza epidemics should be recommended. Lack of evidence from clinical trials should not prevent treatment when clinically indicated. Significant clinical experience of treatment is available and no other optional treatments are available. Although limited evidence is available for this vulnerable patient group, treatment during emerging influenza outbreaks and pandemics should be recommended depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality. Lack of evidence should not prevent treatment when clinically indicated.	Limited evidence is available from RCTs or observational studies. **Expert Opinion** Although limited evidence is available from clinical trials for treatment recommendations of this vulnerable group, treatment during seasonal influenza epidemics should be recommended. Lack of evidence from clinical trials should not prevent treatment when clinically indicated. Significant clinical experience of treatment is available and no other optional treatments are available. Although limited evidence is available for this vulnerable patient group, treatment during emerging influenza outbreaks and pandemics should be recommended depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality. Lack of evidence should not prevent treatment when clinically indicated	Evidence is available from RCTs. **Expert Opinion** Prophylaxis (incl. seasonal) during seasonal influenza epidemics for these vulnerable population groups should be considered, especially for the unvaccinated and immunocompromised (congenital or acquired) who do not respond to vaccination. This is particularly important during years when low vaccine effectiveness is expected due to mismatch between vaccine strains and strains circulating in the populations. Effectiveness of prophylaxis is likely better than treatment.	Evidence from RCTs: In at-risk subgroups, estimates of difference in symptom duration often failed to reach statistical significance due to small sample size, although the direction of effect remained in favour of the NI treatments demonstrated in RCTs [29]. However, oseltamivir decreases time to alleviation of symptoms of ILI in risk groups by 0.74 days (95% CI -1.51 to 0.02) for oseltamivir and 0.98 days (95% CI -1.84 to -0.11) for zanamivir as documented in of conducted RTCs. Seasonal prophylaxis with oseltamivir is associated with an absolute risk reduction of 3.05% (RR 0.45 95% CI 0.30–0.67) in development of symptomatic influenza demonstrated in meta-analysis of RCTs [1]. Prophylactic efficacy of zanamivir at the individual level provided an OR of 0.23 (95% CI 0.16–0.35) in a meta-analysis of RCTs [1]. One RCT provide evidence for statistically significant reduction in frequency of culture positivity (0.4% versus 3.8%, 88% efficacy) or PCR positivity (1.7% versus 8.4%, 75% efficacy) for influenza among transplanted patients that received 75 mg oseltamivir for seasonal prophylaxis (12 weeks) or no prophylaxis [42] [41]. However, it should be noted that the trial failed to demonstrate evidence for laboratory-confirmed symptomatic influenza infection.

	Treatment of patients with medically attended influenza-like illness (ILI)*	Treatment of patients with laboratory-confirmed influenza	Pre- or post-exposure prophylaxis for asymptomatic individuals	Key evidence supporting the Expert Opinion on treatment and prophylaxis recommendations
Healthcare workers	No evidence is available from RCTs or observational studies. **Expert Opinion** Treatment recommendations should follow those for healthy adults.	No evidence is available from RCTs or observational studies. **Expert Opinion** Treatment recommendations should follow those for healthy adults.	No evidence is available from RCTs or observational studies. **Expert Opinion** Prophylaxis during institutional outbreaks of seasonal influenza in order to protect vulnerable patients, especially the unvaccinated and immunocompromised (congenital or acquired), who do not respond to vaccination, should be considered. This is particularly important during years when poor vaccine effectiveness is expected due to a mismatch between vaccine strains and strains circulating in the populations. Effectiveness of prophylaxis is likely better than treatment. Prophylaxis during institutional outbreaks of emerging influenza outbreaks and pandemics should be considered depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	Not addressed specifically in the reviews. See results for healthy adults.
Poultry or swine industry workers/laboratory staff working with influenza viruses	No evidence available from randomized controlled trials or observational studies. **Expert Opinion** See evidence for healthy adults for seasonal influenza. Treatment of poultry or swine industry workers during zoonotic outbreaks in animals should be recommended. Treatment of laboratory workers handling influenza viruses should be recommended. Treatment during emerging influenza outbreaks and pandemics should be recommended on an individual or population basis depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	No evidence available from randomized controlled trials or observational studies. **Expert Opinion** See evidence for healthy adults for seasonal influenza. Treatment of poultry or swine industry workers during zoonotic outbreaks in animals should be recommended. Treatment of laboratory workers handling influenza viruses should be recommended. Treatment during emerging influenza outbreaks and pandemics should be recommended depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	No evidence available from randomized controlled trials or observational studies. **Expert Opinion** See evidence for healthy adults for seasonal influenza. Prophylaxis for poultry and swine industry workers during zoonotic outbreaks in animals should be considered. Prophylaxis for laboratory workers when handling new emerging influenza viruses or known influenza viruses with potential of inducing sever disease in humans should be considered if working with lower biosafety levels than recommended for these viruses. Effectiveness of prophylaxis is likely better than treatment.	Not addressed specifically in the reviews. See results for healthy adults. Evidence from observational study: Decreased development of conjunctivitis following oseltamivir prophylaxis in individuals caring for influenza A(H7N7) infected poultry (efficacy 79%; 95% CI 40–97) [38].

	Treatment of patients with medically attended influenza-like illness (ILI)*	Treatment of patients with laboratory-confirmed influenza	Pre- or post-exposure prophylaxis for asymptomatic individuals	Key evidence supporting the Expert Opinion on treatment and prophylaxis recommendations
Healthy children less than 18 years	Evidence available from RCTs. **Expert Opinion:** Treatment during seasonal influenza epidemics should be considered on an individual basis. Treatment during emerging influenza outbreaks and pandemics should be considered depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	Evidence available RCTs. **Expert Opinion:** Treatment during seasonal influenza epidemics should be recommended on an individual basis. Treatment during emerging influenza outbreaks and pandemics should be recommended depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	Evidence available from observational studies. **Expert Opinion:** Prophylaxis during seasonal influenza epidemics should be considered on an individual basis, e.g. for household members in households with people in risk groups, especially for the unvaccinated and immunocompromised (congenital or acquired) who do not respond to vaccination. This is particularly important during a year when low vaccine effectiveness is expected due to a mismatch between vaccine strains and strains circulating in the populations. Effectiveness of prophylaxis is likely better than treatment. Prophylaxis during emerging influenza outbreaks and pandemics should be considered at an individual or population level depending upon a risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality. Effectiveness of prophylaxis is likely better than treatment.	Evidence from RCTs: Decreased time to alleviation of all symptoms by 29h (95% CI 12–47) if treated with oseltamivir[14], while if oseltamivir was provided within 24 hours from onset of symptoms in laboratory-confirmed influenza infected children less than 3 years, a decreased time to alleviation of 2.8 days (p<0.001) was observed, and a one day (p=0.01) decrease in median duration of children and adolescents irrespective of when treatment started demonstrated in RCTs.
Risk group children including immunocompromised	Limited evidence available from RCTs or observational studies. **Expert Opinion** Although limited evidence is available from clinical trials, treatment during seasonal influenza epidemics should be recommended. Lack of evidence from clinical trials should not prevent treatment when clinically indicated. Significant clinical experience of treatment is available and no other optional treatments are available. Although limited evidence is available, treatment during emerging influenza outbreaks and pandemics should be recommended depending upon risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality. Lack of evidence should not prevent treatment when clinically indicated.	Limited evidence available from RCTs or observational studies. **Expert Opinion** Although limited evidence is available from clinical trials, treatment during seasonal influenza epidemics treatment should be recommended. Lack of evidence from clinical trials should not prevent treatment when clinically indicated. Significant clinical experience of treatment is available and no other optional treatments are available. Although limited evidence is available, treatment during emerging influenza outbreaks and pandemics should be recommended depending upon risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality. Lack of evidence should not prevent treatment when clinically indicated.	Evidence available from RCTs. **Expert Opinion** Prophylaxis (incl. seasonal) during seasonal influenza epidemics for this vulnerable patient group should be considered, especially for the unvaccinated and immunocompromised (congenital or acquired) who do not respond to vaccination. This is particularly important during years when low vaccine effectiveness is expected due to a mismatch between vaccine strains and strains circulating in the populations. Effectiveness of prophylaxis is likely better than treatment.	Evidence from RCTs: In at-risk adolescents, seasonal prophylaxis with zanamivir reduced the absolute risk of influenza infection by 4% (efficacy 83%; 95% CI 56–93) demonstrated in RCTs [19] No effect was seen of oseltamivir offered to laboratory-confirmed influenza infected children suffering from asthma demonstrated in RCTs [14].

	Treatment of patients with medically attended influenza-like illness (ILI)*	Treatment of patients with laboratory-confirmed influenza	Pre- or post-exposure prophylaxis for asymptomatic individuals	Key evidence supporting the Expert Opinion on treatment and prophylaxis recommendations
INPATIENTS				
Hospital-admitted patients of any age, long-term care residents	Evidence is available from observational studies. **Expert Opinion** Although evidence is only available from observational studies, treatment of in-patients (or residents) during seasonal influenza epidemics should be recommended. Lack of evidence from clinical trials should not prevent treatment when clinically indicated. Data from observational studies are supportive of treatment and significant clinical experience of treatment is available and no other optional treatments are available. Although evidence is only available from observational studies, treatment of in-patients (or residents) during emerging influenza outbreaks and pandemics should be recommended depending upon risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	Evidence is available from observational studies. **Expert Opinion** Although evidence is only available from observational studies, treatment of in-patients (or residents) during seasonal influenza epidemics should be recommended. Lack of evidence from clinical trials should not prevent treatment when clinically indicated. Data from observational studies are supportive of treatment and significant clinical experience of treatment is available and no other optional treatments are available. Although evidence is only available from observational studies, treatment of in-patients (or residents) during emerging influenza outbreaks and pandemics should be recommended depending upon risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	Evidence is available from RCTs for long-term care residents. **Expert Opinion** Prophylaxis (incl. seasonal prophylaxis) during seasonal influenza epidemics should be considered, especially in the unvaccinated and immunocompromised (congenital or acquired) who do not respond to vaccination. This is particularly important during years when low vaccine effectiveness is expected due to mismatch between vaccine strains and strains circulating in the populations. Although evidence is only available from observational studies, prophylaxis of in-patients (or residents) during emerging influenza outbreaks and pandemics should be considered depending upon risk assessment considering e.g. antiviral susceptibility, transmissibility, virulence, complication frequency, hospitalisations and case fatality.	Evidence from RCTs: Seasonal prophylaxis with oseltamivir is associated with an absolute risk reduction of 3.05% (RR 0.45 95% CI 0.30–0.67) in development of symptomatic influenza demonstrated in meta-analysis of RCTs [1]. Evidence from observational study: Decreased mortality was associated with use of NAI among hospitalised patients (OR 0.81; 95% CI 0.7–0.9) demonstrated in metanalysis of observational study data [18]. Decreased mortality was associated with use of NAI among hospitalised pregnant women (OR 0.46; 95% CI 0.23–0.89) demonstrated in metanalysis of observational study data [18]. Early (<48 h) versus late treatment (>48h) associated with reduced risk of death in critical care patients (OR 0.65; 95% CI 0.4–0.9) but not other hospitalised patients demonstrated in metanalysis of observational study data [18]. NAIs improve survival in critically ill children aged 0–17 years (OR 0.36; 95% CI 0.2–0.8) [27]. In addition treatment within 48 hours was associated with survival (p=0.04) demonstrated in observational study. Among hospitalised patients treated with NAIs, there was an increase in the hazard with each day's delay in initiation of treatment up to day 5 as compared with treatment initiated 2 days or before of symptom onset (HR 1.23 [95% CI 1.18–1.28] demonstrated in metanalysis of observational study data [18].

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Recommendations for further public health research to strengthen current evidence and preparedness for future pandemics

Observational studies assessing current neuraminidase inhibitors.

Further studies are needed on current neuraminidase inhibitors authorised within the EU/EEA and elsewhere, as well as development of further influenza antivirals to protect the EU/EEA population. The evidence for currently authorised neuraminidase inhibitors in the EU/EEA needs to be expanded in the knowledge of the more rare but severe endpoints such as reduction in mortality, intensive care including mechanical ventilation and ECMO treatment and long-term sequelae. The use of standardised treatment and study protocols would increase comparability between studies and facilitate future meta-analyses. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC; https://isaric.tghn.org/) and Consortium for the Standardization of Influenza Seroepidemiology (CONSISE; https://consise.tghn.org/) are examples of global platforms for sharing of such protocols.

New antivirals

There is a need for improved influenza antivirals, and a number are either authorised or in advanced clinical development:

- Zanamivir for intravenous use (phase 3 trial in hospitalised patients enrolled, results pending)
- Peramivir for intravenous use (novel neuraminidase inhibitor authorised in Japan and South Korea since 2009 and for uncomplicated influenza in the US since 2014)
- Favipiravir for oral use (influenza RNA-polymerase inhibitor; authorised in Japan since 2014 for novel strains; phase 3 trials in outpatient adults with re-emerging influenza enrolled, results pending; limited to cases in which other anti-influenza virus drugs are ineffective or not sufficiently effective)
- Laninamivir (long-acting neuraminidase inhibitor; authorised in Japan since 2010 for treatment of influenza, and for prophylaxis in 2013)
- DAS181 (sialidase that cleaves both $\alpha(2,6)$-linked and $\alpha(2,3)$-linked sialic acid receptors; phase 2 trials)
- Nitazoxanide (oral antiparasitic agent with immunomodulatory effects and blockade of HA maturation; phase 2 clinical trial completed and phase 3 trial including combination of nitazoxanide plus oseltamivir enrolled, results pending)
- human heterosubtypic neutralising monoclonal antibodies for intravenous use (various stages of development).

The clinical development of future products will have to take into account the difficulties and limitations inherent with the type of product and with the availability of drugs already authorised and recommended. Considerations should be given to choice of comparator (i.e. placebo and/or active control) and other aspects of trial design, especially for studies to be conducted in patients with severe influenza, including more or less stringent inclusion criteria (e.g. ILI, rapid antigen tests, RT-PCR), and the definition and relevance of clinical and virological endpoints. It remains to be seen whether these new influenza antiviral compounds will be more effective compared to the currently authorised drugs.

Antivirals in combination therapy

Combination of antiviral agents with different mechanisms of action is a possibility to enhance potency and reduce risk of resistance emergence [47].

Several randomised controlled trials are underway assessing such combinations, e.g. oseltamivir + hyperimmune globulin or oseltamivir + nitazoxanide compared to oseltamivir treatment only, and the results from these studies will guide marketing authorisation as well as public health guidance in the future. Antiviral combination therapies have been successful for other RNA-viruses such as hepatitis C and HIV; in the setting of these chronic viral infections, they provide additive antiviral activity and the reduce risk of antiviral resistance.

Strengths and limitations of methodology

The evidence for this report was synthesised using different methods, and was specifically derived from three new systematic reviews published between 2014 and 2015 summarising data collected in randomised controlled trials, and referrals to additional literature identified by a panel of experts. This approach has with reasonable confidence identified most of the RCTs on efficacy of NAIs; however the observational studies reviewed here will be a subset of the available evidence, and the focus was on identifying larger meta-analyses as well as studies of smaller, clinically relevant subsets of the population, where insufficient evidence was available from RCTs (specific risk groups, such as populations with specific chronic diseases, pregnant women, children, etc.).

This ECDC Expert Opinion is based on the scientific evidence identified through the literature review described above, followed by the formulation of expert opinions by a group of independent experts from public health authorities, regulatory authorities and academic experts, mainly from the EU/EEA, who reviewed the evidence.

The literature included was limited to publications released up to February 2015. The additional literature provided by the experts proved useful as it allowed the inclusion of relevant evidence that would have otherwise been omitted. However, most of the literature included post-hoc was not discussed during the meeting with the experts, only included in the drafting of this opinion.

Next steps

Once this document has gone through a four week public consultation, an updated version of the scientific advice contained in this document will then be disseminated by ECDC through the European Commission's Directorate General for Health, the Health Security Committee, and the ECDC Advisory Forum, as well as published on the ECDC website.

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