



Clinical practice guidelines for influenza

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**World Health
Organization**

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This publication is the update of the document published in 2022 entitled “*Guidelines for the clinical management of severe illness from influenza virus infections*”.

ISBN 978-92-4-009775-9 (electronic version)

ISBN 978-92-4-009776-6 (print version)

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Cataloguing-in-Publication (CIP) data. CIP data are available at <https://iris.who.int/>.

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CORRIGENDA

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ISBN 978-92-4-009775-9 (electronic version)

ISBN 978-92-4-009776-6 (print version)

Table 9.4, lines 3

Delete:

Children < 10 years 20 mg single dose for 2 days

Insert:

Children < 10 years 20 mg single dose

Annex 1, Flow chart

Delete:

Laninamivir 20mg inhaled once daily for 3 days

Insert:

Laninamivir 20mg inhaled once daily for 2 days

These corrections have been incorporated into the electronic file on 17 September 2024.

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Acknowledgements

The World Health Organization would like to thank the collaborative efforts of all those involved in making this process rapid, efficient, trustworthy and transparent.

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Special thanks to the external reviewers: Yaseen Arabi (King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia); Richard Kojan (Alliance for International Medical Action, Democratic Republic of the Congo); Miriam Stegemann (Charité - Universitätsmedizin Berlin, Germany).

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Funding: Office of Global Affairs, United States Department of Health and Human Services.

Abbreviations

ARDS	acute respiratory distress syndrome
CI	confidence interval
DIA	digital immunoassay
DOI	declaration of interests
GDG	Guideline Development Group
HPAI	highly pathogenic avian influenza
HR	hazard ratio
IAV	influenza A virus
IBV	influenza B virus
ICU	intensive care unit
IRP	infectious respiratory particle
LMICs	low- and middle-income countries
LPAI	low pathogenic avian influenza
MD	mean deviation
MID	minimally important difference
mTOR	mammalian target of rapamycin
NAAT	nucleic acid amplification test
NAI	neuraminidase inhibitor
NMA	network meta-analysis
NSAIDs	non-steroidal anti-inflammatory drugs
OR	odds ratio
PICO	population, intervention, comparison, outcome
QALD	quality-adjusted life day
RCT	randomized controlled trial
RdRp	RNA-dependent RNA polymerase
RIDT	rapid influenza diagnostic tests
RNAP	RNA polymerase
RR	relative risk
RT-PCR	reverse transcriptase polymerase chain reaction
WHO	World Health Organization

1. Executive summary

1.1 Clinical questions

1. What is the role of medications in the treatment of patients with influenza virus infection?
2. What is the best diagnostic strategy for patients with suspected influenza virus infection?
3. What is the role of medications in the prevention of influenza virus infection?

1.2 Context

The evidence base for therapeutics for influenza continues to evolve with a number of randomized controlled trials (RCTs) recently completed and others under way. In this update, the scope of the guideline has been expanded from the previously published WHO guideline that focused on the clinical management of patients with severe influenza or at risk of severe influenza.

The purpose of these updated guidelines is to assist clinicians in the care of persons with suspected or confirmed influenza virus infection. This update includes recommendations on the management of both severe and non-severe influenza and also includes recommendations on the use of antiviral medications to prevent influenza virus infection in individuals exposed to the virus in the previous 48 hours. This update applies to patients with seasonal influenza viruses, pandemic influenza viruses and novel influenza A viruses known to cause severe illness in infected humans (zoonotic influenza), such as avian influenza A(H5N1), A(H5N6) and A(H7N9). This update also includes baseline risk estimates for hospitalization and death pooled from observational studies, and proposed definitions of patients at high or extremely high risk of developing severe influenza, so as to enable the recommendations to be targeted appropriately (see *Section 5*).

1.3 Target audience

The guidelines are designed primarily for health care providers who manage patients with influenza virus infection. The guidelines can be applied at all levels of the health system including community-based care, primary care, emergency departments and hospital wards.

The guidelines will also serve as a reference source for policymakers, health managers and health facility administrators to support the development of national, regional and local guidelines for epidemic and pandemic preparedness.

This guideline provide recommendations on the following:

- Treatment with antivirals for both severe and non-severe influenza;
- Treatment with adjunctive therapies for patients with severe influenza, including corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), macrolides and passive immune therapy;
- Use of diagnostic testing strategies to guide treatment of patients with, or at risk of, influenza virus infection;
- Use of antivirals to prevent symptomatic influenza;
- Use of concomitant antibiotics in patients with non-severe influenza.

1.4 New recommendations for antiviral and antibiotic treatment of patients with non-severe influenza

- conditional recommendation for the use of baloxavir for patients with non-severe influenza and at high risk of progression to severe disease;
- conditional recommendation against the use of baloxavir for patients with non-severe influenza at low risk of progression to severe disease;
- conditional recommendation against the use of laninamivir for patients with non-severe influenza;
- strong recommendation against the use of oseltamivir for patients with non-severe influenza;
- conditional recommendation against the use of peramivir for patients with non-severe influenza;
- strong recommendation against the use of zanamivir for patients with non-severe influenza;
- strong recommendation against the use of favipiravir for patients with non-severe influenza;
- conditional recommendation against the use of umifenovir for patients with non-severe influenza;
- strong recommendation against the use of antibiotics for patients with non-severe influenza and low probability of bacterial co-infection.

1.5 New recommendations for antiviral treatment of patients with severe influenza (including infection with novel influenza A associated with high mortality or unknown risk of severe disease)

- conditional recommendation for the use of oseltamivir for patients with severe influenza;

- conditional recommendation against the use of peramivir for patients with severe influenza;
- conditional recommendation against the use of zanamivir for patients with severe influenza.

1.6 New recommendations for adjunctive treatment of patients with severe influenza

- conditional recommendation against the use of macrolides for patients with severe influenza and without bacterial co-infection;
- conditional recommendation against the use of plasma therapy for patients with severe influenza;
- conditional recommendation against the use of mTOR inhibitors for patients with severe influenza;
- conditional recommendation against the use of corticosteroids for patients with severe influenza.

1.7 New recommendations for prevention amongst persons with exposure to seasonal influenza virus but without infection

- conditional recommendation for the use of baloxavir for asymptomatic persons at extremely high risk for hospitalization if they were to develop seasonal influenza;
- conditional recommendation against the use of laninamivir for asymptomatic persons not at extremely high risk for hospitalization if they were to develop seasonal influenza;
- conditional recommendation for the use of oseltamivir for asymptomatic persons at extremely high risk for hospitalization if they were to develop seasonal influenza;
- conditional recommendation against the use of zanamivir for asymptomatic persons not at extremely high risk for hospitalization if they were to develop seasonal influenza.

1.8 New recommendations for prevention amongst persons with exposure to zoonotic influenza virus (novel influenza A associated with high mortality) but without infection

- conditional recommendation for the use of baloxavir;
- conditional recommendation for the use of laninamivir;

- conditional recommendation for the use of oseltamivir;
- conditional recommendation for the use of zanamivir.

1.9 New recommendations for testing strategies for patients with suspected seasonal influenza virus infection

- conditional recommendation for use of nucleic acid amplification test (NAAT) for diagnosis of influenza in patients with suspected severe influenza;
- conditional recommendation for use of digital immunoassay (DIA) or NAAT for diagnosis of influenza in patients with suspected non-severe influenza.

1.10 About these guidelines

This updated guidelines from the World Health Organization (WHO) incorporate available new evidence, enabling updated recommendations on the treatment of influenza virus infection. The Guidelines Development Group (GDG) typically evaluates a therapy when WHO judges sufficient evidence is available to make a recommendation. While the GDG takes an individual patient's perspective in making recommendations, it also considers resource implications, acceptability, feasibility, equity and human rights. The guidelines were developed according to standards and methods for trustworthy guidelines.[1]

1.11 Updates and access

This publication is the update of the document published in 2022 entitled "Guidelines for the clinical management of severe illness from influenza virus infections". The current guidelines and earlier documents are available through the [WHO Clinical management of influenza website](#) and [MAGIC platform](#) (both online and also as PDF outputs for readers with limited internet access).

Guideline summaries are available as flowcharts in PDF and Powerpoint format [2-5].

2. Introduction

Influenza is an acute respiratory viral infection caused by influenza viruses. Worldwide, annual seasonal influenza epidemics are estimated to result in approximately 1 billion annual clinical cases, 3 to 5 million cases of severe illness and approximately 290 000 to 650 000 deaths [6, 7]. In 2018, in children under 5 years, there were an estimated 109.5 million influenza virus episodes globally with 870 000 hospital admissions and up to 34 800 influenza virus associated deaths [8]. Although the effects of seasonal influenza epidemics in low- and middle-income countries (LMICs) are not fully known, research suggests that 99% of deaths in children under 5 years of age with influenza-related lower respiratory tract infections occur in LMICs [9].

There are four types of influenza viruses: types A, B, C and D. Seasonal influenza A and B viruses circulate among humans worldwide. Influenza C viruses are not typically captured by influenza surveillance [10]. Influenza D viruses primarily affect cattle and are not known to cause illness in humans.

Influenza A viruses are further classified into subtypes according to the combinations of the proteins on the surface of the virus.

Influenza B viruses are not classified into subtypes but can be subclassified into two lineages. Currently circulating influenza type B viruses belong to either the B/Yamagata or B/Victoria lineages.

Only influenza type A viruses are known to have caused pandemics.[7]

Current respiratory virus epidemiologic update can be found at: [Global Influenza Programme \(who.int\)](http://Global Influenza Programme (who.int)).

2.1 Seasonal and pandemic influenza

2.1.1 Circulation and transmission

As of March 2024, influenza A viruses circulating in humans are subtype A(H1N1) and A(H3N2) influenza viruses. Currently circulating influenza type B viruses belong to either the B/Yamagata or B/Victoria lineages. The A(H1N1) is also classified as A(H1N1)pdm09 as it caused the pandemic in 2009 and replaced the previous A(H1N1) virus which had circulated prior to 2009. A(H3N2) virus caused the 1968 pandemic and has continued to circulate as a seasonal influenza A virus.

Seasonal influenza A and B viruses and pandemic influenza A viruses can spread readily from person to person, via infectious respiratory particles (IRP), which are transmitted through the air when an infected person coughs or sneezes. These IRPs are dispersed into the air and deposited on the conjunctiva, mouth, nose, throat or pharyngeal mucosa of another susceptible person [11].

The WHO has recently defined these modes of “through the air” transmission as either **airborne transmission**, occurring when IRPs expelled into the air and enter, through inhalation, the respiratory tract of another person; or **direct deposition**, occurring when IRPs are expelled into the air and follow a short-range semi-ballistic trajectory, and directly deposit onto the exposed facial mucosal surfaces (mouth, nose or eyes) of another person, entering the human respiratory tract via these portals [12]. With influenza, smaller IRPs may travel up to 2 m [13].

In addition, the virus can also be potentially spread by the hands of infected individuals via fomites contaminated with influenza virus and subsequent inoculation into the upper respiratory tract [11].

2.1.2 Pandemic Influenza

Rarely, influenza pandemics can result in high illness attack rates as well as high hospitalization and mortality rates due to a lack of immunity by most of the world’s population to a novel pandemic influenza A virus that is antigenically distinct from previously circulating seasonal influenza A viruses. Hospitalization rates for children and non-elderly adults are often substantially higher during pandemic influenza waves than for seasonal influenza epidemics.

The effectiveness of antiviral treatment of patients with pandemic influenza will depend on their susceptibility to these antivirals. If effective, their impact to reduce the risk of hospitalization or death may be higher than for seasonal influenza because untreated persons with pandemic influenza will likely have a higher baseline risk of severe disease and death. It is imperative to rapidly implement clinical trials during pandemics to assess the efficacy and safety of pharmacologic interventions.

2.2 Zoonotic influenza

2.2.1 Circulation and transmission

Humans can be infected sporadically with novel influenza A viruses of animal origin (zoonotic influenza), such as avian influenza A virus subtypes A(H5N1), A(H5N6),

A(H7N9), A(H7N7) and A(H9N2) and swine influenza A virus subtypes A(H1N1), A(H1N2) and A(H3N2) [14]. Human infections are primarily acquired through direct contact or close exposure to infected animals or contaminated environments; these viruses have not acquired the ability of sustained transmission among humans.

2.2.2 Nomenclature

In their avian host, avian influenza A viruses are described as **highly pathogenic (HPAI)**, meaning they cause severe disease in birds vs. **low pathogenic (LPAI)**, meaning they do not cause birds to become severely ill.

Patients with zoonotic influenza virus infection associated with high mortality in humans, include HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9).

2.3 Diagnosis

Clinical diagnosis of influenza is challenging as the signs and symptoms of the disease can be non-specific (many respiratory pathogens can cause a similar illness) and can vary depending on virus type as well as patient host characteristics and other factors. Reverse transcription polymerase chain reaction (RT-PCR) is the gold standard for influenza diagnosis because of its high sensitivity and high specificity for detection of influenza viruses in respiratory specimens. However, RT-PCR requires highly specialized equipment, and the turnaround times for results may not be timely enough to inform clinical management decisions.

Rapid diagnostic tests for respiratory specimens, such as rapid influenza diagnostic tests (RIDTs) that detect influenza virus antigens; digital immunoassays (DIAs) that are RIDTs with analyzer devices; and rapid nucleic acid amplification tests (NAATs or molecular assays) are available in clinical settings and can provide results within 30 minutes.

Diagnostic test accuracy requires proper specimen collection, storage and transport. Key factors for diagnostic accuracy include: a) timing of sample collection (when compared with symptom onset); b) site from which sample is taken (upper vs. lower respiratory tract); and c) processing of specimen and transport. Practical considerations for specimen collection and interpretation of testing results are detailed in a 2019 publication and summarized below:

- Nasopharyngeal or combined nasal and throat swabs are preferred for testing of seasonal influenza A and B viruses or zoonotic influenza viruses in patients without respiratory failure.
- Lower respiratory tract specimens (endotracheal aspirate, bronchoalveolar lavage fluid) may be useful for testing critically ill patients with respiratory failure who test negative for influenza viruses in upper respiratory tract specimens.

This guideline reviews currently available diagnostics and their performance and their utility in diagnostic strategies to inform treatment of patients with non-severe and severe influenza (see *Section 10*).

2.4 Clinical management

Supportive and symptomatic care is important for patients with influenza as well as identifying those patients with either severe disease or at high risk of developing severe disease. The clinical management of patients with severe influenza virus infection requires the provision of optimal supportive care, such as monitoring with pulse oximeter, providing the patient with medical oxygen and respiratory support when indicated, while also administering efficacious specific therapies for influenza. Recommendations on the optimal provision of the supportive therapies for severely ill patients is not in the scope of this guideline.

Baloxavir, a newer antiviral, with a different mechanism of action (selective inhibitor of influenza cap-dependent endonuclease) than Neuraminidase inhibitors (NAIs), has been approved in some jurisdictions for early treatment of paediatric and adult patients with uncomplicated influenza [15]. NAIs are both widely available and active in vitro against all currently circulating seasonal influenza A and B viruses and zoonotic influenza A viruses. Of the four NAIs that are commercially available (inhaled laninamivir, oral oseltamivir, intravenous peramivir, and inhaled zanamivir), oseltamivir is the most widely studied and available.

This guideline presents new recommendations based on systematic reviews of the clinical trial data on safety and efficacy of these antiviral treatments and immunomodulators in patients with non-severe and severe influenza virus infection, and their use as prophylaxis in persons exposed to influenza virus.

3. Guideline development and implementation

3.1 What triggered this update and what is coming next

This is an update of [WHO Guidelines for the clinical management of severe illness from influenza virus infections](#) that was published in 2022.[16] This was triggered by:

- A systematic review of observational data giving an updated baseline risk estimates for hospital admission and death in patients with non-severe and severe influenza virus infections, including those with seasonal and zoonotic influenza A viruses associated with high mortality in humans (see Sections 6.1 and 5.7).
- Updated list of independent risk factors associated with severe disease and mortality based on the prognosis review.
- Updated threshold for an important reduction in risk of hospitalization, mortality and symptom duration based on surveys of the GDG.
- New systematic reviews on antivirals for treatment of severe and non-severe influenza patients [17, 18].
- Updated systematic reviews on adjunctive immunomodulator treatments for treatment of patients with severe influenza [19].
- New systematic reviews on antivirals for prophylaxis for persons exposed to seasonal or zoonotic influenza viruses.
- Updated decision-making model for diagnostic strategies for caring for patients with influenza virus infection (see Section 18).

3.2 How to access and use this guideline

This current PDF-format guideline, and earlier documents, are available through the [WHO Clinical management of influenza website](#).

Additionally, the guideline is provided on [MAGIC platform](#) (both online and also as PDF outputs for readers with limited internet access). The purpose of the online formats and additional tools is to make it easier to navigate and make use of the guideline in busy clinical practice. The online multi-layered formats are designed to allow end-users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making (clinical encounter decision aids).

4. Who do these recommendations apply to?

This guideline applies to patients with influenza virus infection and to persons who are exposed to influenza viruses. Recommendations may differ based on the severity of influenza, according to severity definitions (see below).

4.1 WHO definitions of disease severity for influenza

Non-severe influenza: Uncomplicated, non-severe, influenza illness is characterized by symptoms including a sudden onset of cough, headache, muscle and joint pain, severe malaise, sore throat and rhinorrhea, with or without fever. Most people recover from the fever and other symptoms within a week, without requiring medical attention. Defined as absence of any criteria of severe disease.

Severe influenza: Influenza virus can also cause severe illness (such as sepsis, septic shock, severe pneumonia, acute respiratory distress syndrome [ARDS], multi-organ failure, exacerbation of chronic medical conditions) or death. These conditions would normally require hospitalization and in some severe and critical cases the provision of oxygen, mechanical ventilation (invasive or non-invasive) and/ or vasopressor therapy.

Patients with novel influenza A associated with high mortality, or with an unknown risk of severe disease, should be considered as “severe influenza” even if they do not otherwise fulfil the criteria.

5. Overview of medications, recommendations and key issues to consider when applying them

When applying the recommendations, clinicians should also consider the following key issues:

How to identify patients with non-severe influenza at high risk of hospitalization

In several sections of this guideline WHO recommends using antiviral treatments only for those patients at high risk for hospitalization, because the absolute benefit would be trivial if everyone with non-severe influenza were to receive treatment (see Sections 5.1 and 5.2). The risk factors were developed based on a commissioned systematic review of observational studies of patients with non-severe influenza.

Patients at high risk of hospitalization includes those with at least one major risk factor (odds ratio [OR] > 2.0).

- Age 65 years or more: The risk of a patient developing severe disease increases with an OR of 1.72 for each additional 10 years of age and an OR of 2.94 for an increase of every 20 years of age. The median age of patients included in the analysed studies was 57 years. Based on this analysis a reasonable threshold for high risk of developing severe disease in a patient with non-severe disease was determined to be 65 years;
- Immunocompromising conditions;
- Cardiovascular disease;
- Neurological disease;
- Chronic respiratory disease.

Patients at extremely high risk of hospitalization includes, defined by:

- Age 85 years or more; or
- Any age + multiple major risk factors.

Note: Patients infected with novel influenza A viruses (zoonotic influenza) associated with high mortality in humans are also considered to be high risk for hospitalization. These include HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9). (see Sections 5.1 and 5.2 for more details).

5.1 Risk factors associated with severe disease and death

To support the recommendations in this guideline it was important to determine, for patients with non-severe influenza, the risk factors for these patients developing severe disease. Severe disease is defined as either requiring hospitalization, or as according to specific study definitions. While previous WHO and other guidelines have provided lists of risk factors, for this guideline WHO commissioned a systematic review of observational studies of patients with non-severe influenza to attempt to determine the most significant risk factors for patients with non-severe influenza developing severe disease. Due to the volume of observational data to be analyzed this review was not available until March 2024, after the meeting of the GDG in December 2023.

The review conducted a similar search to the systematic review that was used to determine the baseline risk for influenza. The review only used fully adjusted results from each study for analysis. As most eligible studies reported odds ratios (OR) as the measure of association, if studies reported relative risks (RRs) or hazard ratios (HRs), the review team converted them to ORs and pooled ORs using the random effects model.

In discussion with the Methodology Chair, and subsequently confirmed with the GDG, it was determined that the criteria for determining whether a risk factor was significant for predicting hospitalization in patients with non-severe disease were that, in the review of observational data, the risk factor had an OR of greater than 2.0 and there was at least a moderate certainty of evidence. Additional, but less impactful, risk factors were noted if a risk factor had at least a moderate certainty of evidence and an OR of between 1.7 and 2.0. Those with a low or very low certainty of evidence or an OR of less than 1.7 were not considered significant risk factors.

Table 5.1 Risk factors for hospitalization in non-severe influenza

Risk factor	Study results and measurements	Certainty of the evidence	Summary
Age (per 10 years increase)	Odds ratio: 1.72 (95% CI 1.02 - 2.89) Based on data from 1 study	Moderate Due to serious imprecision	Age is probably associated with increased odds of hospitalization in non-severe patients.
HIV, immunodeficiency, or immunosuppression	Odds ratio: 2.7 (95% CI 1.55 - 4.7) Based on data from 2 studies	High	HIV, immunodeficiency, or immunosuppression is associated with increased odds of hospitalization in non-severe patients.
Anaemia	Odds ratio: 1.39 (95% CI 0.88 - 2.19) Based on data from 2 studies	Moderate Due to serious imprecision	Anaemia is probably associated with little or no increase in hospitalization in non-severe patients.
Asthma	Odds ratio: 1.46 (95% CI 0.95 - 2.24) Based on data from 2 studies	Moderate Due to serious imprecision	Asthma is probably associated with little or no increase in hospitalization in non-severe patients.
Any cardiovascular diseases	Odds ratio: 2.72 (95% CI 1.24 - 5.94) Based on data from 3 studies	Moderate Due to serious inconsistency	Any cardiovascular diseases are probably associated with increased odds of hospitalization in non-severe patients.
Diabetes	Odds ratio: 1.84 (95% CI 1.26 - 2.67) Based on data from 4 studies	Moderate Due to serious inconsistency	Diabetes is probably associated with increased odds of hospitalization in non-severe patients.
Hypertension	Odds ratio: 1.61 (95% CI 0.92 - 2.83) Based on data from 2 studies	Moderate Due to serious imprecision	Hypertension is probably associated with little or no increase in hospitalization in non-severe patients.
Any liver diseases	Odds ratio: 1.87 (95% CI 0.89 - 3.94) Based on data from 3 studies	Very low Due to serious inconsistency. Due to very serious imprecision	We are uncertain whether any liver diseases are associated with increased odds of hospitalization in non-severe patients.
Malignancy	Odds ratio: 1.75 (95% CI 1.12 - 2.75) Based on data from 3 studies	High	Malignancy is associated with increased odds of hospitalization in non-severe patients.
Any neurological diseases	Odds ratio: 2.31 (95% CI 1.65 - 3.24)	High	Any neurological diseases are associated with increased odds of

	Based on data from 4 studies		hospitalization in non- severe patients.
Obesity	Odds ratio: 1.02 (95% CI 0.98 - 1.07) Based on data from 1 study	Moderate Due to serious imprecision	Obesity is associated with little or no increase in hospitalization in non-severe patients.
Pregnancy	Odds ratio: 1.88 (95% CI 1.73 - 2.05) Based on data from 1 study	High	Pregnancy is associated with increased odds of hospitalization in non-severe patients.
Any renal diseases	Odds ratio: 1.66 (95% CI 1.54 - 1.79) Based on data from 2 studies	High	Any renal diseases are associated with increased odds of hospitalization in non-severe patients.
Respiratory diseases (unspecified)	Odds ratio: 1.74 (95% CI 0.95 - 3.19) Based on data from 3 studies	Very low Due to serious inconsistency. Due to very serious imprecision	We are uncertain whether unspecified respiratory diseases are associated with increased odds of hospitalization in non-severe patients.
Chronic respiratory diseases (unspecified)	Odds ratio: 2.24 (95% CI 1.9 - 2.64) Based on data from 2 studies	High	Chronic respiratory diseases (unspecified) are associated with increased odds of hospitalization in non-severe patients.
Sex (male vs. female)	Odds ratio: 1.01 (95% CI 0.86 - 1.18) Based on data from 5 studies	Low Due to serious inconsistency. Due to serious imprecision	Males may have little or no increase in hospitalization compared with females in non-severe patients.

The analysis clearly demonstrated the impact of increasing age on the risk of a patient developing severe disease with an OR of 1.72 for each additional 10 years of age. Further analysis confirmed that there was an OR of 2.94 for an increase of every 20 years of age. The median age of the patients included in the analysed studies was 57 years. Based on this analysis a reasonable threshold for high risk of developing severe disease in a patient with non-severe disease was determined to be 65 years.

The major risk factors, other than age, noted to meet the specified criteria as significant risk factors for patients with non-severe influenza developing severe disease are:

- immunocompromise
- cardiovascular disease

- neurological disease
- chronic respiratory disease.

Additional risk factors that had an OR of 1.7 - 2 include:

- malignancy
- pregnancy
- diabetes.

Therefore, a patient could be considered high risk for severe disease if they had one of the major risk factors OR were 65 years or older. Evidently, as patients become older their risk of severe disease increases significantly. Furthermore, the presence of multiple risk factors also increases their risk.

In order to assist clinicians in interpretation of the guidance provided by the GDG it also is necessary to define a group of patients that are extremely high risk for severe disease. This would include patients above 85 years old with or without additional risk factors or patients at a younger age that have multiple major and additional risk factors that the clinician determines places the patient at extremely high risk of severe disease.

As an additional analysis of observational data, risk factors were also assessed for their impact on mortality (see *Table 5.2*).

5.2 Influenza baseline risks (prognosis)

In order to inform the recommendations within this guideline and to assist clinicians managing influenza it was recognized by the steering committee that as accurate an estimate as possible of the baseline risks of hospitalization and mortality for influenza, both seasonal and zoonotic, needed to be determined. Therefore, a systematic review of prognosis from observational studies assessing the prognosis for patients with influenza was undertaken in 2023.

With the aid of an expert librarian, the review team searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Global Health from database inception to 26 October 2023. The search terms included "influenza", "hospital", "death", "mortality", and "fatality". To identify any additional studies meeting our eligibility criteria, the review team screened the reference lists of eligible studies and relevant systematic reviews. The review included studies of patients with laboratory-confirmed influenza virus infections reporting hospitalization and/ or mortality among the influenza patients. To avoid overlapping population data, the review included only cohort studies or studies with surveillance data. To estimate pooled

hospitalization and mortality rates and their associated 95% confidence intervals (CIs), the review team conducted meta-analyses of proportions using fixed effects models.

Due to the volume of studies, this analysis was not able to be completed prior to the meeting of the GDG in December 2023. Therefore, for the purposes of the GDG discussion, estimates of baseline risk were determined based on a small number of high-quality observational studies and data from the included RCTs.

However, in March 2024 the systematic review of observational studies was completed and we are now able to provide baseline risks (prognosis) for patients with non-severe and severe seasonal influenza and for zoonotic influenza (see Table 5.3).

For non-severe patients it had been proposed that these observational data would be able to provide differential estimates of hospitalization and mortality risk for patients at high risk of severe disease and for patients at low risk of severe disease. Unfortunately, however, there was a high degree of heterogeneity in how the reviewed studies assessed a patient's risk of developing severe disease. Therefore, mortality and hospitalization are presented for patients with non-severe disease without differentiating between high- and low-risk patients.

Importantly, the prognostic reviews accurately reflected the baseline risks that were estimated from RCTs and used for the GDG deliberations on the recommendations contained within this guideline.

For the purposes of this review the zoonotic diseases included in the analysis were those novel influenza A viruses associated with severe disease in infected humans, specifically HPAI A (H5N1), A(H5N6) and A(H7N9) viruses and LPAI A(H7N9) virus, and not all novel influenza A virus infections.

Table 5.2. Risk factors associated with mortality in non-severe influenza

Outcome	Study results and measurements	Certainty of the evidence	Summary
Age (per 10 years increase)	Odds ratio: 1.68 (95% CI 1.52 - 1.86) Based on data from 1 study	High	Age is associated with increased odds of all-cause mortality in non-severe patients.
Charlson comorbidity index per point increase)	Odds ratio: 1.28 (95% CI 1.23 - 1.33) Based on data from 1 study	High	Charlson comorbidity index is associated with increased odds of all-cause mortality in non-severe patients.
Any cardiovascular diseases	Odds ratio: 1.14 (95% CI 0.9 - 1.45) Based on data from 1 study	Moderate Due to serious imprecision	Any cardiovascular diseases are probably associated with little or no increase in all-cause mortality in non-severe patients.
Diabetes	Odds ratio: 0.9 (95% CI 0.68 - 1.19) Based on data from 1 study	Low Due to very serious imprecision	Diabetes may be associated with little or no increase in all-cause mortality in non-severe patients.
Hypertension	Odds ratio: 1.07 (95% CI 0.79 - 1.47) Based on data from 1 study	Low Due to very serious imprecision	Hypertension may be associated with little or no increase in all-cause mortality in non-severe patients.
Sex (male vs. female)	Odds ratio: 1.41 (95% CI 0.96 - 2.08) Based on data from 2 studies	Moderate Due to serious imprecision	Males probably have little or no increase in all-cause mortality compared with females in non-severe disease.
Smoking	Odds ratio: 1.4 (95% CI 1.09 - 1.81) Based on data from 1 study	High	Smoking is associated with increased odds of all-cause mortality in non-severe patients.

Table 5.3 Baseline risks for non-severe and severe influenza

Outcome	Percentage (95% CI)	Baseline risk
Mortality – non-severe illness (seasonal)	0.10% (0.10 - 0.11)	1 per 1000
Mortality – severe disease (seasonal)	2.97% (2.93 - 3.01)	30 per 1000

Mortality – zoonotic disease (AH5N1, AH7N9, AH5N6)	38.30% (36.4 - 40.11)	383 per 1000
Hospitalization – non-severe (seasonal)	0.8% (0.79 - 0.80)	8 per 1000

6. What are the mechanisms of action of the antivirals?

Existing small molecule directly acting antiviral drugs for influenza target four stages of the viral lifecycle, which are the M2 ion channel, fusion, RNA-dependent RNA polymerase (RdRp) and neuraminidase [20]. Thus, available medicines distinctly target entry, replication or budding. Drugs targeting the RdRp can be further differentiated according to their specific mechanism of action as either nucleoside RNA polymerase (RNAP) inhibitors or cap-snatching inhibitors. Certain mechanisms of action are specific to influenza A virus (IAV) whereas others are also relevant to influenza B virus (IBV), and some drugs are more predisposed to selection of drug resistance than others. At the time of the GDG meeting, widespread global resistance was recognized for M2 ion channel inhibitors such as amantadine and rimantadine, and for this reason adamantanes were not considered during the discussions.

Directly acting antiviral drugs for influenza are dosed via different routes of administration and these include oral, intravenous, or inhaled delivery. The panel noted that oral and intravenous delivery routes provide higher drug concentrations systemically, and that inhalation enables the drug to be delivered directly to the respiratory tract, but that systemic exposure is limited for this route. Furthermore, intravenous administration is the only route that enables the entire dose to be absorbed into the systemic circulation, and that different drugs have different bioavailability when administered orally. Consideration of the route of administration may be important because while most seasonal influenza viruses exhibit replication that is overwhelmingly restricted to the respiratory tract, some influenza viruses (particularly avian) also have tropisms to the gastrointestinal tract, eye and/or brain [21]. The following sections summarize the mechanisms of action for drug classes considered by the GDG as part of guideline development.

6.1 Baloxavir/ cap-snatching inhibitors

The sole cap-snatching inhibitor considered by the GDG was baloxavir marboxil [22]. Due to its long pharmacokinetic half-life, baloxavir is dosed orally as a single dose (40 mg if 40–80 kg; 80 mg if \geq 80 kg). However, the GDG noted that while the plasma concentration are highest over the days following administration, there is a subsequent tail of low exposure lasting for several weeks [23], which may have implications for selection of resistance if the virus is not cleared rapidly. The influenza

RdRp complex includes a subunit with endonuclease activity, which provides a “cap-snatching function” to steal short 5'-capped RNA primers from host mRNAs. The drug is given as a carboxyl pro-drug that is hydrolyzed to the active form, which inhibits this endonuclease activity and thereby block viral replication.

Resistance: Importantly, mutations in the endonuclease subunit which confer reduced susceptibility to baloxavir have been reported from in vitro selection studies and in clinical isolates [24]. Furthermore, treatment-emergent substitutions have been more common in children than adults and more common with some influenza subtypes than others.

Pregnancy: In non-clinical reproduction studies, no adverse developmental effects of baloxavir marboxil were observed in rats or rabbits when administered orally at doses providing plasma concentrations > 5-fold higher than those achieved at the maximum human dose [25]. Due to lack of safety and efficacy data for baloxavir treatment of pregnant and postpartum women, baloxavir is currently not recommended for use in pregnant people [26].

Lactation: Baloxavir and its related metabolites were excreted in the milk of lactating rats administered baloxavir marboxil but no effects on growth or postnatal development were observed in nursing pups.

Children: Baloxavir marboxil has been studied clinically in patients > 5 years of age with adverse events similar to those reported in adults [27]. However, limited data are available for patients ≤ 5 years of age [28].

6.2 Neuraminidase inhibitors

Neuraminidase serves to remove terminal sialic acid residues, which enables detachment of new virions from the host cell; neuraminidase inhibitors therefore prevent release and spread of progeny virions [22, 29]. Some evidence suggests that these drugs may also block neuraminidase-mediated cellular attachment and entry for some influenza viruses. Importantly, drugs in this class target all neuraminidase subtypes and are therefore active against IAV and IBV viruses. However, differences in the chemical structure between drugs in this class mean that there are important differences in pharmacokinetics, route of administration, and/ or susceptibility profile, which warrant further consideration.

6.2.1 Laninamivir, for treatment of influenza

Laninamivir is administered by inhalation as a single dose as an octanyl ester prodrug and exhibits better pharmacokinetic properties in the respiratory tract and slower dissociation from influenza than other drugs in this class.

Resistance: Emergent variants with reduced susceptibility during treatment are rare but have been reported to be selected *in vitro*. Importantly, some influenza virus variants with loss of susceptibility to oseltamivir and peramivir remain sensitive to laninamivir [30].

Pregnancy: Insufficient human data are available to robustly assess safety of laninamivir during pregnancy [26].

Children: Laninamivir has been used clinically in children, with different doses for children < 10 years of age than for adults or children ≥ 10 years of age [31].

6.2.2 Oseltamivir, for treatment of influenza

Oseltamivir is administered orally.

Resistance: The prevalence of oseltamivir resistance was very high among circulating seasonal influenza A during 2008–2009. Notwithstanding, the subsequent emergent and dominant pandemic influenza A (pdm09) virus exhibits low prevalence of oseltamivir resistance [32]. However, treatment-emergent resistance occurs with a single amino acid change and may be more common in young children [33].

Pregnancy: Observational studies of oseltamivir use during pregnancy suggest that it is safe during pregnancy and does not result in adverse pregnancy outcomes [34].

Children: Other authorities have approved oseltamivir for treatment of influenza in children ≥ 14 days old [35].

6.2.3 Peramivir, for treatment of influenza

Peramivir is administered intravenously and exhibits a long pharmacokinetic half-life and a higher potency than other drugs in this class.

Resistance: Certain variants with loss of susceptibility to oseltamivir are cross-resistant to peramivir [30].

Pregnancy: Insufficient human data are available to robustly assess safety of peramivir during pregnancy [26].

Children: Some authorities have approved peramivir for use in children \geq 6 months of age [36].

6.2.4 Zanamivir, for treatment of influenza

Zanamivir is administered by inhalation. It should not be used in adults or children with underlying respiratory disease (including asthma and other chronic lung diseases) [37].

Resistance: Emergent variants with reduced susceptibility during treatment have been rare but have been reported (particularly in immunocompromised patients). However, some influenza virus variants with loss of susceptibility to oseltamivir remain sensitive to zanamivir [32].

Pregnancy: Observational studies of zanamivir use during pregnancy suggest that it is safe during pregnancy and does not result in adverse pregnancy outcomes [26].

Children: Some authorities have approved zanamivir for treatment of influenza in children \geq 7 years of age [37].

6.3 Favipiravir (RNAP inhibitor)

The sole RNA Polymerase (RNAP) inhibitor considered by the GDG was favipiravir, which is dosed orally twice daily at 200 mg with a higher dose on the first day. Following metabolic activation, favipiravir is incorporated by the influenza RNAP into the RNA copy of the influenza genome [22, 38]. Favipiravir exhibits a multifaceted mechanism of action. The activated drug is incorporated in place of guanine or adenine into the copy of the viral genome, which renders subsequent copies mutated and unable to form viable progeny (a mechanism referred to as lethal mutagenesis). Additionally, when two consecutive incorporations occur, it results in delayed chain termination and RNAP backtracking.

Resistance: Favipiravir exhibits broad *in vitro* and *in vivo* activity against RNA viruses and is active against IAV and IBV [39].

Pregnancy: Favipiravir is a mutagen and based on data from animal studies, it should not be used during pregnancy [40].

Children: Favipiravir has been used in children but major uncertainties remain.

6.4 Umifenovir (fusion inhibitor)

The sole fusion inhibitor considered by the GDG was umifenovir, which is also sometimes referred to as arbidol. Umifenovir is an orally administered indol derivative with purported broad-spectrum antiviral activity for respiratory viruses [41]. Umifenovir has been demonstrated to interact with the pre-fusion conformations of haemagglutinin, stabilizing it against the low pH transition to its fusogenic state and thereby preventing fusion of virus and host membranes.

Resistance: Influenza viruses with reduced umifenovir susceptibility are selected *in vitro* with a single amino acid substitution, but no naturally occurring variants with loss of susceptibility have been documented to date.

Specific populations: In Russian Federation and China, the medication has been used for both IAV and IBV [42], but it should be noted that insufficient human data are available for use of umifenovir during pregnancy, breastfeeding or in children [22].

7. Recommendations for patients with non-severe symptomatic influenza (suspected or confirmed)

The following briefly describes how all relevant elements were used in decision-making, with further detail provided in *Section 11.1*. The key patient characteristics were the likelihood of progression to severe influenza and patient values and preferences. Key outcomes included the need for hospitalization, the duration of symptoms, the frequency and severity of adverse effects, and convenience of therapy on the one hand and burden of therapy on the other.

With regard to values and preferences, the panel inferred that most patients would choose to use a medication that had a small but important effect on outcomes they consider important, provided that there is a low likelihood of adverse effects, and that adverse effects when they do occur are mild. Further, the panel inferred that most patients would be reluctant to use a medication for which there was considerable uncertainty regarding its benefits and would only do so if the low certainty evidence suggested a benefit, there was a low likelihood of adverse effects, and that adverse effects when they do occur are mild.

Key to the decision-making was the threshold of importance that the panel inferred for each outcome of importance. To provide an example, the GDG inferred that the threshold for the use of baloxavir treatment of patients with non-severe influenza at high risk of progression to severe disease would be a reduction in hospitalization of 15 per 1000.

In addition to these considerations, the panel also inferred that convenience versus burden were important to patients. For instance, with respect to baloxavir, the panel noted that the drug is given as a single oral dose. This is convenient for patients and increases the appeal of this intervention.

Finally, in addition to taking an individual patient perspective, the GDG also considered a population perspective in which feasibility, acceptability, equity and cost were important considerations.

7.1 Antiviral therapies for patients with non-severe symptomatic influenza (suspected or confirmed)

7.1.1 Baloxavir

Conditional recommendation for

In patients with suspected or confirmed non-severe influenza virus infection and at high risk of progression to severe influenza, we **suggest administering baloxavir** (conditional recommendation, low-quality evidence).

- Patients with non-severe influenza and at high risk of developing severe disease include the following (see Sections 5.1 and 5.2):
 - Patients 65 years and older; or
 - Patients with one or more major risk factors for severe influenza.
- Patients with zoonotic influenza virus infection associated with high mortality in humans, including HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9), were not included in the clinical trials that informed this recommendation. The GDG agreed that evidence would indirectly apply to this population as well, in case they would present early to care with mild symptoms.
- Treatment should be administered as early as possible, and within 2 days of symptom onset.

7.1.1.1 Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

In patients with non-severe influenza virus infection and at high risk of progression to severe influenza, baloxavir treatment probably reduces time to alleviation of symptoms, may reduce admission to hospital but has little or no effect on mortality. Baloxavir does not increase adverse events related to treatment and probably has little or no effect on serious adverse events. Baloxavir may increase the risk of antiviral resistance emerging.

In clinical trials, baloxavir was administered to participants within 2 days of symptom onset of non-severe influenza virus infection. The benefit of administering baloxavir treatment to patients with non-severe influenza virus

infection and at high risk of progression to severe influenza more than 2 days after symptom onset is unknown.

Certainty of the evidence	Moderate
The evidence summary on baloxavir treatment of patients with non-severe influenza virus infection and at high risk of progression to severe influenza was informed by 3 RCTs and the number of patients informing estimates varied across outcomes from between 700 and 800 to over 2000.	
We have high certainty of little or no effect on mortality. Certainty of evidence was also rated as high for adverse events related to treatment. Certainty of evidence was rated as moderate for time to alleviation of symptoms, and serious adverse events related to treatment, and rated as low for admission to hospital and emergence of baloxavir resistance.	
Values and preferences	No substantial variability expected
Applying the agreed upon values and preferences (see <i>Section 11.2</i>), the GDG inferred that almost all well-informed patients with non-severe influenza virus infection and at high risk for complications and progression to severe influenza would choose to use baloxavir.	
Resources and other considerations	No important issues with the recommended alternative
<i>Acceptability and feasibility</i>	
Baloxavir treatment for non-severe influenza virus infection is a single oral dose, which provides an advantage for compliance.	
Baloxavir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that the use of baloxavir should, in many or perhaps most settings, be reserved for those at high risk of hospital admission.	
Due to cost and availability, barriers to access in LMICs may prove formidable. Those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing and treatments, and thus less access to the interventions. If advantaged patients in these settings receive the intervention, this may exacerbate health inequity. It is important that countries integrate the influenza clinical care pathway in the parts of the health system that provide care for patients with non-severe influenza (i.e., primary care, community care settings).	

The recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention. In promoting access, WHO has released an Expression of Interest for prequalification of baloxavir (to be done). Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly.

Access to influenza diagnostics

Due to the cost of antiviral medication such as baloxavir and their limited availability the GDG emphasized the importance of accurate diagnosis of influenza early in the disease course for those patients with an influenza-like illness and at risk of severe disease. This includes ensuring diagnostic results are available within the treatment window of 2 days of the development of symptoms. As this recommendation involves ideally administering treatment with baloxavir within 2 days of symptom onset, increasing access and ensuring appropriate use of diagnostic tests is essential for implementation. Thus, availability and use of appropriate influenza diagnostic tests is needed to improve access to medications, especially those targeting the early phase of disease. Health care systems must, however, gain expertise in choosing and implementing diagnostic tests, choosing those most applicable to their settings.

7.1.1.2 Justification

The conditional recommendation for baloxavir for patients at high risk of progression to severe disease rests on its possible reduction in hospitalization, its probable effect on reduction in duration of symptoms, its low likelihood of adverse effects, and on practical considerations. Baloxavir is given as a single oral dose. This is convenient for patients and increases the appeal of this intervention.

The GDG inferred that the threshold for the use of baloxavir treatment of patients with non-severe influenza at high risk of progression to severe disease would be a reduction in hospitalization of 15 per 1000. The estimated effect of baloxavir on hospitalization was 16 per 1000, just over the GDG threshold of importance, with a lower bound of the 95% CI of 4 more and an upper bound of 20 less.

The GDG inferred that the threshold for use of baloxavir treatment of patients with non-severe influenza virus infection would be a reduction in time to alleviation of symptoms by 1 day. The estimated effect of baloxavir treatment on time to alleviation of symptoms is a 1.02 days reduction, just over the GDG's threshold of importance, with a lower bound of the 95% CI of 0.63 days less.

As the baseline risk for dying from influenza in this population is only 2 per 1000 and our minimal important difference is 3 per 1000, even if baloxavir prevented all deaths the effect would not be considered important.

The GDG emphasized the high-quality evidence that baloxavir treatment of non-severe influenza virus infection does not increase adverse events, and moderate quality evidence that baloxavir treatment has little to no effect on serious adverse events. Thus, we have moderate certainty evidence of an important benefit, and at least moderate certainty of evidence of little or no adverse effects.

If GDG inferences regarding patient values and preferences are accurate, a majority of fully informed high-risk patients would choose baloxavir treatment. The recommendation was conditional because of the remaining uncertainty regarding low-quality evidence of reduction in hospitalization. The GDG discussed and was aware of the possibility of resistance, but considered that onward transmission of a resistant virus would be unlikely and this also contributed to baloxavir receiving a conditional recommendation only for patients at high risk of progression to severe disease.

7.1.1.2.1 Applicability

Though pregnancy alone does not represent a major risk factor for severe influenza (see prognosis) in those with non-severe influenza, pregnant and postpartum woman with a major risk factor, might consider using medication that reduces the risk of disease progression. However, baloxavir, the medication the WHO recommends most highly in the context of non-severe illness for patients at high risk of hospitalization, was not formally tested in pregnancy, and concerns regarding undesirable effects in both pregnant individual and fetus immediately arise, although animal studies have shown no adverse developmental effects of baloxavir marboxil at plasma concentrations > 5-fold higher than those achieved at the maximum human dose [25]. The GDG concluded baloxavir should not be given to pregnant or postpartum women until more evidence on safety is available. Lack of other effective alternatives for this subpopulation is a major research gap.

Children were enrolled in some of the included trials, and those with major risk factors could consider using baloxavir if infected with influenza. Note, younger children and infants were not enrolled in trials that inform this recommendation, and limited data are available for patients ≤ 5 years of age [28]. WHO will monitor for evidence generated in this population and update this recommendation when that efficacy and safety data become available.

Other high-risk patient populations were also not enrolled into some of the trials, but the GDG felt that the efficacy and safety profiles would similarly apply to those higher risk patients; however, they did feel caution about use in immunocompromised patients due to the risk of resistance and prolonged viral replication.

Patients with novel influenza A infections associated with high mortality in humans, such as avian influenza A viruses HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9), were not included in the clinical trials that informed this recommendation. The GDG agreed that evidence would indirectly apply to this population as well, in case they would present early to care with mild symptoms.

7.1.1.3 Practical info

7.1.1.3.1 Route, dosage and duration

Baloxavir is given orally as a **single dose**, based on body weight, see Table 7.1.

Table 7.1 Dosing of baloxavir by weight

Body weight	Dose of baloxavir
< 20 kg	2 mg/kg (as suspension)
20 kg to 79 kg	40 mg (tablet)
80 kg and over	80 mg (tablet)

Treatment should be administered as early as possible, and within 2 days of symptom onset.

Children: Baloxavir marboxil has been studied in treatment trials of patients > 5 years of age with adverse events similar to those reported in adults [27]. However, limited data are available for patients ≤ 5 years of age [28]. The pharmacokinetics of baloxavir in paediatric patients below 1 year of age have not been established [25].

7.1.1.3.2 Other considerations

Pregnancy: Due to lack of safety and efficacy data for treatment of pregnant and postpartum women, baloxavir is currently not recommended for use in pregnant people [26].

Immunocompromised patients: Baloxavir may increase the risk of antiviral resistance emerging, and its use in immunocompromised patients is therefore cautioned.

The manufacturer's summary of product characteristics contains additional details on animal studies and pharmacokinetics, adverse events and drug interactions [25].

7.1.1.4 Summary

The evidence regarding baloxavir versus placebo or standard care was informed by three RCTs, which enrolled 2776 patients with non-severe illnesses (studies provided the direct comparison for any outcomes of interest). Two studies enrolled patients without comorbidities, one study included 39% of patients with comorbidities such as asthma, chronic lung disease, and cardiovascular disease. Neither of the included studies enrolled children under 12 years of age or pregnant individuals. Study characteristics, risk of bias ratings, and effect estimates by outcome for baloxavir used here have been published [17].

For patients with non-severe influenza, the GRADE Summary of Findings table shows the relative and absolute effects of baloxavir compared with standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses
- Confirmed vs. suspected infection
- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk of poor outcomes vs. not

The review team conducted within-trial subgroup analyses for baloxavir versus placebo by different age groups (12 to 17 years vs. 18 to 65 years vs. < 75 years vs. 75+ years) for the following outcomes: mortality, admission to hospital, adverse events, and serious adverse events. The within-trial subgroup analyses did not reveal any subgroup effects.

Sufficient data were not available to inform other pre-specified subgroup analyses. Studies did not enrol patients with zoonotic influenza. The proportion of vaccinated individuals ranged from 21.62% to 30.5%. All studies enrolled mixed types of influenza virus, such as H1N1, H3N2, and type B.

Table 7.2 Summary of findings for baloxavir vs. standard care in patients with suspected or confirmed non-severe influenza virus infection and at high risk of progression to severe influenza

Outcome Timeframe	Study results and measurement s	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care/ placebo	Baloxavir		
Mortality (low-risk)	Relative risk: 0.83 (CI 95% 0.14 - 4.82) Based on data from 2144 participants in 2 studies	0.2 per 1000	0.17 per 1000	High	Baloxavir has little or no effect on mortality.
		Difference: 0.03 fewer per 1000 (CI 95% 0.17 fewer - 0.76 more)			
Mortality (high-risk)	Relative risk: 0.83 (CI 95% 0.14 - 4.82) Based on data from 2144 participants in 2 studies	2.0 per 1000	1.66 per 1000	High 1	Baloxavir has little or no effect on mortality.
		Difference: 0.34 fewer per 1000 (CI 95% 1.72 fewer - 7.64 more)			
Admission to hospital (low-risk)	Relative risk: 0.24 (CI 95% 0.05 - 1.19) Based on data from 1461 participants in 2 studies	3 per 1000	1 per 1000	High 2	Baloxavir has little or no effect on admission to hospital.
		Difference: 2 fewer per 1000 (CI 95% 3 fewer - 1 more)			
Admission to hospital (high-risk)	Relative risk: 0.24 (CI 95% 0.05 - 1.19) Based on data from 1461 participants in 2 studies	21 per 1000	5 per 1000	Low Due to very serious imprecision ³	Baloxavir may reduce the risk of admission to hospital.
		Difference: 16 fewer per 1000 (CI 95% 20 fewer - 4 more)			
Emergence of resistance (%)	: 9.97 (CI 95% 0.02 - 31.79) Based on data from 717 participants in 3 studies	0 per 1000	100 per 1000	Low Due to serious inconsistency, serious imprecision ⁴	Baloxavir may increase emergence of resistance.
		Difference: 100 more per 1000 (CI 95% 0 more - 318 more)			
Adverse events related to treatments	Relative risk: 0.74 (CI 95% 0.57 - 0.95) Based on data from 2776 participants in 3 studies	122 per 1000	90 per 1000	High 5	Baloxavir does not increase adverse events related to treatments.
		Difference: 32 fewer per 1000 (CI 95% 52 fewer - 6 fewer)			
Serious adverse events	Risk difference (CI 95% not calculable)	Difference: 1 more per 1000 (CI 95% 4 fewer - 5 more)		Moderate Due to serious imprecision ⁶	Baloxavir probably has little or no effect on serious adverse events.

Based on data from 2776 participants in 3 studies					
Time to alleviation of symptoms	Measured by: Scale: - lower better Based on data from 1855 participants in 3 studies	4.92 Mean	3.90 Mean	Moderate Due to serious imprecision ⁷	Baloxavir probably reduces time to alleviation of symptoms.
		Difference: MD 1.02 lower (CI 95% 1.41 lower - 0.63 lower)			

1. *Imprecision: no serious. Wide confidence intervals;*
2. *Imprecision: no serious. Due to optimal information size not meet;*
3. *Imprecision: very serious.*
4. *Inconsistency: serious. The magnitude of statistical heterogeneity was high.; Imprecision: serious.*
5. *Imprecision: no serious. Wide confidence intervals;*
6. *Imprecision: serious. Wide confidence intervals;*
7. *Imprecision: serious. Wide confidence intervals.*

Baloxavir (patients with low risk of disease progression)

Conditional recommendation against

In patients with suspected or confirmed non-severe influenza virus infection and at low risk of progression to severe influenza, we **suggest not administering baloxavir** (conditional recommendation, low-moderate quality evidence).

7.1.1.5 Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives
In patients with non-severe influenza virus infection and at low risk for progression to severe influenza, baloxavir treatment probably reduces time to alleviation of symptoms, but has little or no effect on admission to hospital or mortality because of the very low absolute risk of severe influenza. Baloxavir does not increase adverse events related to treatment and probably has little or no effect on serious adverse events.	
In clinical trials of baloxavir versus placebo, baloxavir was administered to participants within 2 days of symptom onset of non-severe influenza virus infection. The benefit of administering baloxavir treatment to patients with non-severe influenza virus infection and at low risk of progression to severe influenza more than 2 days after symptom onset is unknown.	
Certainty of the evidence	Moderate
The evidence summary on baloxavir treatment of patients with non-severe influenza virus infection and at low risk for progression to severe influenza, was informed by three RCTs.	
Certainty of evidence was rated as high for admission to hospital and mortality, and adverse events related to treatment. Certainty of evidence was rated as moderate for time to alleviation of symptoms, and for serious adverse events related to treatment. The certainty of evidence was rated as low for emergence of baloxavir resistance.	
Values and preferences	No substantial variability expected

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed patients with non-severe influenza virus infection and at low risk for progression to severe influenza would choose not to use baloxavir.

Resources and other considerations

No important issues with the recommended alternative

Acceptability and feasibility

Baloxavir treatment for non-severe influenza virus infection is a single oral dose, which provides an advantage for compliance.

Baloxavir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that the use of baloxavir should, in many or perhaps most settings, be reserved for those at high risk of hospital admission.

Due to cost and availability, barriers to access in LMICs may prove formidable. Those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing and treatments, and thus less access to the interventions. If advantaged patients in these settings receive the intervention, this may exacerbate health inequity.

7.1.1.6 Justification

As the baseline risk for dying was only 2 per 1,000 and our minimal important difference is 3 per 1000, even if baloxavir prevented all deaths the effect would not be considered important. Thus, we have high certainty of little or no effect on mortality. The same is true for hospitalization in non-severe patients at low risk of complications.

As is the case for high-risk patients, in low-risk patients baloxavir probably has an important reduction in duration of symptoms, a low likelihood of adverse effects, and practical advantages due to single dose administration. However, In contrast to high-risk patients in which baloxavir may reduce hospitalization, in low risk patients we have high certainty evidence that it does not. It is this difference that led the GDG to suggest in favour of baloxavir in high-risk patients and against in low-risk patients.

7.1.1.7 Summary

The evidence regarding baloxavir versus placebo or standard care was informed by three RCTs, which enrolled 2776 patients with non-severe illnesses (studies provided the direct comparison for any outcomes of interest). Two studies enrolled patients without comorbidities, one study included 39% of patients with comorbidities such as asthma, chronic lung disease, and cardiovascular disease. Neither of the included studies enrolled children under 12 years of age or pregnant individuals. Study characteristics, risk of bias ratings, and effect estimates by outcome for baloxavir used here have been published [17].

For patients with non-severe influenza, the GRADE Summary of Findings table shows the relative and absolute effects of baloxavir compared with standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses
- Confirmed vs. suspected infection
- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk of poor outcomes vs. not

The review team conducted within-trial subgroup analyses for baloxavir versus placebo by different age groups (12 to 17 years vs. 18 to 65 years vs. < 75 years vs. 75+ years) for the following outcomes: mortality, admission to hospital, adverse events, and serious adverse events. The within-trial subgroup analyses did not reveal any subgroup effects.

Sufficient data were not available to inform other pre-specified subgroup analyses. Studies did not enrol patients with zoonotic influenza. The proportion of vaccinated individuals ranged from 21.62% to 30.5%. All studies enrolled mixed types of influenza virus, such as H1N1, H3N2, and type B.

Table 7.3 Summary of findings for baloxavir vs. standard care in patients with suspected or confirmed non-severe influenza virus infection and at low risk of progression to severe influenza

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care/ placebo	Baloxavir		
Mortality (low-risk)	Relative risk: 0.83 (CI 95% 0.14 - 4.82) Based on data from 2144 participants in 2 studies	0.2 per 1000	0.17 per 1000	High	Baloxavir has little or no effect on mortality.
		Difference: 0.03 fewer per 1000 (CI 95% 0.17 fewer - 0.76 more)			
Mortality (high-risk)	Relative risk: 0.83 (CI 95% 0.14 - 4.82) Based on data from 2144 participants in 2 studies	2.0 per 1000	1.66 per 1000	High ¹	Baloxavir has little or no effect on mortality.
		Difference: 0.34 fewer per 1000 (CI 95% 1.72 fewer - 7.64 more)			
Admission to hospital (low-risk)	Relative risk: 0.24 (CI 95% 0.05 - 1.19) Based on data from 1461 participants in 2 studies	3 per 1000	1 per 1000	High ²	Baloxavir has little or no effect on admission to hospital.
		Difference: 2 fewer per 1000 (CI 95% 3 fewer - 1 more)			
Admission to hospital (high-risk)	Relative risk: 0.24 (CI 95% 0.05 - 1.19) Based on data from 1461 participants in 2 studies	21 per 1000	5 per 1000	Low Due to very serious imprecision ³	Baloxavir may reduce the risk of admission to hospital.
		Difference: 16 fewer per 1000 (CI 95% 20 fewer - 4 more)			
Emergence of resistance (%)	: 9.97 (CI 95% 0.02 - 31.79) Based on data from 717 participants in 3 studies	0 per 1000	100 per 1000	Low Due to serious inconsistency, serious imprecision ⁴	Baloxavir may increase emergence of resistance.
		Difference: 100 more per 1000 (CI 95% 0 more - 318 more)			
Adverse events related to treatment	Relative risk: 0.74 (CI 95% 0.57 - 0.95) Based on data from 2776 participants in 3 studies	122 per 1000	90 per 1000	High ⁵	Baloxavir does not increase adverse events related to treatments.
		Difference: 32 fewer per 1000 (CI 95% 52 fewer - 6 fewer)			
Serious adverse events	Risk difference (CI 95% not calculable) Based on data from 2776 participants in 3 studies	Difference: 1 more per 1000 (CI 95% 4 fewer - 5 more)		Moderate Due to serious imprecision ⁶	Baloxavir probably has little or no effect on serious adverse events.

Time to of symptoms	Measured by: Scale: - lower better Based on data from 1855 participants in 3 studies	4.92 Mean	3.90 Mean	Moderate Due to serious imprecision ⁷	Baloxavir probably reduces time to alleviation of symptoms.
<hr/>					

1. *Imprecision: no serious. Wide confidence intervals;*
2. *Imprecision: no serious. Due to optimal information size not meet;*
3. *Imprecision: very serious.*
4. *Inconsistency: serious. The magnitude of statistical heterogeneity was high.; Imprecision: serious.*
5. *Imprecision: no serious. Wide confidence intervals;*
6. *Imprecision: serious. Wide confidence intervals;*
7. *Imprecision: serious. Wide confidence intervals;*

7.1.2 Favipiravir

Strong recommendation against

In patients with suspected or confirmed non-severe influenza virus infection, we **recommend not administering favipiravir** (strong recommendation, moderate quality evidence).

7.1.2.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients with non-severe influenza virus infection, favipiravir treatment probably has little or no effect on time to alleviation of symptoms and has little or no effect on mortality. Whether favipiravir treatment reduces hospital admission in patients at high risk of severe influenza is very uncertain. Favipiravir treatment has little or no effect on hospital admission for patients at low risk of progression to severe influenza. Favipiravir probably has little or no effect on serious adverse events and may not increase important adverse events. No data were available on emergence of resistance.

In clinical trials, favipiravir was administered to participants within 2 days of symptom onset of non-severe influenza virus infection.

Certainty of the evidence

Moderate

Certainty of evidence was rated as high for mortality. Certainty of evidence was rated as high for hospital admission for patients at low risk of progression to severe influenza and was rated as very low for hospital admission for patients at high risk of progression to severe influenza. Certainty of evidence was moderate for time to alleviation of symptoms, low for adverse events, and moderate for serious adverse events. No data were available to assess emergence of resistance or serious adverse events.

Values and preferences

No substantial variability expected

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that nearly all well-informed patients with non-severe influenza virus infection would choose not to use favipiravir.

Resources and other considerations	Important issues, or potential issues not investigated
<p><i>Acceptability and feasibility</i></p> <p>Favipiravir is an oral medication that requires a loading dose. Favipiravir is not widely available.</p>	

7.1.2.2 Justification

The GDG inferred that the threshold for use of favipiravir treatment of non-severe influenza virus infection would be a reduction in time to alleviation of symptoms by 1 day. The estimated effect of favipiravir treatment on time to alleviation of symptoms is 0.46 days fewer with a lower bound of the 95% CI of 0.03 days fewer and an upper bound of 0.96 days fewer, and evidence was judged to be moderate certainty. There was no effect on hospitalization or mortality.

The GDG noted the moderate quality evidence that favipiravir treatment of non-severe influenza virus infection probably has little or no effect on serious adverse events, and low-quality evidence that favipiravir may not increase important adverse events. No data were available on emergence of resistance.

If GDG inferences regarding patient values and preferences are accurate, nearly all fully informed patients would not choose favipiravir treatment. A strong recommendation against use of favipiravir treatment was made due to the moderate certainty evidence that favipiravir probably has little or no effect on time to alleviation of symptoms, high certainty evidence that favipiravir has little or no effect on hospital admission for low-risk patients, and very low certainty evidence whether favipiravir reduces hospital admission in high-risk patients. Thus, there is no evidence supporting a benefit, and considerable evidence suggesting little or no benefit.

7.1.2.3 Summary

The evidence regarding favipiravir versus placebo or standard care was informed by three RCTs, which enrolled 2517 patients with non-severe illnesses (studies provided the direct comparison for any outcomes of interest). Two studies enrolled patients without comorbidities; one study did not report the details of comorbidities. All studies enrolled adults (18+ years), and no study enrolled pregnant individuals. Studies did not enrol patients with zoonotic influenza. Study characteristics, risk of

bias ratings, and effect estimates by outcome for favipiravir used here have been published [17].

For patients with non-severe influenza, the GRADE Summary of Findings table shows the relative and absolute effects of favipiravir compared with placebo or standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses
- Confirmed vs. suspected infection
- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk of poor outcomes vs. not

The review team conducted a within-trial subgroup analysis for favipiravir versus placebo or standard care by different age groups (18 to 49 years versus 50+ years) for time to alleviation of symptoms. The within-trial subgroup analysis did not reveal any subgroup effects.

Sufficient data were unavailable to inform other pre-specified subgroup analyses.

Table 7.4 Summary of findings for favipiravir vs. standard care in patients with suspected or confirmed non-severe influenza virus infection

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care/ placebo	Favipiravir		
Mortality (low-risk)	Relative risk: 0.57 (CI 95% 0.04 - 9.15) Based on data from 1999 participants in 2 studies	0.2 per 1000	0.11 per 1000	High 1	Favipiravir has little or no effect on mortality.
		Difference: 0.09 fewer per 1000 (CI 95% 0.19 fewer - 1.63 more)			
Mortality (high-risk)	Relative risk: 0.57 (CI 95% 0.04 - 9.15) Based on data from 1999 participants in 2 studies	2.0 per 1000	1.14 per 1000	High 2	Favipiravir have little or no effect on mortality.
		Difference: 0.86 fewer per 1000 (CI 95% 1.92 fewer - 16.3 more)			
Admission to hospital (low-risk)	Relative risk: 0.57 (CI 95% 0.04 - 9.15) Based on data from 1999 participants in 2 studies	3 per 1000	2 per 1000	High 3	Favipiravir have little or no effect on admission to hospital.
		Difference: 1 fewer per 1000 (CI 95% 3 fewer - 24 more)			
Admission to hospital (high-risk)	Relative risk: 0.57 (CI 95% 0.04 - 9.15) Based on data from 1999 participants in 2 studies	21 per 1000	12 per 1000	Very low Due to serious risk of bias, very serious imprecision ⁴	Whether favipiravir reduces admission to hospital is very uncertain.
		Difference: 9 fewer per 1000 (CI 95% 20 fewer - 171 more)			
Emergence of resistance	No RCT data (CI 95% not calculable)				Whether favipiravir increases emergence of resistance is very uncertain.
Adverse events related to treatments	Relative risk: 0.89 (CI 95% 0.66 - 1.2) Based on data from 1999 participants in 2 studies	122 per 1000	109 per 1000	Low Due to serious risk of bias, serious imprecision. ⁵	Favipiravir may not increase important adverse events related to treatments.
		Difference: 13 fewer per 1000 (CI 95% 41 fewer - 24 more)			
Serious adverse events	Risk difference (CI 95% not calculable) Based on data from 2517 participants in 3 studies	Difference: 2 fewer per 1000 (CI 95% 7 fewer - 4 more)		Moderate Due to serious risk of bias ⁶	Favipiravir probably have little or no effect on serious adverse events.
Time to alleviation	Measured by: Scale: - lower better	4.92 Mean	4.46 Mean	Moderate	Favipiravir probably has little or no effect

of symptoms	Based on data from 1317 participants in 2 studies	Difference: MD 0.46 lower (CI 95% 0.96 lower - 0.03 higher)	Due to serious risk of bias ⁷	on time to alleviation of symptoms.
<ol style="list-style-type: none"> 1. <i>Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: no serious. Due to optimal information size not meet;</i> 2. <i>Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: serious. Wide confidence intervals;</i> 3. <i>Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: serious.</i> 4. <i>Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: very serious.</i> 5. <i>Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Inconsistency: no serious. High heterogeneity.; Imprecision: serious. Wide confidence intervals;</i> 6. <i>Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: serious. Wide confidence intervals;</i> 7. <i>Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias;</i> 				

7.1.3 Laninamivir

Conditional recommendation against

In patients with suspected or confirmed non-severe influenza virus infection, we **suggest not administering laninamivir** (conditional recommendation, low-quality evidence).

7.1.3.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients with non-severe influenza virus infection, laninamivir treatment may have no important effect on time to alleviation of symptoms and has little or no effect on admission to hospital or mortality because of the low absolute risk of severe influenza. Laninamivir treatment probably has little or no effect on serious adverse events and may have no important effect on time to alleviation of symptoms. It is very uncertain whether laninamivir increases emergence of resistance or increases adverse events.

In the clinical trial of laninamivir versus placebo, laninamivir was administered to participants within 2 days of symptom onset of non-severe influenza virus infection.

Certainty of the evidence

Moderate

Only one RCT was identified with 639 participants. Certainty of evidence was rated as high for admission to hospital for low-risk patients and for mortality, and moderate for serious adverse events. Certainty of evidence was low for admission to hospital for high-risk patients and for time to alleviation of symptoms.

Values and preferences

No substantial variability expected

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that almost all well-informed patients with non-severe influenza virus infection would choose not to use laninamivir.

Resources and other considerations

Important issues, or potential issues not investigated

Acceptability and feasibility

Laninamivir is an inhaled powdered medication that must be used with a specific inhaler device as a single treatment dose. Young children and older adults might not be able to properly inhale laninamivir into the respiratory tract. Patients with chronic pulmonary disease should avoid laninamivir because of the increased risk of bronchospasm. These precautions for use and its limited availability worldwide also contribute to GDG to conditional recommend against.

7.1.3.2 Justification

We have high certainty evidence of no effect of the medication on mortality in all patients, and high certainty evidence in the low risk and low certainty in the high risk of no important difference in hospitalization. The GDG inferred that the threshold for use of laninamivir treatment of non-severe influenza virus infection would be a reduction in time to alleviation of symptoms by 1 day. The estimated effect of laninamivir treatment on time to alleviation of symptoms is 0.57 days lower with a lower bound of the 95% CI of 0.14 days lower and an upper bound of 1.01 days lower, and evidence was judged to be low certainty.

The GDG emphasized the moderate quality evidence that laninamivir treatment of non-severe influenza virus infection probably has little to no effect on serious adverse events. There is very low certainty evidence whether laninamivir treatment increases adverse events or emergence of resistance.

With no convincing evidence of benefit, the GDG inferred that the majority of fully informed patients would decline the treatment. A conditional recommendation against use of laninamivir treatment was made due to the low certainty evidence that laninamivir may not have an important effect on the time to alleviation of symptoms and the residual uncertainty in impact of hospitalization in high-risk patients.

7.1.3.3 Summary

The evidence regarding laninamivir versus placebo or standard care was informed by 1 RCT, which enrolled 639 patients with non-severe illnesses (studies provided the direct comparison for any outcomes of interest). The study enrolled patients aged from 18 years to 64 years and did not report the details of comorbidities, the proportion of pregnant individuals, influenza virus types, or patients who were vaccinated. Study characteristics, risk of bias ratings, and effect estimates by outcome for laninamivir used here have been published [17].

For patients with non-severe influenza, the GRADE Summary of Findings table shows the relative and absolute effects of laninamivir compared with placebo or standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses
- Confirmed vs. suspected infection
- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk of poor outcomes vs. not

Sufficient data were unavailable to inform pre-specified subgroup analyses.

Table 7.5 Summary of findings for laninamivir vs. standard care in patients with suspected or confirmed non-severe influenza virus infection

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care/ placebo	Laninamivir		
Mortality (low-risk)	Relative risk: 0.5 (CI 95% 0.01 - 24.96) Based on data from 639 participants in 1 study	0.2 per 1000	0.1 per 1000	High 1	Laninamivir have little or no effect on mortality.
		Difference: 0.1 fewer per 1000 (CI 95% 0.2 fewer - 4.79 more)			
Mortality (high-risk)	Relative risk: 0.5 (CI 95% 0.01 - 24.96) Based on data from 639 participants in 1 study	2.0 per 1000	1.0 per 1000	High 2	Laninamivir have little or no effect on mortality.
		Difference: 1.0 fewer per 1000 (CI 95% 1.98 fewer - 47.92 more)			
Admission to hospital (low-risk)	Relative risk: 1.1 (CI 95% 0.02 - 55.19) Follow up Indirect evidence	3 per 1000	3 per 1000	High 3	Laninamivir have little or no effect on admission to hospital.
		Difference: 0 fewer per 1000 (CI 95% 3 fewer - 163 more)			
Admission to hospital (high-risk)	Relative risk: 1.1 (CI 95% 0.02 - 55.19) Follow up Indirect evidence	21 per 1000	23 per 1000	Low Due to serious risk of bias, serious imprecision ⁴	Laninamivir may have little or no effect on admission to hospital.
		Difference: 2 more per 1000 (CI 95% 21 fewer - 979 more)			
Emergence of resistance	No RCT data (CI 95% not calculable)				Whether laninamivir increases emergence of resistance is very uncertain.
Adverse events related to treatment⁵	No RCT data (CI 95% not calculable)				Whether laninamivir increases adverse events related to treatments is very uncertain.
Serious adverse events	Risk difference (CI 95% not calculable) Based on data from 634 participants in 1 study	Difference: 4 fewer per 1000 (CI 95% 11 fewer - 3 more)		Moderate Due to serious risk of bias. ⁶	Laninamivir probably have little or no effect on serious adverse events.
Time to alleviation	Measured by: Scale: - lower better	4.92 Mean	4.35 Mean	Low	Laninamivir may have no important effect

of symptoms	Based on data from 231 participants in 1 study	Difference: MD 0.57 lower (CI 95% 1.01 lower - 0.14 lower)	Due to serious risk of bias, serious imprecision ⁷	on time to alleviation of symptoms.
<ol style="list-style-type: none"> 1. <i>Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: no serious. Wide confidence intervals;</i> 2. <i>Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: no serious. Wide confidence intervals;</i> 3. <i>Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: very serious. Wide confidence intervals;</i> 4. <i>Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: serious. Wide confidence intervals;</i> 5. <i>undefined</i> 6. <i>Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: no serious. Wide confidence intervals;</i> 7. <i>Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: serious. Wide confidence intervals;</i> 				

7.1.4 Oseltamivir

Strong recommendation against

In patients with suspected or confirmed non-severe seasonal influenza virus infection, we **recommend not administering oseltamivir** (strong recommendation, moderate quality evidence).

7.1.4.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients with non-severe influenza virus infection, oseltamivir treatment probably has no important effect on time to alleviation of symptoms and has little or no effect on admission to hospital or mortality in patients at high or low risk of progressing to severe disease, because of the low absolute risk of severe influenza. Oseltamivir treatment probably increases adverse events but probably has little or no effect on serious adverse events related to treatment. It is very uncertain whether oseltamivir increases emergence of resistance.

In clinical trials of oseltamivir versus placebo, oseltamivir was administered to participants within 36 to 48 hours of symptom onset of non-severe influenza virus infection.

Certainty of the evidence

Moderate

Certainty of evidence was rated as high for admission to hospital and mortality, and moderate for time to alleviation of symptoms, adverse events and serious adverse events related to treatment. Certainty of evidence was rated as very low for emergence of resistance.

Values and preferences

No substantial variability expected

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that almost all well-informed patients with non-severe influenza virus infection would choose not to use oseltamivir.

Resources and other considerations	No important issues with the recommended alternative
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Acceptability and feasibility

Previously, WHO had recommendations for use of oseltamivir in patients with non-severe influenza virus infection at high risk for severe disease [16]. In this guideline, the recommendation has been updated based on the accumulated evidence.

Changing clinical practice may prove to be challenging as oseltamivir is widely available and affordable. Proper dissemination of information regarding these updated recommendations within the medical community and policymakers will be key to ensure proper use of oseltamivir in the future (see recommendations for severe disease and prophylaxis). WHO will inform the Essential Medicines List with this new information to update its indication as a complementary medicine on this list.

7.1.4.2 Justification

The GDG inferred that the threshold for use of oseltamivir treatment of non-severe influenza virus infection would be a reduction in time to alleviation of symptoms by 1 day. The entire confidence interval lies below the minimally important difference (MID) of a single day, leaving us with high certainty that oseltamivir has no important effect on symptom duration. We are also confident of no impact on mortality or hospitalization in patients at high and low risk of severe disease.

We have moderate quality evidence that oseltamivir treatment of non-severe influenza virus infection probably increases adverse events. Thus, with high certainty evidence of no important benefit, and moderate certainty evidence of adverse effects, the recommendation against oseltamivir is clear.

7.1.4.3 Summary

The evidence regarding oseltamivir versus placebo or standard care was informed by 22 RCTs, which enrolled 14 718 patients with non-severe illnesses (studies provided the direct comparison for any outcomes of interest). Most studies enrolled less than 20% of patients with comorbidities or did not report the details of comorbidities, 3 studies included all or almost all patients with comorbidities such as asthma. Neither of the included studies enrolled infants (under 1 year of age) nor pregnant individuals. Study characteristics, risk of bias ratings, and effect estimates by outcome for oseltamivir used here have been published [17].

For patients with non-severe influenza, the GRADE Summary of Findings table shows the relative and absolute effects of oseltamivir compared with placebo or standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses
- Confirmed vs. suspected infection
- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk of poor outcomes vs. not

The review team conducted within-trial subgroup analyses for oseltamivir versus placebo or standard care by different age groups (1 to 17 years vs. 18+ years vs. < 75 years vs. 75+ years) for serious adverse events. The within-trial subgroup analyses did not reveal any subgroup effects.

Sufficient data were unavailable to inform other pre-specified subgroup analyses. Studies did not enrol patients with zoonotic influenza. The proportion of vaccinated individuals ranged from 0% to 65.38%. All studies enrolled mixed types of influenza virus, such as H1N1, H3N2, and type B, except one study, which enrolled patients infected with H1N1.

Table 7.6 Summary of findings for oseltamivir vs. standard care in patients with suspected or confirmed non-severe influenza virus infection

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care/ placebo	Oseltamivir		
Mortality (low-risk)	Relative risk: 0.84 (CI 95% 0.34 - 2.07) Based on data from 12008 participants in 17 studies	0.2 per 1000	0.17 per 1000	High	Oseltamivir has little or no effect on mortality.
		Difference: 0.03 fewer per 1000 (CI 95% 0.13 fewer - 0.21 more)			
Mortality (high-risk)	Relative risk: 0.84 (CI 95% 0.34 - 2.07) Based on data from 12008 participants in 17 studies	2.0 per 1000	1.68 per 1000	High	Oseltamivir has little or no effect on mortality.
		Difference: 0.32 fewer per 1000 (CI 95% 1.32 fewer - 2.14 more)			
Admission to hospital (low-risk)	Relative risk: 0.8 (CI 95% 0.54 - 1.18) Based on data from 12589 participants in 20 studies	3 per 1000	2 per 1000	High	Oseltamivir has little or no effect on admission to hospital.
		Difference: 1 fewer per 1000 (CI 95% 1 fewer - 1 more)			
Admission to hospital (high-risk)	Relative risk: 0.8 (CI 95% 0.54 - 1.18) Based on data from 12589 participants in 20 studies	21 per 1000	17 per 1000	High	Oseltamivir has little or no effect on admission to hospital.
		Difference: 4 fewer per 1000 (CI 95% 10 fewer - 4 more)			
Emergence of resistance (%)	: 0.42 (CI 95% 0.0 - 3.06) Based on data from 579 participants in 7 studies	0 per 1000	4 per 1000	Very low Due to serious risk of bias, serious inconsistency, serious imprecision. ¹	Whether oseltamivir increases emergence of resistance is very uncertain.
Adverse events related to treatments	Relative risk: 1.23 (CI 95% 1.1 - 1.39) Based on data from 6782 participants in 12 studies	122 per 1000	150 per 1000	Moderate Due to serious risk of bias ²	Oseltamivir probably increases adverse events related to treatments.
		Difference: 28 more per 1000 (CI 95% 12 more - 48 more)			
Serious adverse events	Risk difference: 0.0 (CI 95% -0.03 - 0.02) Based on data from 14718 participants in 22 studies	Difference: 0 fewer per 1000 (CI 95% 3 fewer - 2 more)		Moderate Due to serious risk of bias ³	Oseltamivir probably has little or no effect on serious adverse events.

Time to alleviation of symptoms	Measured by: Scale: - lower better Based on data from 9078 participants in 22 studies	4.92 Mean	4.17 Mean	Moderate Due to serious risk of bias ⁴	Oseltamivir probably has no important effect on time to alleviation of symptoms.
<hr/>					

1. *Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inconsistency: serious. High heterogeneity.; Imprecision: serious. Wide confidence intervals;*
2. *Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Inconsistency: no serious. High heterogeneity.; Imprecision: no serious. Due to optimal information size not meet;*
3. *Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias;*
4. *Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias;*

7.1.5 Peramivir

Conditional recommendation against

In patients with suspected or confirmed non-severe influenza virus infection, we **suggest not administering peramivir** (conditional recommendation, low-quality evidence).

7.1.5.1 Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives
In patients with non-severe influenza virus infection, peramivir treatment may have no important effect on time to alleviation of symptoms and because of the low absolute risk of severe influenza has little or no effect on mortality. It is very uncertain whether peramivir treatment reduces hospital admission. Peramivir may not have an important reduction in time to alleviation of symptoms and may not increase adverse events or serious adverse events. It is very uncertain whether peramivir increases emergence of resistance or increases adverse events.	
In clinical trials, peramivir was administered to participants within 2 days of symptom onset of non-severe influenza virus infection.	
Certainty of the evidence	High
We have high certainty of no effect on mortality. Certainty of evidence was low for time to alleviation of symptoms, adverse events, and serious adverse events. No data were available to assess hospital admission. Certainty of evidence was very low for emergence of resistance.	
Values and preferences	No substantial variability expected
Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed patients with non-severe influenza virus infection would choose not to use peramivir.	

Resources and other considerations

Important issues, or potential issues not investigated

Acceptability and feasibility

Peramivir is administered intravenously and therefore requires a clinical setting where intravenous access is available and may not be feasible for many patients. Peramivir has limited availability worldwide.

7.1.5.2 Justification

We have high certainty evidence of no effect of the medication on mortality and no trial data on hospitalization. The GDG inferred that the threshold for use of peramivir treatment of non-severe influenza virus infection would be a reduction in time to alleviation of symptoms by 1 day. The estimated effect of peramivir treatment on time to alleviation of symptoms is a 0.95 days reduction with a lower bound of the 95% CI of 0.62 days reduction and an upper bound of 1.28 days reduction, and evidence was judged to be low certainty.

With no convincing evidence of benefit, the GDG judged that the majority of fully informed patients would decline the medication. A conditional recommendation against use of peramivir treatment was made due to the low certainty evidence that peramivir may not have an important effect on the time to alleviation of symptoms and the lack of evidence on whether peramivir has any effect on hospital admission.

7.1.5.3 Summary

The evidence regarding peramivir versus placebo or standard care was informed by five RCTs, which enrolled 1199 patients with non-severe illnesses (studies provided direct comparisons for any outcomes of interest). Three studies enrolled patients without comorbidities; two studies did not report the details of comorbidities. Neither of the included studies enrolled children under 15 years or pregnant individuals. All studies administered peramivir intravenous. Studies did not enrol patients with zoonotic influenza. All studies enrolled either mixed types of influenza virus or did not provide information on vaccine status.

Three studies enrolled unvaccinated patients for influenza; 2 studies did not report the details of vaccination. Study characteristics, risk of bias ratings, and effect estimates by outcome for peramivir used here have been published [17].

For patients with non-severe influenza, the GRADE Summary of Findings table shows the relative and absolute effects of peramivir compared with placebo or standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses
- Confirmed vs. suspected infection
- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk of poor outcomes vs. not

Sufficient data were unavailable to inform pre-specified subgroup analyses.

Table 7.7 Summary of findings for peramivir vs. standard care in patients with suspected or confirmed non-severe influenza virus infection

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care/ placebo	Peramivir		
Mortality (low-risk)	Relative risk: 0.39 (CI 95% 0.04 - 4.04) Based on data from 82 participants in 1 study	0.2 per 1000	0.08 per 1000	High 1	Peramivir has little or no effect on mortality.
		Difference: 0.12 fewer per 1000 (CI 95% 0.19 fewer - 0.61 more)			
Mortality (high-risk)	Relative risk: 0.39 (CI 95% 0.04 - 4.04) Based on data from 82 participants in 1 study	2.0 per 1000	0.78 per 1000	High 2	Peramivir has little or no effect on mortality.
		Difference: 1.22 fewer per 1000 (CI 95% 1.92 fewer - 6.08 more)			
Admission to hospital	No RCT data (CI 95% not calculable)				Whether peramivir increases admission to hospital is very uncertain.
Emergence of resistance (%)	: 4.35 (CI 95% 0.07 - 12.66) Based on data from 46 participants in 1 study	0 per 1000	44 per 1000	Very low Due to serious risk of bias, very serious imprecision. ³	Whether peramivir increases emergence of resistance is very uncertain.
		Difference: 44 more per 1000 (CI 95% 1 more - 127 more)			
Adverse events related to treatments	Relative risk: 0.99 (CI 95% 0.74 - 1.32) Follow up Indirect evidence	122 per 1000	121 per 1000	Low Due to serious risk of bias, serious imprecision. ⁴	Peramivir may not increase adverse events related to treatments.
		Difference: 1 fewer per 1000 (CI 95% 32 fewer - 39 more)			
Serious adverse events	Risk difference (CI 95% not calculable) Based on data from 1199 participants in 5 studies	Difference: 0 fewer per 1000 (CI 95% 7 fewer - 6 more)		Low Due to serious risk of bias, serious imprecision ⁵	Peramivir may not increase serious adverse events.
Time to alleviation of symptoms	Measured by: Scale: - lower better Based on data from 1046 participants in 5 studies	4.92 Mean	3.97 Mean	Low Due to serious risk of bias, serious imprecision ⁶	Peramivir may not have an important reduction in time to alleviation of symptoms.
		Difference: MD 0.95 lower (CI 95% 1.28 lower - 0.62 lower)			

1. *Imprecision: no serious. Due to optimal information size not meet;* 2. *Imprecision: no serious. Wide confidence intervals;* 3. *Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inconsistency: no serious. High heterogeneity.; Imprecision: very serious. Wide confidence intervals, Wide confidence intervals;* 4. *Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Inconsistency: no serious. High heterogeneity.; Imprecision: serious. Wide confidence intervals;* 5. *Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: serious. Wide confidence intervals;* 6. *Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: serious. Wide confidence intervals.*

7.1.6 Umifenovir

Conditional recommendation against

In patients with suspected or confirmed non-severe influenza virus infection, we **suggest not administering umifenovir** (conditional recommendation, low-quality evidence).

7.1.6.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients with non-severe influenza virus infection, umifenovir treatment may reduce time to alleviation of symptoms and has little or no effect on mortality.

Whether umifenovir treatment reduces hospital admission in patients at high risk of severe influenza is very uncertain. Umifenovir treatment has little or no effect on hospital admission for patients at low risk of progression to severe influenza.

Whether umifenovir increases adverse events, serious adverse events, or emergence of resistance is very uncertain.

In clinical trials, umifenovir was administered to participants within 2 days of symptom onset of non-severe influenza virus infection.

Certainty of the evidence

Moderate

Certainty of evidence was rated as high for mortality. Certainty of evidence was rated as high for hospital admission for patients at low risk of progression to severe influenza and was rated as very low for hospital admission for patients at high risk of progression to severe influenza. Certainty of evidence was low for time to alleviation of symptoms, and very low for adverse events. No data were available to assess emergence of resistance or serious adverse events.

Values and preferences

No substantial variability expected

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed patients with non-severe influenza virus infection would choose not to use umifenovir.

Resources and other considerations	No important issues with the recommended alternative
<p><i>Acceptability and feasibility</i></p> <p>Umifenovir is an oral medication. Umifenovir is not widely available. Different frequencies of dosing have been used in clinical trials.</p>	

7.1.6.2 Justification

The GDG inferred that the threshold for use of umifenovir treatment of non-severe influenza virus infection would be a reduction in time to alleviation of symptoms by 1 day. The estimated effect of umifenovir treatment on time to alleviation of symptoms is a 1.1 day reduction with a lower bound of the 95% CI of 0.63 days reduction and an upper bound of 1.57 days reduction, and evidence was judged to be low certainty.

The GDG emphasized that, due to very low-quality evidence, it is very uncertain whether umifenovir treatment of non-severe influenza virus infection increases adverse events. No data were available on adverse events or serious adverse events.

The GDG determined that as the evidence suggested that a reduction in death or hospitalization is unlikely and the evidence for a reduction in duration of illness is of low-quality, as well as uncertainty as to the effect on adverse events, that a majority of fully informed patients would not choose umifenovir treatment. A conditional recommendation against the use of umifenovir treatment was made due to the low certainty evidence that umifenovir may reduce time to alleviation of symptoms and residual uncertainty of impact on the need for hospitalization in high-risk persons.

7.1.6.3 Summary

The evidence regarding umifenovir versus placebo or standard care was informed by 1 RCT, which enrolled 232 patients with non-severe illnesses (studies provided the direct comparison for any outcomes of interest). The study reported adverse events related to treatment or time to alleviation of symptoms. No data are available on mortality, admission to hospital, or other outcomes of interest; the results were informed by indirect comparisons. Studies did not enrol patients with zoonotic influenza, and the types of influenza virus infections were not reported. Study characteristics, risk of bias ratings, and effect estimates by outcome for umifenovir used here have been published [17].

For patients with non-severe influenza, the GRADE Summary of Findings table shows the relative and absolute effects of umifenovir compared with placebo or standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses
- Confirmed vs. suspected infection
- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk of poor outcomes vs. not

Sufficient data were unavailable to inform pre-specified subgroup analyses.

Table 7.8 Summary of findings for umifenovir vs. standard care in patients with suspected or confirmed non-severe influenza virus infection

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care/ placebo	Umifenovir		
Mortality (low-risk)	Relative risk: 0.85 (CI 95% 0.02 - 47.31)	0.2 per 1000	0.17 per 1000	High 1	Umifenovir has little or no effect on mortality.
	Follow up Indirect evidence	Difference: 0.03 fewer per 1000 (CI 95% 0.2 fewer - 9.26 more)			
Mortality (high-risk)	Relative risk: 0.85 (CI 95% 0.02 - 47.31)	2.0 per 1000	1.7 per 1000	High 2	Umifenovir has little or no effect on mortality.
	Follow up Indirect evidence	Difference: 0.3 fewer per 1000 (CI 95% 1.96 fewer - 92.62 more)			
Admission to hospital (low-risk)	Relative risk: 0.27 (CI 95% 0.01 - 6.72)	3 per 1000	1 per 1000	High 3	Umifenovir has little or no effect on admission to hospital.
	Follow up Indirect evidence	Difference: 2 fewer per 1000 (CI 95% 3 fewer - 17 more)			
Admission to hospital (high-risk)	Relative risk: 0.27 (CI 95% 0.01 - 6.72)	21 per 1000	6 per 1000	Very low Due to serious risk of bias, very serious imprecision ⁴	Whether umifenovir reduces admission to hospital is very uncertain.
	Follow up Indirect evidence	Difference: 15 fewer per 1000 (CI 95% 21 fewer - 120 more)			
Emergence of resistance	No RCT data (CI 95% not calculable)			Whether umifenovir increases emergence of	

					resistance is very uncertain.
Adverse events related to treatments	Relative risk: 0.57 (CI 95% 0.23 - 1.37) Based on data from 232 participants in 1 study	122 per 1000	70 per 1000	Very low Due to serious risk of bias, very serious imprecision. ⁵	Whether umifenovir increases adverse events related to treatments is very uncertain.
		Difference: 52 fewer per 1000 (CI 95% 94 fewer - 45 more)			
Serious adverse events	No RCT data (CI 95% not calculable)				Whether umifenovir increases serious adverse events is very uncertain.

1. *Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: no serious. Wide confidence intervals;*
2. *Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: very serious. Wide confidence intervals;*
3. *Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: serious. Wide confidence intervals;*
4. *Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: very serious. Wide confidence intervals;*
5. *Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Inconsistency: no serious. High heterogeneity; Imprecision: very serious. Wide confidence intervals;*
6. *Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: serious. Wide confidence intervals.*

7.1.7 Zanamivir

Strong recommendation against

In patients with suspected or confirmed non-severe influenza virus infection, we **recommend not administering zanamivir** (strong recommendation, moderate quality evidence).

7.1.7.1 Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

In patients with non-severe influenza virus infection, zanamivir treatment may have no important effect on time to alleviation of symptoms and has little or no effect on mortality or hospital admission because of the low absolute risk of severe influenza. Zanamivir may have little or no effect on adverse events or serious adverse events, or on emergence of resistance.

In clinical trials, zanamivir was administered to participants within 2 days of symptom onset of non-severe influenza virus infection.

Certainty of the evidence

Moderate

Certainty of evidence was rated as high for mortality and hospital admission. Certainty of evidence was moderate for time to alleviation of symptoms, and low for adverse events, serious adverse events, and emergence of resistance.

Values and preferences

No substantial variability expected

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that almost all well-informed patients with non-severe influenza virus infection would choose not to use zanamivir.

Resources and other considerations

No important issues with the recommended alternative

Acceptability and feasibility

Zanamivir is an inhaled powdered medication that must be used with an inhaler device. Young children and older adults might not be able to properly inhale

zanamivir into the respiratory tract. Patients with chronic pulmonary disease should avoid inhaled zanamivir because of the increased risk of bronchospasm. Zanamivir may not be available in some countries.

7.1.7.2 Justification

The GDG inferred that the threshold for use of zanamivir treatment of non-severe influenza virus infection would be a reduction in time to alleviation of symptoms by 1 day. The estimated effect of zanamivir treatment on time to alleviation of symptoms is a 0.68 days reduction with a lower bound of the 95% CI of 0.43 days reduction and an upper bound of 0.93 days reduction, and evidence was judged to be moderate certainty.

With moderate to high certainty evidence of no important benefit on hospitalization, in high- and low-risk patients for severe disease, mortality and symptom improvement, the GDG felt confident that all or almost all fully informed patients would decline the medication.

7.1.7.3 Summary

The evidence regarding zanamivir versus placebo or standard care was informed by 19 RCTs, which enrolled 7735 patients with non-severe illnesses (studies provided the direct comparison for any outcomes of interest). Most studies enrolled less than 20% of patients with comorbidities or did not report the details of comorbidities, two studies included over 80% of patients with comorbidities. Neither of the included studies enrolled infants (under 5 years of age) nor pregnant individuals. Study characteristics, risk of bias ratings, and effect estimates by outcome for zanamivir used here have been published [17].

For patients with non-severe influenza, the GRADE Summary of Findings table shows the relative and absolute effects of zanamivir compared with placebo or standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses
- Confirmed vs. suspected infection
- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk of poor outcomes vs. not

The review team conducted within-trial subgroup analyses for zanamivir versus placebo or standard care by different types of influenza virus (type A versus type B) and influenza diagnosis (confirmed influenza versus suspected influenza) for time to alleviation of symptoms, high risk versus low risk for any adverse events and serious adverse events. The within-trial subgroup analyses did not reveal any subgroup effects.

Sufficient data were unavailable to inform other pre-specified subgroup analyses. Studies did not enrol patients with zoonotic influenza. The proportion of vaccinated individuals ranged from 0% to 45.81%. All studies enrolled mixed types of influenza virus, such as H1N1, H3N2, and type B.

Table 7.9 Summary of findings for zanamivir vs. standard care in patients with suspected or confirmed non-severe influenza virus infection

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care/ placebo	Zanamivir		
Mortality (low-risk)¹	Relative risk: 0.88 (CI 95% 0.34 - 2.28) Based on data from 7174 participants in 16 studies	0.2 per 1000	0.18 per 1000	High	Zanamivir has little or no effect on mortality.
		Difference: 0.02 fewer per 1000 (CI 95% 0.13 fewer - 0.26 more)			
Mortality (high-risk)²	Relative risk: 0.88 (CI 95% 0.34 - 2.28) Based on data from 7174 participants in 16 studies	2.0 per 1000	1.76 per 1000	High	Zanamivir has little or no effect on mortality.
		Difference: 0.24 fewer per 1000 (CI 95% 1.32 fewer - 2.56 more)			
Admission to hospital (low-risk)	Relative risk: 1.18 (CI 95% 0.81 - 1.72) Based on data from 1160 participants in 3 studies	3 per 1000	4 per 1000	High 3	Zanamivir has little or no effect on admission to hospital.
		Difference: 1 more per 1000 (CI 95% 1 fewer - 2 more)			
Admission to hospital (high-risk)	Relative risk: 1.18 (CI 95% 0.81 - 1.72) Based on data from 1160 participants in 3 studies	21 per 1000	25 per 1000	High 4	Zanamivir has little or no effect on admission to hospital.
		Difference: 4 more per 1000 (CI 95% 4 fewer - 15 more)			
	: 0.0 (CI 95% 0.0 - 11.66)	0	0	Low	Zanamivir may have little or no impact

Emergence of resistance (%)	Based on data from 200 participants in 2 studies	per 1000	per 1000	Due to very serious imprecision ⁵	on emergence of resistance.
		Difference: 0 more per 1000 (CI 95% 0 fewer - 117 more)			
Adverse events related to treatments	Relative risk: 1.05 (CI 95% 0.9 - 1.21) Based on data from 7257 participants in 17 studies	122 per 1000	128 per 1000	Low Due to serious risk of bias, serious imprecision. ⁶	Zanamivir may not increase adverse events related to treatments.
		Difference: 6 more per 1000 (CI 95% 12 fewer - 26 more)			
Serious adverse events	Risk difference (CI 95% not calculable) Based on data from 7735 participants in 19 studies	Difference: 2 more per 1000 (CI 95% 1 fewer - 6 more)		Low Due to serious risk of bias, serious imprecision. ⁷	Zanamivir may have little or no effect on serious adverse events.
Time to alleviation of symptoms	Measured by: Scale: - lower better Based on data from 6617 participants in 15 studies	4.92 Mean	4.24 Mean	Moderate Due to serious risk of bias. ⁸	Zanamivir probably has no important effect on time to alleviation of symptoms.

1. undefined

2. undefined

3. Imprecision: no serious. Wide confidence intervals;

4. Imprecision: no serious. Wide confidence intervals;

5. Imprecision: very serious. Wide confidence intervals;

6. Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Inconsistency: no serious. High heterogeneity.; Imprecision: serious. Wide confidence intervals;

7. Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: serious. Wide confidence intervals;

8. Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias.

7.2 Concomitant use of antibiotics for patients with non-severe confirmed symptomatic influenza

7.2.1 Antibiotics

Strong recommendation against

In patients with suspected or confirmed non-severe influenza virus infection and low probability of bacterial co-infection we **recommend not administering antibiotics** (strong recommendation, low-quality evidence).

7.2.1.1 Evidence to decision

Benefits and harms

Antibiotics are of possible use in influenza either for treatment of concomitant bacterial infection or the proposed use of macrolide antibiotics for their potential anti-inflammatory effect. However, the systematic review found very limited evidence regarding the impact of antibiotic administration on most outcomes for patients with non-severe suspected or confirmed influenza and a low probability of bacterial infection.

It is very uncertain whether antibiotics have any impact on the progression of disease in patients with non-severe influenza and a low probability of bacterial infection. If there was any effect on mortality it would be very small simply because only a very small proportion of patients progress to severe illness and death in this group of patients.

The information on adverse events from antibiotics was limited from the small patient numbers in the available direct evidence. However, there is indirect evidence available in regard to the adverse effects of antibiotics from alternative sources, including a large observational study that demonstrated the adverse effects from widespread use of antibiotics. In addition, the GDG felt that the widespread use of antibiotics in a disease as prevalent as influenza will likely lead to the emergence of antimicrobial-resistant bacteria that limit the availability of future antibiotic treatment options for bacterial respiratory tract infections.

For all other outcomes we are very uncertain of the impact of antibiotic use in this population.

Certainty of the evidence	Very low
The evidence summary on concomitant antibiotics for patients with non-severe influenza virus infection and at low probability of bacterial infection was informed by a small number of RCTs.	Very low

The evidence summary on concomitant antibiotics for patients with non-severe influenza virus infection and at low probability of bacterial infection was informed by a small number of RCTs.

In the single RCT of 107 patients that informed the mortality estimate there were no deaths in either group and this is consistent with the low baseline risk of mortality in non-severe pneumonia. Given the low risk of death in this group, we therefore have a high level of certainty of concomitant antibiotics having little or no effect on mortality.

We have moderate certainty in our estimate of adverse effects from indirect evidence with antibiotics in other conditions.

For all other outcomes the certainty of evidence proved very low.

Values and preferences

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that almost all well-informed patients with non-severe influenza virus infection at low risk of bacterial infection would choose not to take concomitant antibiotics.

Resources and other considerations

Antibiotics are an extremely valuable clinical resource and the GDG were cognizant of the risk of induced antibiotic resistance caused by the widespread use of antibiotics. Given the high global prevalence of influenza, it was noted that if antibiotics were recommended for influenza then this would potentially lead to a very high volume of antibiotic usage. The GDG noted the importance of ensuring that bacterial infections remain treatable by antibiotics, therefore there was a strong preference for avoiding the use of concomitant antibiotics in patients with a low probability of a concurrent bacterial infection.

7.2.1.2 Justification

The GDG specified that the target population for this recommendation are patients with a less than 20% risk of bacterial infection. There were only small, limited RCTs on

the use of antibiotics for treatment of this population (clinical experts judged whether the trials in fact enrolled the target population).

Indirect evidence provides moderate certainty of an increase in adverse effects. The panel also put high importance on the likelihood of emergence of resistant organisms with the widespread use of antibiotics in a condition as common as influenza.

For all other outcomes we have only low certainty evidence. In general, the WHO does not make strong recommendations when evidence of critical outcomes is only low certainty. However, GRADE guidance has identified that when low-quality evidence suggests benefit and moderate or high-quality evidence of harm exists, strong recommendations may be appropriate. This is such a situation.

Given the significant risk of adverse events with antibiotics and no evidence suggesting benefit in any of the outcomes of interest, the GDG judged that the majority of patients would not choose to use antibiotics in the setting of non-severe influenza with a low probability of bacterial infection.

7.2.1.3 Summary

The evidence regarding concomitant use of antibiotics versus no antibiotics was informed by four RCTs, which enrolled 331 non-hospitalized patients with confirmed symptomatic influenza. One study enrolled children aged 6 months or older and three enrolled individuals aged 18 years or older. The studies enrolled patients with mixed types of influenza virus infections, such as H1N1, H3N2, and type B.

Summary of study characteristics, risk of bias ratings, and effect estimates by outcome for antibiotics versus no antibiotics are available as an online annex, [here](#) [43].

For patients with non-severe confirmed influenza, the GRADE Summary of Findings table shows the relative and absolute effects of antibiotics compared with no antibiotics for the outcomes of interest, with certainty ratings, informed by meta-analyses or single study data depending on the outcome. None of the studies reported admission to hospital or the emergence of antibiotic resistance.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses
- Probability of a concomitant bacterial infection

- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk for severe disease based on health status versus those not at risk (pregnant/ post-partum, obese, underlying chronic respiratory conditions or immunosuppressed)

Insufficient data were available to inform pre-specified subgroup analyses.

Indirect study data for adverse events

The evidence for adverse effects associated with concomitant use of antibiotics versus no antibiotics was collected using indirect data from one RCT, which enrolled 479 non-hospitalized patients with urinary tract infection. The study enrolled patients aged 18 to 80.

Table 7.10 Summary of findings for antibiotics vs. no antibiotics in patients with suspected or confirmed non-severe influenza virus infection and low probability of bacterial co-infection

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		No antibiotic	Antibiotic		
Mortality	Relative risk (CI 95% not calculable) Based on data from 107 participants in 1 study Follow up 5 days	0.0	0.0	Low Due to serious imprecision, serious indirectness ¹	Antibiotics may have little or no difference on mortality
		Difference: 0 fewer			
Progression of disease: reconsultation	Relative risk: 0.63 (CI 95% 0.24 - 1.71) Based on data from 37 participants in 1 study Follow up 28 days	375 per 1000	236 per 1000	Very low Due to serious indirectness and extremely serious imprecision ²	The evidence is very uncertain about the effect of antibiotics on progression of disease: reconsultation.
		Difference: 139 fewer per 1000 (CI 95% 285 fewer - 266 more)			
Progression of disease: Development of pneumonia	Relative risk: 0.91 (CI 95% 0.06 - 14.19) Based on data from 141 participants in 1 study Follow up 5 days	15 per 1000	14 per 1000	Very low Due to serious risk of bias, serious imprecision, serious indirectness ³	The evidence is very uncertain about the effect of antibiotics on progression of disease: development of pneumonia
		Difference: 1 fewer per 1000 (CI 95% 14 fewer - 198 more)			
Adverse events (indirect)⁴	Odds ratio: 1.19 (CI 95% 1.09 - 1.3) Based on data from 3969 participants in 17 studies	242 per 1000	275 per 1000	Moderate Due to serious indirectness ⁵	Antibiotics probably increase adverse events.
		Difference: 33 more per 1000			

				(CI 95% 16 more - 51 more)
Adverse events related to the study drug⁶	Relative risk: 1.37 (CI 95% 0.39 - 4.83) Based on data from 107 participants in 1 study Follow up 5 days	71 per 1000	97 per 1000	Low Due to serious indirectness, serious imprecision. ⁷ Antibiotics may have little or no difference on adverse events related to the study drug
Duration of fever, hours⁸	Measured by: Scale: - lower better Based on data from 161 participants in 2 studies	48.53 Mean	44.56 Mean	Very low Due to serious risk of bias, serious imprecision, serious indirectness ⁹ The evidence is very uncertain about the effect of antibiotics on duration of fever
Duration of myalgia/arthralgia, hours	Measured by: Scale: - lower better Based on data from 15 participants in 1 study Follow up 5 days	34.2 Mean	39.3 Mean	Very low Due to extremely serious imprecision, serious indirectness. ¹⁰ The evidence is very uncertain about the effect of antibiotics on duration of myalgia/ arthralgia
Duration of rhinorrhea , hours¹¹	Measured by: Scale: - lower better Based on data from 13 participants in 1 study	73.1 Mean	59.6 Mean	Very low Due to extremely serious imprecision. ¹² The evidence is very uncertain about the effect of antibiotics on duration of rhinorrhea
Duration of cough, hours¹³	Measured by: Scale: - lower better Based on data from 159 participants in 2 studies	134.07 Mean	144.2 Mean	Very low Due to serious risk of bias, serious imprecision, serious indirectness ¹⁴ The evidence is very uncertain about the effect of antibiotics on duration of cough
Duration of sputum, hours¹⁵	Measured by: Scale: - lower better Based on data from 153 participants in 2 studies	123.89 Mean	130.94 Mean	Very low Due to serious risk of bias, serious imprecision, serious indirectness ¹⁶ The evidence is very uncertain about the effect of antibiotics on duration of sputum
Duration of sore throat, hours¹⁷	Measured by: Scale: - lower better Based on data from 155 participants in 2 studies	89.79 Mean	96.26 Mean	Very low Due to serious risk of bias, serious imprecision, serious indirectness ¹⁸ The evidence is very uncertain about the effect of antibiotics on duration of sore throat
Duration of general malaise, hours¹⁹	Measured by: Scale: - lower better Based on data from 156 participants in 2 studies	67.32 Mean	64.27 Mean	Very low Due to serious risk of bias, serious inconsistency, serious The evidence is very uncertain about the effect of antibiotics on duration of general malaise

imprecision,
serious
indirectness²⁰

1. *Indirectness: serious. RCTs focus on immunomodulatory effect of antibiotic; Imprecision: serious. Only data from one study, Low number of patients; Publication bias: no serious. Publication bias was not formally assessed;*
2. *Indirectness: serious. Differences between the population of interest and those studied (paediatric population at risk for severe disease); Imprecision: extremely serious. Fewer than 40 patients with confirmed influenza; Publication bias: no serious. Publication bias was not formally assessed;*
3. *Risk of bias: serious. Inadequate sequence generation/ generation of comparable groups and concealment of allocation during randomization process, resulting in potential for selection bias; Indirectness: serious. RCTs focus on immunomodulatory effect of antibiotic; Imprecision: serious. Wide confidence intervals, Low number of patients; Publication bias: no serious. Publication bias was not formally assessed;*
4. *Relative effects are reported based on 3 vs. 7 day antibiotic use in patients with any indication from an umbrella review by Curran et al. 2022. Absolute effects are estimated using data for 3 vs. 7 day antibiotic use from an RCT by Flack, 1988 in community patients with urinary tract infection. No data to inform absolute effect estimates were reported in Curran et al. 2020 and so the RCT with the largest sample size which reported useable data for adverse effects was selected.*
5. *Indirectness: serious. Results for n=17 RCTs are taken from an umbrella review (systematic reviews of RCTs with individual study meta-analysis) estimating antibiotic harms for common infections. Odds ratio represents the cumulative odds of a patient experiencing an adverse event at 7 days versus 3 days. Harms were consistent across setting and age groups.;*
6. *undefined*
7. *Indirectness: serious. Differences between the population of interest and those studied (paediatric population at risk for severe disease); Imprecision: serious. Wide confidence intervals. Low number of patients. Data from only one study.; Publication bias: no serious. Publication bias was not formally assessed;*
8. *undefined*
9. *Risk of bias: serious. Inadequate sequence generation/ generation of comparable groups and concealment of allocation during randomization process, resulting in potential for selection bias; Indirectness: serious. RCTs focus on immunomodulatory effect of antibiotic; Imprecision: serious. Low number of patients; Publication bias: no serious. Publication bias was not formally assessed;*
10. *Indirectness: serious. RCTs focus on immunomodulatory effect of antibiotic.; Imprecision: extremely serious. Low number of patients (< 20). Wide confidence intervals.; Publication bias: no serious. Publication bias was not formally assessed.;*
11. *undefined*
12. *Imprecision: extremely serious. Low number of patients (< 15). Wide confidence intervals; Publication bias: no serious. Publication bias was not formally assessed.;*
13. *undefined*
14. *Risk of bias: serious. Inadequate sequence generation/ generation of comparable groups and concealment of allocation during randomization process, resulting in potential for selection bias; Indirectness: serious. RCTs focus on immunomodulatory effect of antibiotic; Imprecision: serious. Wide confidence intervals, Low number of patients; Publication bias: no serious. Publication bias was not formally assessed;*
15. *undefined*
16. *Risk of bias: serious. Inadequate sequence generation/ generation of comparable groups and concealment of allocation during randomization process, resulting in potential for selection bias; Indirectness: serious. RCTs focus on immunomodulatory effect of antibiotic; Imprecision: serious. Low number of patients; Publication bias: no serious. Publication bias was not formally assessed;*
17. *undefined*

18. Risk of bias: serious. Inadequate sequence generation/ generation of comparable groups and concealment of allocation during randomization process, resulting in potential for selection bias; Indirectness: serious. RCTs focus on immunomodulatory effect of antibiotic; Imprecision: serious. Low number of patients;

19. undefined

20. Risk of bias: serious. Inadequate sequence generation/ generation of comparable groups and concealment of allocation during randomization process, resulting in potential for selection bias; Inconsistency: serious. I-Squared = 60%; Indirectness: serious. RCTs focus on immunomodulatory effect of antibiotic; Imprecision: serious. Low number of patients, Wide confidence intervals; Publication bias: no serious. Publication bias was not formally assessed;

References [43-47]

8. Recommendations for patients with severe symptomatic influenza (suspected or confirmed)

8.1 Antiviral therapies for patients with severe symptomatic influenza (suspected or confirmed)

8.1.1 Oseltamivir

Conditional recommendation for

In patients with suspected or confirmed severe influenza virus infection, we **suggest administering oseltamivir** (conditional recommendation, very low-quality evidence).

- Treatment should be administered as early as possible, and within 2 days of symptom onset.
- This recommendation applies to patients with novel influenza A virus infection associated with high mortality, or with an unknown risk of severe disease, even where they do not otherwise fulfil criteria for severe influenza.

8.1.1.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients with severe influenza virus infection, oseltamivir treatment may reduce duration of hospitalization. Whether oseltamivir treatment of patients with severe influenza virus infection reduces intensive care unit (ICU) admission or mortality for seasonal influenza is very uncertain. Whether oseltamivir treatment of patients with severe influenza virus infection reduces mortality due to novel influenza A viruses associated with high mortality in infected humans (zoonotic influenza viruses) is very uncertain.

Certainty of the evidence

Low

Only one RCT with mortality outcome was identified. Certainty of evidence was rated as low for duration of hospitalization, and very low for ICU admission and mortality due to seasonal influenza and novel zoonotic influenza A viruses associated with high mortality.

Values and preferences	No substantial variability expected
Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed patients with severe influenza virus infection would choose to use oseltamivir.	
Resources and other considerations	No important issues with the recommended alternative
<i>Acceptability and feasibility</i>	
Previously, WHO had recommendations for use of oseltamivir in patients with severe influenza virus infection and this update does not change this recommendation [16] as the accumulated evidence continues to show uncertainty for the effects of oseltamivir.	
Oseltamivir is widely available, primarily in generic formulations and has a low probability of causing adverse drug reactions. Oseltamivir is listed as a complementary medicine on the WHO Essential Medicines List [48]. Oseltamivir is an oral medicine and is well absorbed when given enterically by orogastric or nasogastric tube.	
<i>Access to influenza diagnostics</i>	
The GDG emphasized the importance of accurate and early diagnosis of influenza as this recommendation involves treatment within 2 days of symptom onset. This demands improved access pathways, and appropriate use of diagnostic tests. Health care systems must provide these in context-sensitive manner.	

8.1.1.2 Justification

Data from clinical trials are very limited for oseltamivir in patients with severe influenza virus infection. The GDG inferred that for severe seasonal influenza virus infection, the threshold for use of oseltamivir treatment would be a reduction in mortality of 3 in 1000. For both seasonal influenza and zoonotic influenza (novel influenza A viruses associated with high mortality) it is very uncertain if oseltamivir increases or reduces mortality or ICU admission.

The GDG inferred that the threshold for use of oseltamivir treatment of severe influenza virus infection would be a reduction in duration of hospitalization by 1 day

for seasonal influenza, and the low certainty evidence suggests that oseltamivir decreases the duration of hospitalization.

However, previous recommendations by WHO [16] recommended to use oseltamivir in severe patients and the GDG, after significant deliberations, did not desire to change direction of recommendation without any new evidence to the contrary. Thus, as patients with severe influenza have a substantial risk of dying and given the likelihood of minimal adverse effects, even with only very low certainty evidence, the GDG judged that the majority of patients would choose to use the drug because of the possibility of benefit. The GDG noted that there is considerable experience in using oseltamivir for patients with severe influenza. The GDG also acknowledged that there are ongoing trials in severe influenza which are evaluating antivirals, and that this recommendation should be re-evaluated as new data emerge.

8.1.1.2.1 Applicability

Oseltamivir can be administered to pregnant and lactating women and children, including neonates.

8.1.1.3 Practical info

8.1.1.3.1 Route, dosage and duration – treatment of influenza

Oseltamivir is given **orally** as a dose, based on age and body weight, as below. It is available as capsules of 30 mg, 45 mg and 75 mg, and as oral powder for reconstitution.

Table 8.1 Dosing of oseltamivir for treatment

Age	Body weight	Dose and duration of oseltamivir for treatment of influenza
Adults and those 13 years and over	> 40 kg	75 mg twice daily for 5 days*
Children from 1 year up to 13 years	10 kg to 15 kg	30 mg twice daily for 5 days*
	> 15 kg to 23 kg	45 mg twice daily for 5 days*
	> 23 kg to 40 kg	60 mg twice daily for 5 days*
	> 40 kg	75 mg twice daily for 5 days*
Children under 1 year		3 mg/kg twice daily for 5 days*

Treatment should be administered as early as possible, and within 2 days of symptom onset.

* Longer duration of oseltamivir treatment can be considered for severe influenza virus infection, including due to zoonotic influenza, and for immunocompromised patients.

Baloxavir might be considered as an alternative to oseltamivir where the latter is not available (indirect evidence from non-severe seasonal influenza, very low certainty).

8.1.1.3.2 Dose adjustment for renal impairment – treatment of influenza

Dose adjustment is recommended for adults and those 13 years and over who have moderate or severe renal impairment, as below:

Table 8.2 Dosing of oseltamivir for treatment in patients with renal impairment

Creatinine clearance (mL/min)	Dose of oseltamivir for treatment of influenza
> 60	75 mg twice daily
> 30 to 60	30 mg twice daily
> 10 to 30	30 mg once daily
≤ 10	Not recommended. No data available
Haemodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients	30 mg single dose

There is insufficient clinical data available in those under 13 years of age with renal impairment to be able to make any dosing recommendation.

8.1.1.3.3 Other considerations

Pregnancy: Observational studies of oseltamivir use during pregnancy (more than 1000 exposed outcomes during the first trimester) indicate that it is safe during pregnancy with no malformative nor fetal/ neonatal toxicity. Pregnant women can be offered oseltamivir when the potential benefits of using the drug are more likely than the potential risk of harm to the woman or their baby [34].

Lactation: Limited information is available. Manufacturer advised administration of oseltamivir may be considered where there are clear potential benefits to breastfeeding mothers.

Administration: Oseltamivir can be administered enterically via orogastric or nasogastric tube to intubated patients and is well absorbed, but is contraindicated in patients with malabsorption, gastric stasis, ileus or gastrointestinal bleeding.

Pharmacokinetics: The manufacturer's summary of product characteristics contains additional details on animal studies and pharmacokinetics and drug interactions [34].

8.1.1.4 Summary

The evidence regarding oseltamivir versus placebo or standard care was informed by 2 RCTs, which enrolled 104 patients with severe illnesses (studies provided the direct comparison for any outcomes of interest). One study enrolled pediatric patients (0–9 years), and one study enrolled adults (18+ years). Studies did not enrol patients with zoonotic influenza. The status of vaccination for the influenza virus was not reported. One study enrolled patients with mixed types of influenza virus infections, such as H1N1, H3N2, and type B. One study did not report the types of influenza viruses. Study characteristics, risk of bias ratings, and effect estimates by outcome for oseltamivir used here have been published.[18]

For patients with severe influenza, the GRADE Summary of Findings table shows the relative and absolute effects of oseltamivir compared with placebo or standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses
- Confirmed vs. suspected infection
- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk of poor outcomes vs. not

Sufficient data were unavailable to inform pre-specified subgroup analyses.

Table 8.3 Summary of findings for oseltamivir vs. standard care in patients with suspected or confirmed severe influenza virus infection

Outcome	Study results and measurements	Absolute effect estimates	Certainty of the evidence	Summary
		Standard care/ placebo	Oseltamivir	

Mortality (Seasonal influenza)	Relative risk: 0.53 (CI 95% 0.07 - 4.24) Based on data from 74 participants in 1 study	30 per 1000	16 per 1000	Very low Due to extremely serious imprecision ¹	Whether oseltamivir reduces mortality is very uncertain.
		Difference: 14 fewer per 1000 (CI 95% 28 fewer - 97 more)			
Mortality (Zoonotic influenza)	Relative risk: 0.53 (CI 95% 0.07 - 4.24)	387 per 1000	205 per 1000	Very low Due to extremely serious imprecision ²	Whether oseltamivir reduces mortality is very uncertain.
		Difference: 182 fewer per 1000 (CI 95% 360 fewer - 613 more)			
Admission to ICU	Risk difference: 0.02 (CI 95% -0.09 - 0.12)	Difference: 15.0 more per 1000 (CI 95% 89.0 fewer - 118.0 more)		Very low Due to serious risk of bias, very serious imprecision ³	Whether oseltamivir reduces admission to ICU is very uncertain.
Duration of hospitalization	Measured by: Scale: - lower better Based on data from 104 participants in 2 studies	5.00 Mean	3.37 Mean	Low Due to serious imprecision, serious risk of bias ⁴	Oseltamivir may reduce duration of hospitalization.
		Difference: MD 1.63 lower (CI 95% 2.81 lower - 0.45 lower)			

1. *Imprecision: extremely serious. Wide confidence intervals;*
2. *Imprecision: extremely serious. Wide confidence intervals, Low number of patients;*
3. *Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: very serious. Wide confidence intervals;*
4. *Risk of bias: serious. Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: serious. Wide confidence intervals, Low number of patients.*

8.1.2 Peramivir

Conditional recommendation against

In patients with suspected or confirmed severe influenza virus infection, we **suggest not administering peramivir** (conditional recommendation, very low-quality evidence).

8.1.2.1 Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives
In patients with severe influenza virus infection due to seasonal influenza, peramivir treatment may reduce duration of hospitalization. Whether peramivir treatment of patients with severe influenza virus infection due to seasonal influenza reduces ICU admission or mortality is very uncertain. Whether peramivir treatment of patients with severe influenza virus infection due to zoonotic influenza (novel influenza A viruses associated with high mortality) reduces mortality is also very uncertain.	
Certainty of the evidence	Low
Only one RCT was identified. Certainty of evidence was rated as low for duration of hospitalization, and very low for ICU admission and mortality due to seasonal influenza. Certainty of evidence was rated as very low for mortality due to zoonotic influenza.	
Values and preferences	No substantial variability expected
Applying the agreed upon values and preferences (see Section 11.2) (see Section 11.2), the GDG inferred that the majority of well-informed patients with severe influenza virus infection would choose not to use peramivir.	
Resources and other considerations	Important issues, or potential issues not investigated
Acceptability and feasibility	

Peramivir is an intravenous medication that is not widely available and is more expensive than oral antivirals. Influenza viruses that are resistant to oseltamivir are usually also resistant to peramivir.

The GDG did consider that peramivir may be an option for patients with severe influenza virus infection with contraindications to oral or enteric antiviral treatment (e.g., malabsorption, gastric stasis, ileus, gastrointestinal bleeding).

The optimal duration of peramivir treatment for patients with severe influenza virus infection is unknown.

8.1.2.2 Justification

Data from clinical trials are very limited for peramivir in patients with severe influenza virus infection. The GDG inferred that for severe influenza virus infection, the threshold for use of peramivir treatment would be a reduction in mortality of 0.3%. For both severe seasonal influenza and for zoonotic influenza (novel influenza A viruses associated with high mortality), the GDG noted the evidence to be uncertain on whether peramivir increases or reduces mortality.

The GDG inferred that the threshold for use of peramivir treatment of severe influenza virus infection would be a reduction in duration of hospitalization by 1 day for seasonal influenza. The estimated effect of peramivir treatment on duration of hospitalization was 1.73 days fewer with a lower bound of the 95% CI of 0.13 days fewer and an upper bound of 3.33 days deemed to be of low certainty.

If GDG inferences regarding patient values and preferences are accurate, a majority of fully informed patients would not choose peramivir treatment. A conditional recommendation against use of peramivir treatment was made due to the possibility that peramivir may reduce duration of hospitalization and the uncertainty of whether peramivir increases or reduces mortality. The GDG did consider that peramivir may be an option for patients with severe influenza virus infection with contraindications to oral or enteric antiviral treatment (e.g., malabsorption, gastric stasis, ileus, gastrointestinal bleeding).

8.1.2.3 Summary

The evidence regarding peramivir versus placebo or standard care was informed by 1 RCT, which enrolled 114 patients with severe illnesses in our analysis (studies provided the direct comparison for any outcomes of interest). The study enrolled patients aged 11 or older, with a mean age of 42.58 years. Studies did not enrol

patients with zoonotic influenza. The proportion of patients who got vaccinated for the influenza virus was 4.96%. The study enrolled patients with mixed types of influenza virus infections, such as H1N1, H3N2, and type B. Study characteristics, risk of bias ratings, and effect estimates by outcome for peramivir used here have been published [18].

For patients with severe influenza, the GRADE Summary of Findings table shows the relative and absolute effects of peramivir compared with placebo or standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses
- Confirmed vs. suspected infection
- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk of poor outcomes vs. not

Sufficient data were unavailable to inform pre-specified subgroup analyses.

Table 8.4 Summary of findings for peramivir vs. standard care in patients with suspected or confirmed severe influenza virus infection

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care/ placebo	Peramivir		
Mortality (Seasonal influenza)	Relative risk: 0.4 (CI 95% 0.03 - 4.72) Based on data from 114 participants in 1 study	30 per 1000	12 per 1000	Difference: 18 fewer per 1000 (CI 95% 29 fewer - 112 more)	Very low Due to serious risk of bias, extremely serious imprecision ¹ Whether peramivir reduces mortality is very uncertain.
Mortality (Zoonotic influenza)	Relative risk: 0.4 (CI 95% 0.03 - 4.72)	387 per 1000	155 per 1000	Difference: 232 fewer per 1000 (CI 95% 375 fewer - 613 more)	Very low Due to serious risk of bias, extremely serious imprecision ² Whether peramivir reduces mortality is very uncertain.
Admission to ICU	Risk difference: 0.03 (CI 95% -0.1 - 0.04)	Difference: 29.0 fewer per 1000 (CI 95% 97.0 fewer - 40.0 more)	Very low Due to serious risk of bias, Whether peramivir reduces admission to ICU is very uncertain.		

Based on data from 98 participants in 1 study			very serious imprecision ³		
Duration of hospitalization	Measured by: Scale: - lower better	5.00 Mean	3.27 Mean	Low Due to serious imprecision, serious risk of bias ⁴	Peramivir may reduce duration of hospitalization.
	Follow up Indirect evidence	Difference: MD 1.73 lower (CI 95% 3.33 lower - 0.13 lower)			

1. *Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: extremely serious. Wide confidence intervals, Low number of patients;*
2. *Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: extremely serious. Wide confidence intervals, Low number of patients;*
3. *Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: very serious. Wide confidence intervals;*
4. *Risk of bias: serious. Imprecision: serious. Wide confidence intervals.*

8.1.3 Zanamivir

Conditional recommendation against

In patients with suspected or confirmed severe influenza virus infection, we **suggest not administering zanamivir** (conditional recommendation, very low-quality evidence).

8.1.3.1 Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives
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In patients with severe influenza virus infection due to seasonal influenza, it is very uncertain whether zanamivir treatment reduces duration of hospitalization, ICU admission or mortality. Whether zanamivir treatment of patients with severe influenza virus infection due to zoonotic influenza (novel influenza A viruses associated with high mortality) reduces mortality is also very uncertain.

Certainty of the evidence	Low
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Certainty of evidence was rated as low for duration of hospitalization due to seasonal influenza, and very low for ICU admission and mortality. Certainty of evidence was rated as very low for mortality due to zoonotic influenza novel influenza A viruses associated with high mortality. No direct comparisons were available for zanamivir versus placebo. Indirect comparisons informed the evidence regarding zanamivir versus placebo or standard care.

Values and preferences	No substantial variability expected
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Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed patients with severe influenza virus infection would choose not to use zanamivir.

Resources and other considerations	Important issues, or potential issues not investigated
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Acceptability and feasibility

Inhaled zanamivir is an inhaled powdered medication that must be used with an inhaler device. Young children and older adults might not be able to properly inhale zanamivir into the respiratory tract. Patients with chronic pulmonary disease should avoid inhaled zanamivir because of the increased risk of bronchospasm. The manufacturer recommends that zanamivir must NOT be made into an extemporaneous solution for administration by nebulization or mechanical ventilation and that the inhalation powder must only be administered using the device provided. This is due to the risk of lactose in the formulation obstructing oxygen delivery devices [49].

Intravenous zanamivir is available in a small number of countries. The intravenous zanamivir formulation should not be administered via nebulizer to intubated patients.

8.1.3.2 Justification

The evidence was judged to be very low certainty that zanamivir reduces mortality.

The effect of zanamivir treatment on admission to ICU and on duration of hospitalization could not be estimated.

If GDG inferences regarding patient values and preferences are accurate, a majority of fully informed patients would not choose zanamivir treatment. A conditional recommendation against the use of zanamivir treatment was made due to the uncertainty of whether zanamivir increases or reduces mortality and lack of data on whether zanamivir reduces ICU admission or duration of hospitalization.

8.1.3.3 Summary

No direct comparisons were available for zanamivir versus placebo. Indirect comparisons informed the evidence regarding zanamivir versus placebo or standard care. Study characteristics, risk of bias ratings, and effect estimates by outcome for zanamivir used here have been published [18].

For patients with severe influenza, the GRADE Summary of Findings table shows the relative and absolute effects of zanamivir compared with placebo or standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Four pre-specified subgroup analyses were requested by the GDG:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses

- Confirmed vs. suspected infection
- Age: children < 2 years, children vs. adults and adolescents vs. older adults (≥ 65 years)
- Patients at increased risk of poor outcomes vs. not

Sufficient data were unavailable to inform pre-specified subgroup analyses.

Table 8.5 Summary of findings for zanamivir vs. standard care in patients with suspected or confirmed severe influenza virus infection

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care/ placebo	Zanamivir		
Mortality (seasonal influenza)	Relative risk: 0.58 (CI 95% 0.06 - 5.29)	30 per 1000	17 per 1000	Very low Due to serious risk of bias, extremely serious imprecision ¹	Whether zanamivir reduces mortality is very uncertain.
		Difference: 13 fewer per 1000 (CI 95% 28 fewer - 129 more)			
Mortality (zoonotic influenza)	Relative risk: 0.58 (CI 95% 0.06 - 5.29)	387 per 1000	224 per 1000	Very low Due to serious risk of bias, extremely serious imprecision ²	Whether zanamivir reduces mortality is very uncertain.
		Difference: 163 fewer per 1000 (CI 95% 364 fewer - 613 more)			
Admission to ICU	No RCT data (CI 95% not calculable)				Whether zanamivir reduces admission to ICU is very uncertain.
Duration of hospitalization	No RCT data				Whether zanamivir reduces duration of hospitalization is very uncertain.

1. Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: extremely serious. Wide confidence intervals, Low number of patients;
2. Risk of bias: serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: extremely serious. Wide confidence intervals, Low number of patients;
3. undefined

8.2 Adjunctive immunomodulatory therapy for patients with severe influenza (confirmed)

Adjunctive immunomodulatory therapy vs. no immunomodulatory therapy. For systematic review details, see [19].

8.2.1 Corticosteroids

Conditional recommendation against

In patients with suspected or confirmed severe influenza virus infection, we **suggest not administering corticosteroids** (conditional recommendation, very low-quality evidence).

- There is a possibility of important benefit from corticosteroid treatment, especially where the clinical diagnosis overlaps with ARDS.

8.2.1.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients with severe influenza virus infection, it is uncertain whether use of corticosteroids for adjunctive immunomodulatory therapy has any effect on duration of hospitalization, admission to ICU, mechanical ventilation, hospital-acquired infection, or mortality.

Corticosteroids possibly decrease mortality in the late phase of ARDS, a known complication of severe influenza virus infection, but no direct evidence was identified from clinical trials for patients with ARDS that was caused by influenza virus.

The reviewed evidence demonstrated very low certainty on whether corticosteroids cause adverse events. However, the GDG noted that corticosteroids are associated with side-effects, including adrenal insufficiency, hyperglycaemia, immunosuppression, and avascular necrosis of joints, which can occur with high cumulative doses[50].

Certainty of the evidence

Low

No RCTs have been conducted of corticosteroids for adjunctive immunomodulatory therapy of severe influenza virus infection. The evidence summary was based on a systematic review of observational studies in severe influenza patients (direct evidence) and from a meta-analysis from clinical trials in ARDS. Certainty of evidence was rated as very low for length of hospitalization, ICU admission, mechanical ventilation, hospital-acquired infection and mortality from the direct evidence in severe influenza. Certainty of evidence was rated as low-quality for mortality from indirect evidence in ARDS.

Values and preferences

No substantial variability expected

Applying the agreed upon values and preferences (see *Section 11.2*), the GDG inferred that a majority of well-informed patients with severe influenza virus infection would choose not to use corticosteroids for adjunctive immunomodulatory therapy.

Resources and other considerations

No important issues with the recommended alternative

Acceptability and feasibility

Corticosteroids are widely available and have been used for adjunctive immunomodulatory therapy of patients with severe COVID-19. Corticosteroids are available in oral and intravenous formulations. The optimal dose, duration and timing of initiation of corticosteroids for adjunctive immunomodulatory therapy of severe influenza virus infection are unknown.

8.2.1.2 Justification

The GDG inferred that for severe influenza virus infection, the threshold for use of corticosteroids for adjunctive immunomodulatory therapy would be a reduction in mortality of 0.3% and the threshold for use of corticosteroids for adjunctive immunomodulatory therapy would be a reduction in the duration of hospitalization by 1 day.

It is very uncertain whether corticosteroids as a treatment in severe influenza virus increase or reduce hospital length of stay, ICU admission, mechanical ventilation, hospital-acquired infection, and mortality; this is based on direct evidence available from observational studies. However, using indirect evidence, the effect estimates of

benefit of possible corticosteroid treatment in patients with ARDS, was 8%, with lower limit of 2.2 and upper limit of 12.5%.

The GDG inferred that most patients would decline an intervention when there is high uncertainty of any benefit as the evidence demonstrated with corticosteroids as adjunctive therapy. If GDG inferences regarding patient values and preferences are accurate, a majority of fully informed patients would not choose corticosteroids as adjunctive immunomodulatory therapy for severe influenza virus infection. A conditional recommendation against the use of corticosteroids was made due to the lack of direct data from clinical trials, and the uncertainty of whether corticosteroids increase or reduce hospital length of stay, ICU admission, mechanical ventilation, and hospital-acquired infection. Impact on mortality also remains uncertain from direct very low-quality evidence, despite the possible benefit of corticosteroids on mortality from indirect trials on ARDS. The GDG noted that clinical trials were ongoing in severe influenza infection to evaluate corticosteroids as a treatment and those results should inform further updates of this recommendation.

The conditional recommendation reflects the very low certainty of the evidence and acknowledgment that values and preferences will differ among patients, and that some may choose to receive treatment when the possibility of important benefit remains, as may be considered in some patients with ARDS or severe pneumonia.

8.2.1.3 Summary

Systematic review of RCTs (indirect evidence from COVID-19 and non-COVID-19 ARDS) [51]. An updated systematic review of RCTs was specifically commissioned for this GDG [19].

Observational data systematic review [50].

Table 8.6 Summary of findings for systemic corticosteroids vs. no systemic corticosteroids in patients with suspected or confirmed severe influenza virus infection

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		No systemic corticosteroids	Systemic corticosteroids		
Mortality (observa-	Odds ratio: 4.79 (CI 95% 2.35 - 9.79)	70 per 1000	209 per 1000	Very low	We are uncertain whether systemic

tional, unadjusted)¹ 30 days	Based on data from 1006 participants in 10 studies ²	Difference: 139 more per 1000 (CI 95% 90 more - 197 more)	Due to very serious risk of indication bias, and serious inconsistency (unadjusted odds ratios and varying definition of mortality). ³	corticosteroids increase or decrease mortality
Mortality (observational, adjusted) 30 days	Odds ratio: 2.23 (CI 95% 1.54 - 3.24) Based on data from 1206 participants in 5 studies ⁴	70 per 1000	144 per 1000	Very low Due to very serious risk of indication bias, and serious inconsistency (varying definition of mortality). ⁵
	Difference: 74 more per 1000 (CI 95% 34 more - 126 more)			We are uncertain whether systemic corticosteroids increases or decreases mortality
Mortality (ARDS, RCT, indirect)	Relative risk: 0.82 (CI 95% 0.72 - 0.95) Based on data from 2740 participants in 16 studies ⁶	446 per 1000	366 per 1000	Low Due to serious indirectness. ⁷
	Difference: 80 fewer per 1000 (CI 95% 125 fewer - 22 fewer)			Corticosteroids possibly decrease mortality.
Mortality (zoonotic) 30 days	Odds ratio: 2.23 (CI 95% 1.54 - 3.24) Based on data from 1206 participants in 5 studies ⁸	386 per 1000	584 per 1000	Very low Due to very serious risk of indication bias, and serious inconsistency (varying definition of mortality). ⁹
	Difference: 198 more per 1000 (CI 95% 106 more - 285 more)			We are uncertain whether systemic corticosteroids increase or decreases mortality
Mechanical ventilation (observational, lowest estimate)¹⁰	Odds ratio: 1.78 (CI 95% 1.35 - 2.35) Based on data from 4364 participants in 4 studies	418 per 1000	561 per 1000	Very low Due to very serious risk of bias, serious imprecision. ¹¹
	Difference: fewer per 1000			We are very uncertain if there is an effect of systematic corticosteroids on mechanical ventilation.
Admission to ICU (observational)	Odds ratio: 5.13 (CI 95% 4.26 - 6.17) Based on data from 2141 participants in 1 study	260 per 1000	643 per 1000	Very low Due to serious imprecision, very serious risk of bias. ¹²
	Difference: 383 more per 1000 (CI 95% 339 more - 424 more)			We are very uncertain if there is an effect of systematic corticosteroids on admission to an Intensive Care Unit
Adverse events (hospital- acquired infection)	Odds ratio: 2.74 (CI 95% 1.51 - 4.95) Based on data from 6114 participants in 7 studies ¹³	72 per 1000	175 per 1000	Very low Due to high risk of indication bias and clinical/statistical heterogeneity. ¹⁴
	Difference: 103 more per 1000 (CI 95% 33 more - 205 more)			We are uncertain whether systemic corticosteroids increase or decreases adverse events (hospital-acquired infection)

Mechanical ventilation (observational, highest estimate)¹⁵	Odds ratio: 11.29 (CI 95% 8.25 - 15.44) Based on data from 4364 participants in 4 studies	418 per 1000	890 per 1000	Very low Due to very serious risk of bias, serious imprecision	We are very uncertain if there is an effect of systematic corticosteroids on mechanical ventilation.
Length of stay in hospital (ARDS, RCT, indirect)	Measured by: Days Scale: - lower better Based on data from 344 participants in 4 studies ¹⁶	26.4 Median	18.3 Median	Very low Due to serious risk of bias, very serious indirectness ¹⁷	We are very unsure of the effect of systemic corticosteroids on length of hospital stay

1. undefined
2. Supporting references [52].
3. Risk of bias: very serious. high risk of indication bias; Inconsistency: serious. Unadjusted estimates of odds ratio for mortality were presented in some studies, and the definition of mortality varied across the studies,;
4. Systematic review . Baseline/ comparator Control arm of reference used for intervention . Supporting references [52].
5. Risk of bias: very serious. Inconsistency: serious.
6. Systematic review . Baseline/ comparator No studies available . Supporting references [51].
7. Indirectness: serious. Differences between the population of interest and those studied; Indirect evidence from COVID 19 and non-COVID 19 ARDS applied to populations with influenza
8. Systematic review . Baseline/ comparator Control arm of reference used for intervention . Supporting references [52].
9. Risk of bias: very serious. Inconsistency: serious.
- 10.undefined
- 11.Risk of bias: very serious. High risk of indication bias; Imprecision: serious. Unadjusted odds ratios used in all studies;
- 12.Risk of bias: very serious. High risk of indication bias; Imprecision: serious. Only data from one study;
- 13.Systematic review . Baseline/ comparator Control arm of reference used for intervention . Supporting references [52].
- 14.Risk of bias: very serious. Inconsistency: serious. (unadjusted estimates of odds ratio for hospital-acquired infection were presented in some studies, and the definitions of hospital-acquired infection varied across the studies)
15. Estimates could not be pooled, and so are presented as ranges of the extracted odds ratios
16. Systematic review . Baseline/ comparator Control arm of reference used for intervention . Supporting references [51].
- 17.Risk of bias: serious. Indirectness: very serious.

References [52-54]

8.2.2 Macrolide

Conditional recommendation against

In patients with suspected or confirmed severe influenza virus infection, we **suggest not administering a macrolide** (conditional recommendation, very low-quality evidence).

- The GDG note that this is a recommendation in regard to the use of macrolide antibiotics as immunomodulatory therapy in severe influenza virus infection. It does not relate to the use of macrolide antibiotics as therapy for bacterial co-infection in suspected or confirmed severe influenza.

8.2.2.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients with severe influenza virus infection, it is very uncertain whether treatment with macrolide antibiotics increases or reduces duration of hospitalization, mortality or adverse events.

Treatment with macrolides, including azithromycin, has been associated with prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes* [55].

The GDG noted that WHO has provided guidance on antibiotic stewardship and limiting the use of antibiotics to instances when they are likely to have clinical benefit. Importantly WHO has classified the macrolide antibiotics azithromycin and erythromycin as "Watch" antibiotics. Watch antibiotics are broader spectrum antibiotics, generally with higher costs and are recommended only as first choice options for patients with more severe clinical presentations or for infections where the causative pathogens are more likely to be resistant [56].

Certainty of the evidence

Very low

Certainty of evidence based on one small study with 50 participants was rated as very low for duration of hospitalization, mortality and adverse events.

Values and preferences	No substantial variability expected
Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that a majority of well-informed patients with severe influenza virus infection would choose not to use a macrolide antibiotic as adjunctive immunomodulatory therapy.	
The recommendation against administration reflects a high value on avoiding treatment when there is high uncertainty of any benefit. The conditional recommendation reflects the very low certainty of the evidence and acknowledgment that values and preferences will differ among patients, and that some may choose to receive treatment when the possibility of important benefit remains.	
Resources and other considerations	Important negative issues
<i>Acceptability and feasibility</i>	
Macrolide antibiotics for oral administration are widely available worldwide. Macrolide antibiotics for intravenous administration may not be as widely available. The GDG noted that WHO has provided guidance on antibiotic stewardship and limiting the use of antibiotics to instances when they are likely to have clinical benefit.	

8.2.2.2 Justification

The GDG inferred that for severe influenza virus infection, the minimally important difference or threshold for a reduction in mortality for adjunctive therapies would be a reduction in mortality of 0.3% and a reduction in the duration of hospitalization by 1 day.

The GDG inferred that most patients would decline an intervention when there is high uncertainty of any benefit as the evidence demonstrated with macrolide antibiotics as adjunctive therapy. If the GDG inferences regarding patient values and preferences are accurate, a majority of fully informed patients would not choose macrolides for adjunctive therapy for severe influenza virus infection. A conditional recommendation against the use of macrolides was made due to the uncertainty that macrolides may increase or reduce hospital length of stay, ICU admission or mortality.

The conditional recommendation reflects the very low certainty of the evidence and acknowledgment that values and preferences will differ among patients, and that some may choose to receive treatment when the possibility of important benefit remains.

8.2.2.3 Summary

A systematic review of RCTs was specifically commissioned for this GDG [19].

Table 8.7 Summary of findings for macrolides vs. standard care in patients with suspected or confirmed severe influenza virus infection

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care	Macrolides		
Mortality	Relative risk (CI 95% not calculable) Based on data from 50 participants in 1 study	30 per 1000	per 1000	Very low	There were too few who experienced mortality, to determine whether macrolides made a difference
		Difference: fewer per 1000			
Mortality (zoonotic)	Relative risk (CI 95% not calculable) Based on data from 50 participants in 1 study	387 per 1000	per 1000	Very low	There were too few who experienced mortality, to determine whether macrolides made a difference
		Difference: fewer per 1000			
Adverse events	Relative risk: 1.13 (CI 95% 0.52 - 2.44) Based on data from 50 participants in 1 study	320 per 1000	362 per 1000	Very low Due to extremely serious imprecision ¹	We are uncertain whether macrolides increases or decreases adverse events
		Difference: 42 more per 1000 (CI 95% 154 fewer - 461 more)			
Length of stay in hospital	Measured by: Days Scale: - high better Based on data from 50 participants in 1 study	4.8 Median	4.5 Median	Very low Due to extremely serious imprecision ²	We are uncertain whether macrolides increase or decrease length of stay in hospital
		Difference: MD 0.3 lower (CI 95% 1.4 lower - 0.8 higher)			

1. *Imprecision: extremely serious. Wide confidence intervals, Low number of patients, Only data from one study;*
2. *Imprecision: extremely serious. Wide confidence intervals, Low number of patients, Only data from one study.*

References [57]

8.2.3 mTOR inhibitors

Conditional recommendation against

In patients with suspected or confirmed severe influenza virus infection, we **suggest not administering mTOR inhibitors** (conditional recommendation, very low-quality evidence).

8.2.3.1 Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives
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In patients with severe influenza virus infection due to seasonal influenza, it is very uncertain whether treatment with mammalian target of rapamycin (mTOR) inhibitors reduces mortality or adverse events including ventilator-associated pneumonia.

Certainty of the evidence	Very low
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The certainty of evidence based on one small study with 38 patients was rated as very low for mortality and for adverse events such as ventilator-associated pneumonia. No data available for other outcomes.

Values and preferences	No substantial variability expected
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Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that a majority of well-informed patients with severe influenza virus infection would choose not to use an mTOR inhibitor for adjunctive immunomodulatory therapy.

Resources and other considerations	Important issues, or potential issues not investigated
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Acceptability and feasibility

mTOR inhibitors are oral medications used for treatment of cancer, autoimmune diseases and to prevent rejection of kidney transplants, and may not be widely available in many jurisdictions or hospitals.

8.2.3.2 Justification

The GDG inferred that for severe influenza virus infection, the MID or threshold for a reduction in mortality for adjunctive therapies would be a reduction in mortality of 0.3% and a reduction in the duration of hospitalization by 1 day.

The GDG inferred that most patients would decline an intervention when there is high uncertainty of any benefit as the evidence demonstrated with mTOR inhibitors as adjunctive therapy.

If GDG inferences regarding patient values and preferences are accurate, a majority of fully informed patients would not choose mTOR inhibitors for adjunctive immunomodulatory therapy of severe influenza virus infection. A conditional recommendation against the use of mTOR inhibitors was made due to the very low certainty evidence that mTOR inhibitors increase or reduce mortality or adverse events such as ventilator-associated pneumonia.

8.2.3.3 Summary

A systematic review of RCTs was specifically commissioned for this GDG [19].

Table 8.8 Summary of findings for mTOR inhibitors vs. standard care in patients with suspected or confirmed severe influenza virus infection

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care	mTOR inhibitors		
Mortality	Relative risk: 0.38 (CI 95% 0.12 - 1.2) Based on data from 38 participants in 1 study	421 per 1000	160 per 1000	Very low Due to extremely serious imprecision ¹	We are uncertain whether mtor inhibitors increase or decrease mortality
		Difference: 261 fewer per 1000 (CI 95% 370 fewer - 84 more)			
Adverse events (ventilator associated pneumonia)	Relative risk: 0.5 (CI 95% 0.15 - 1.71) Based on data from 38 participants in 1 study	316 per 1000	158 per 1000	Very low Due to extremely serious imprecision ²	We are uncertain whether mtor inhibitors increase or decrease adverse events (ventilator associated pneumonia)
		Difference: 158 fewer per 1000 (CI 95% 269 fewer - 224 more)			

1. *Imprecision: extremely serious. Wide confidence intervals, Low number of patients, Only data from one study;*
2. *Imprecision: extremely serious. Low number of patients, Wide confidence intervals, Only data from one study.*

References [58]

8.2.4 NSAIDs

Conditional recommendation against

In patients with suspected or confirmed severe influenza virus infection, we **suggest not administering NSAIDs** (conditional recommendation, very low-quality evidence).

- The GDG noted that NSAIDs could be used for symptomatic management (i.e., fever, pain control) in patients with influenza virus infection though caution should be exercised in patients with severe influenza, as other complications may preclude their use.

8.2.4.1 Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives
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In patients with severe influenza virus infection, it is very uncertain whether treatment with NSAIDS reduces duration of hospitalization, admission to ICU or mortality. There was no direct evidence available on the impact of NSAIDs on adverse events.

Certainty of the evidence	Very low
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Certainty of evidence based on one study with 120 participants was rated as very low for duration of hospitalization, ICU admission and mortality.

Values and preferences	No substantial variability expected
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Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that a majority of well-informed patients with severe influenza virus infection would choose not to use a NSAID for adjunctive immunomodulatory therapy.

The recommendation against administration reflects a high value on avoiding treatment when there is high uncertainty or any benefit. The conditional recommendation reflects the very low certainty of the evidence and acknowledgment that values and preferences will differ among patients, and that

some may choose to receive treatment when the possibility of important benefit remains.

Resources and other considerations	No important issues with the recommended alternative
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Acceptability and feasibility

NSAIDs are widely available and used worldwide for anti-pyretic and anti-inflammatory effects. NSAIDs are available for oral and intravenous administration.

8.2.4.2 Justification

The GDG inferred that for severe influenza virus infection, the minimally important difference or threshold for a reduction in mortality for adjunctive therapies would be a reduction in mortality of 0.3% and a reduction in the duration of hospitalization by 1 day.

The estimated effect of NSAIDs for adjunctive immunomodulatory therapy on mortality and hospital length of stay for patients with severe influenza virus infection was judged to be of very low certainty.

The GDG inferred that most patients would decline an intervention when there is high uncertainty of any benefit as the evidence demonstrated with NSAIDs as adjunctive therapy. If the GDG inferences regarding patient values and preferences are accurate, a majority of fully informed patients would not choose NSAIDS for adjunctive therapy for severe influenza virus infection. A conditional recommendation against the use of NSAIDS was made due to the uncertainty that NSAIDs may increase or reduce hospital length of stay, ICU admission or mortality.

The conditional recommendation reflects the very low certainty of the evidence and acknowledgment that values and preferences will differ among patients, and that some may choose to receive treatment when the possibility of important benefit remains.

8.2.4.3 Summary

A systematic review of RCTs was specifically commissioned for this GDG [19].

Table 8.9 Summary of findings for NSAID vs. standard care in patients with suspected or confirmed severe influenza virus infection

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Standard care	NSAID		
Mortality	Relative risk: 0.44 (CI 95% 0.19 - 0.99) Based on data from 120 participants in 1 study	30 per 1000	13 per 1000	Very low Due to very serious imprecision, serious risk of bias ¹	We are uncertain whether NSAIDs increase or decrease mortality
		Difference: 17 fewer per 1000 (CI 95% 24 fewer - 0 fewer)			
Mortality (zoonotic)	Relative risk: 0.44 (CI 95% 0.19 - 0.99) Based on data from 120 participants in 1 study	387 per 1000	170 per 1000	Very low Due to very serious imprecision, serious risk of bias ²	We are uncertain whether NSAIDs increase or decrease mortality
		Difference: 217 fewer per 1000 (CI 95% 313 fewer - 4 fewer)			
Admission to ICU	Relative risk: 0.92 (CI 95% 0.46 - 1.86) Based on data from 120 participants in 1 study	217 per 1000	200 per 1000	Very low Due to serious risk of bias, very serious imprecision ³	We are uncertain whether NSAIDs increase or decrease admission to ICU
		Difference: 17 fewer per 1000 (CI 95% 117 fewer - 187 more)			
Length of stay in hospital	Measured by: Days Scale: - high better Based on data from 120 participants in 1 study	9.5 Mean	9.3 Mean	Very low Due to serious risk of bias. Due to very serious imprecision. ⁴	We are uncertain whether NSAIDs increase or decrease length of stay in hospital
		Difference: MD 0.2 lower (CI 95% 1.5 lower - 1.1 higher)			

1. Risk of bias: serious. due to trial data being unpublished and not available on a public repository such as clinicaltrials.gov; Imprecision: very serious. Low number of patients, Only data from one study, Wide confidence intervals;
2. Risk of bias: serious. due to trial data being unpublished and not available on a public repository such as clinicaltrials.gov; Imprecision: very serious. Low number of patients, Only data from one study, Wide confidence intervals, Only data from one study, Only data from one study, Only data from one study;
3. Risk of bias: serious. Imprecision: very serious.
4. Risk of bias: serious. Imprecision: very serious.

References [59]

8.2.5 Passive immune therapy

Conditional recommendation against

In patients with suspected or confirmed severe influenza virus infection, we **suggest not administering passive immune therapy** (conditional recommendation, very low-quality to moderate quality evidence).

8.2.5.1 Evidence to decision

Benefits and harms

In patients with severe influenza virus infection, passive immune therapy for adjunctive immunomodulatory therapy probably has little or no effect on duration of hospitalization, serious adverse events and mortality. Whether passive immune therapy reduces ICU admission is very uncertain.

Certainty of the evidence

The evidence summary was informed by five studies with 619 patients for mortality and three studies with 259 patients for hospital length of stay. Certainty of evidence was rated as moderate for serious adverse events, low for length of hospital stay and very low for ICU admission. Certainty of evidence was rated as low for mortality due to seasonal influenza and very low for mortality due to zoonotic influenza.

Values and preferences

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that a majority of well-informed patients with severe influenza virus infection due to seasonal or zoonotic influenza would choose not to use passive immune therapy for adjunctive immunomodulatory therapy.

Resources and other considerations

Acceptability and feasibility

Passive immune therapy is administered through intravenous infusion. Passive immune therapy is not a standardized product and may differ between jurisdictions and it may also not be available in all hospital settings. Use of passive immune therapy may divert resources from use of other beneficial treatments.

8.2.5.2 Justification

The GDG inferred that for severe influenza virus infection, the threshold for use of passive immune therapy for adjunctive immunomodulatory therapy would be a reduction in mortality of 0.3%.

The GDG inferred that for severe influenza virus infection, the threshold for use of passive immune therapy for adjunctive immunomodulatory therapy would be a reduction in the duration of hospitalization by 1 day. For seasonal influenza, the estimated effect of passive immune therapy for adjunctive immunomodulatory therapy on hospital length of stay was a reduction of 2.2 days and the evidence was judged to be low certainty.

If GDG inferences regarding patient values and preferences are accurate, a majority of fully informed patients would not choose passive immune therapy as adjunctive immunomodulatory therapy for severe influenza virus infection. A conditional recommendation against use of passive immune therapy was made due to the low certainty evidence that passive immune therapy may have an impact on shortening hospitalization and probably has little or no impact on mortality in seasonal influenza but its effect on ICU admission and mortality in novel influenza A are uncertain. The high resource utilization for uncertain or any possible benefit led to this conditional recommendation against.

8.2.5.3 Summary

A systematic review of RCTs was specifically commissioned for this GDG [19].

Table 8.10 Summary of findings for passive immunotherapy vs. no passive immunotherapy in patients with suspected or confirmed severe influenza virus infection

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		No passive immune therapy	Passive immune therapy		
Mortality	Relative risk: 0.91 (CI 95% 0.48 - 1.72) Based on data from 619 participants in 5 studies	30 per 1000	27 per 1000	Low Due to very serious imprecision ¹	Passive immune therapy may have little or no difference on mortality
		Difference: 3 fewer per 1000 (CI 95% 16 fewer - 22 more)			
Mortality (zoonotic)	Relative risk: 0.91 (CI 95% 0.48 - 1.72) Based on data from 619 participants in 5 studies	300 per 1000	273 per 1000	Very low Due to extremely serious imprecision ²	Passive immune therapy on mortality is uncertain.
		Difference: 27 fewer per 1000 (CI 95% 156 fewer - 216 more)			
Admission to ICU	Relative risk: 3.77 (CI 95% 0.2 - 70.4) Based on data from 78 participants in 1 study	0 per 1000	59 per 1000	Very low Due to extremely serious imprecision ³	We are uncertain whether passive immune therapy increases or decreases admission to ICU
		Difference: 59 more per 1000 (CI 95% 30 fewer - 140 more)			
Serious adverse events	Relative risk: 0.82 (CI 95% 0.55 - 1.23) Based on data from 604 participants in 4 studies	233 per 1000	191 per 1000	Moderate Due to serious imprecision ⁴	Passive immune therapy probably has little or no difference on serious adverse events
		Difference: 42 fewer per 1000 (CI 95% 105 fewer - 54 more)			
Length of stay in hospital	Measured by: Days Scale: - high better Based on data from 259 participants in 3 studies	5.5 Median	3.3 Median	Low Due to very serious imprecision ⁵	Passive immune therapy may shorten length of stay in hospital
		Difference: MD 2.2 lower (CI 95% 6.2 lower - 1.9 higher)			

1. Inconsistency: no serious. Point estimates vary widely; Imprecision: very serious. Wide confidence intervals, Low number of patients;
2. Inconsistency: no serious. Point estimates vary widely; Imprecision: very serious. Wide confidence intervals, Low number of patients;
3. Imprecision: extremely serious. Wide confidence intervals, Low number of patients, Only data from one study;
4. Imprecision: serious. Wide confidence intervals;
5. Imprecision: serious. Low number of patients.

References [60-64]

9. Antivirals for preventing influenza among persons with exposure to influenza virus but without infection

9.1 Persons exposed to seasonal influenza viruses

9.1.1 Baloxavir in persons exposed to seasonal influenza

Conditional recommendation for

For asymptomatic persons, who are at extremely high risk of severe illness if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 2 days, we **suggest administering baloxavir** (conditional recommendation, moderate quality evidence).

- Antiviral post-exposure prophylaxis does not replace influenza vaccination.
- Extremely high-risk patients are considered those patients over 85 years old with or without risk factors for severe disease or younger patients with multiple risk factors.

9.1.1.1 Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives
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For asymptomatic persons, regardless of risk of severe disease if they develop influenza and who are exposed to **seasonal influenza viruses** in the preceding 48 hours, baloxavir treatment probably reduces the risk of developing laboratory-confirmed symptomatic influenza by about 5% and has little or no impact on mortality. There is no information from the available evidence on whether baloxavir leads to a reduction in hospitalization. Baloxavir probably does not increase adverse events.

Certainty of the evidence	Moderate
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The certainty of evidence was rated as moderate for prevention of laboratory-confirmed symptomatic influenza, mortality and severe adverse events.

Values and preferences	No substantial variability expected
Applying the agreed upon values and preferences (see <i>Section 11.2</i>), the GDG inferred that the majority of extremely high-risk well-informed patients exposed to seasonal influenza virus infection in the previous 48 hours would choose to use baloxavir.	
The panel considered that most patients who are at extremely high risk of developing severe disease if they develop influenza would consider a 5% absolute reduction (8% to 3%) in the probability of developing symptomatic influenza important. This is despite the fact that any reduction in the likelihood of developing severe influenza would be very small.	
Resources and other considerations	Important issues, or potential issues not investigated
Baloxavir for prevention of influenza virus infection is a single oral dose, which provides an advantage for compliance compared with antivirals with longer duration of administration. Baloxavir has limited availability worldwide.	
Baloxavir is unlikely to be available for all individuals who, given the option, would choose to receive the medicine. This reinforces that the use of baloxavir should, in many or perhaps most settings, be reserved for those at extremely high risk for severe disease if they were to develop influenza after exposure.	
<i>Access to treatment</i>	
Due to cost and availability, barriers to access in LMICs may prove formidable. Those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing and treatments, and thus less access to the interventions. If advantaged patients in these settings receive the intervention, this may exacerbate health inequity. It is important that countries integrate the influenza prevention clinical care pathway in the parts of the health system that provide care for patients with extremely high-risk patients (i.e., primary care, nursing homes).	
The recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention. Individual countries may	

formulate their guidelines considering available resources and prioritize therapeutic options accordingly.

9.1.1.2 Justification

The GDG inferred that the threshold for the use of baloxavir for the prevention of laboratory-confirmed symptomatic influenza infection in persons who are at extremely high risk of severe illness would be a 5% absolute reduction. That is, typical patients, at extremely high risk of severe disease if they develop influenza, would consider an effect over 5% as important and under 5% unimportant. This is despite the fact that this 5% reduction would result in only extremely small reductions in the incidence of severe infection.

The absolute effect estimate was 44 per 1000 (4.4%) with a 95% CI between 1.6% and 6.0%. Thus, the point estimate is at the border of importance and the CI includes both important and unimportant effects. There is moderate certainty evidence that baloxavir has little or no effect on adverse events.

The GDG also took into consideration that baloxavir is not widely available. These considerations, and the very low reduction in severe infections, are reasons for the conditional recommendation.

9.1.1.2.1 Applicability

Pregnant and postpartum women exposed to seasonal influenza virus infection might consider using medication that reduces the risk of disease progression if they were at extremely high risk for developing severe disease. However, baloxavir was not formally tested in pregnancy, and concerns regarding undesirable effects in both the pregnant individual and fetus immediately arise. Thus the GDG concluded baloxavir should not be given to pregnant or postpartum women until more evidence on safety is available. In this use case, other alternatives for this subpopulation are available, such as neuraminidase inhibitors.

Adolescents were enrolled in some of the trials; prophylactic baloxavir could be considered in this population. Note, younger children and infants were not enrolled in baloxavir trials. In this use case other alternatives for this subpopulation are available, such as neuraminidase inhibitors for younger children at extremely high risk for disease progression.

9.1.1.3 Practical info

9.1.1.3.1 Route, dosage and duration

Baloxavir is given orally as a **single dose**, based on body weight, see Table 9.1.

Table 9.1 Dosing of baloxavir by weight

Body weight	Dose of baloxavir
< 20 kg	2 mg/kg (as suspension)
20 kg to 79 kg	40 mg (tablet)
80 kg and over	80 mg (tablet)

Prophylaxis should be administered as early as possible, and within 2 days of symptom onset.

Children: Baloxavir marboxil has been studied in treatment trials clinically in patients > 5 years of age with adverse events similar to those reported in adults [27]. However, limited data are available for patients ≤ 5 years of age [28]. The pharmacokinetics of baloxavir in paediatric patients below 1 year of age have not been established [25].

9.1.1.3.2 Other considerations

Pregnancy: Due to lack of safety and efficacy data for treatment of pregnant and postpartum women, baloxavir is currently not recommended for use in pregnant people [26].

Immunocompromised patients: Baloxavir may increase the risk of antiviral resistance emerging, and its use in immunocompromised patients is therefore cautioned.

9.1.1.4 Summary

The NMA for baloxavir was informed by one RCT, which enrolled 749 participants exposed to seasonal influenza. The trial assessed antivirals for post-exposure prophylaxis against seasonal or pandemic influenza. Study characteristics, risk of bias ratings, and effect estimates by outcome for baloxavir used here have been published [65].

For participants exposed to seasonal influenza, the GRADE Summary of Findings table shows the relative and absolute effects of baloxavir compared with placebo for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Six pre-specified subgroup analyses were requested by the GDG:

- Influenza virus type: pandemic influenza versus seasonal influenza versus zoonotic influenza;
- Age: young children (< 2 years) versus children (2-12 years) versus older adults (≥ 65 years);
- Exposure status: unprotected vs. protected exposure (wearing versus no masks);
- Exposure to the source of infection: exposure to human vs. animal source;
- Vaccination status: vaccinated versus unvaccinated;
- Patients at increased risk of severe disease vs. not
 - Women who are pregnant or up to 2 weeks postpartum;
 - Obesity (BMI > 40);
 - Patients with underlying health conditions – including chronic respiratory, cardiovascular disease
 - Patients who are immunosuppressed.

Sufficient data were unavailable to inform any of the pre-specified subgroup analyses.

Table 9.2 Summary of findings for baloxavir vs. placebo in asymptomatic persons, who are at extremely high risk of severe illness and are exposed to seasonal influenza viruses

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo	Baloxavir		
Lab-confirmed symptomatic influenza	Relative risk: 0.43 (CI 95% 0.23 - 0.79) Based on data from 749 participants in 1 study	78 per 1000	34 per 1000	Moderate Due to serious imprecision ¹	Baloxavir probably reduce lab-confirmed symptomatic influenza
Admission to hospital	no RCT data (CI 95% not calculable)				Baloxavir has little or no effect on admission to hospital due to the baseline risk being lower than the minimal important difference.

Mortality	Risk difference (CI 95% not calculable) Based on data from 749 participants in 1 study	Difference: 0.0 fewer (CI 95% 5.0 fewer - 5.0 more)	Moderate Due to serious imprecision ²	Baloxavir probably has little or no effect on the risk of mortality
Adverse events related to drugs	Relative risk: 1.17 (CI 95% 0.4 - 3.45) Based on data from 749 participants in 1 study	36 per 1000	42 per 1000	Low Due to serious risk of bias, serious imprecision ³
		Difference: 6 more per 1000 (CI 95% 22 fewer - 88 more)		Baloxavir may have little or no difference on the incidence of adverse events related to drugs
Serious adverse events	Risk difference (CI 95% not calculable) Based on data from 749 participants in 1 study	Difference: 3.0 fewer (CI 95% 10.0 fewer - 5.0 more)	Moderate Due to serious risk of bias ⁴	Baloxavir probably not increase the risk of serious adverse events.

1. *Imprecision: serious.*
2. *Imprecision: serious. Wide confidence intervals;*
3. *Risk of bias: serious. Imprecision: serious. Wide confidence intervals;*
4. *Risk of bias: serious.*

References [66]

Baloxavir in persons not at extremely high risk of severe illness exposed to seasonal influenza

Conditional recommendation against

For asymptomatic persons, who are NOT at extremely high risk of severe illness if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 2 days, we **suggest not administering baloxavir** (conditional recommendation, moderate quality evidence).

9.1.1.5 Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives
For asymptomatic persons, regardless of risk of severe disease if they develop influenza and who are exposed to seasonal influenza viruses in the prior 48 hours, baloxavir treatment probably reduces the risk of developing laboratory-confirmed symptomatic influenza by about 5% and has little or no impact on mortality. There is no information from the available evidence on whether baloxavir leads to a reduction in hospitalization. Baloxavir probably does not increase adverse events.	
Certainty of the evidence	Moderate
The certainty of evidence was rated as moderate for prevention of laboratory-confirmed symptomatic influenza, mortality and severe adverse events.	
Values and preferences	No substantial variability expected
Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed patients who are exposed to seasonal influenza virus in the previous 48 hours and not at extremely high risk of developing severe disease would choose not to use baloxavir.	
As any consequent reduction in the occurrence of serious influenza would be extremely small, the panel considered that most patients not at extremely high risk of severe disease if they develop influenza infection would consider a 5% absolute reduction (8% to 3%) in incidence of influenza unimportant.	

Resources and other considerations	Important issues, or potential issues not investigated
Baloxavir treatment for prevention of influenza virus infection is a single oral dose, which provides an advantage for compliance compared with antivirals with longer duration of treatment. Baloxavir has limited availability worldwide.	
Baloxavir is unlikely to be available for all individuals who, given the option, would choose to receive the medicine. This reinforces that the use of baloxavir should, in many or perhaps most settings, be reserved for those at extremely high risk for severe disease if they were to develop influenza after exposure.	
If advantaged and not at extremely high-risk persons receive the intervention, this may exacerbate health inequity.	

9.1.1.6 Justification

The GDG inferred that the threshold for use of baloxavir for the prevention of laboratory-confirmed symptomatic influenza infection in patients not at extremely high risk would be a 5% absolute reduction. However, the panel considered that most patients not at extremely high risk of severe disease if they developed influenza would consider a 5% absolute reduction (8% to 3%) in incidence of influenza unimportant as any consequent reduction in the occurrence of serious influenza would be extremely small. Consistent with this inference, we have moderate certainty evidence that baloxavir does not reduce the risk of death to a degree that typical patients would consider important. This is the reason for the recommendation against using the medication in this group of patients.

However, the GDG were cognizant that patients not at extremely high risk are very unlikely to have complications from influenza. That is the reason for the suggestion against using the medication in this group of patients.

However, particularly considering that we have moderate certainty evidence that baloxavir has little or no effect on adverse events, there may be some patients who consider an extremely small reduction in serious influenza important. That is the reason for the conditional recommendation.

9.1.1.7 Summary

The NMA for baloxavir was informed by one RCT, which enrolled 749 participants exposed to seasonal influenza. The trial assessed antivirals for post-exposure

prophylaxis against seasonal or pandemic influenza. Study characteristics, risk of bias ratings, and effect estimates by outcome for baloxavir used here have been published [65].

For participants exposed to seasonal influenza, the GRADE Summary of Findings table shows the relative and absolute effects of baloxavir compared with placebo for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Six pre-specified subgroup analyses were requested by the GDG:

- Influenza virus type: pandemic influenza versus seasonal influenza versus zoonotic influenza;
- Age: young children (< 2 years) versus children (2-12 years) versus older adults (≥ 65 years);
- Exposure status: unprotected vs. protected exposure (wearing versus no masks);
- Exposure to the source of infection: exposure to human vs. animal source;
- Vaccination status: vaccinated versus unvaccinated;
- Patients at increased risk of severe disease vs. not
 - Women who are pregnant or up to 2 weeks postpartum;
 - Obesity (BMI > 40);
 - Patients with underlying health conditions – including chronic respiratory, cardiovascular disease
 - Patients who are immunosuppressed.

Sufficient data were unavailable to inform any of the pre-specified subgroup analyses.

Table 9.3 Summary of findings for baloxavir vs. placebo in asymptomatic persons, who are NOT at extremely high risk of severe illness and are exposed to seasonal influenza viruses

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo	Baloxavir		
Lab-confirmed symptomatic influenza	Relative risk: 0.43 (CI 95% 0.23 - 0.79) Based on data from 749 participants in 1 study	78 per 1000	34 per 1000	Moderate Due to serious imprecision ¹	Baloxavir probably reduce lab-confirmed symptomatic influenza
		Difference: 44 fewer per 1000 (CI 95% 60 fewer - 16 fewer)			
Admission to hospital	no RCT data (CI 95% not calculable)				Baloxavir has little or no effect on admission to hospital due to the baseline risk being lower than the minimal important difference.
Mortality	Risk difference (CI 95% not calculable) Based on data from 749 participants in 1 study	Difference: 0.0 fewer (CI 95% 5.0 fewer - 5.0 more)		Moderate Due to serious imprecision ²	Baloxavir probably has little or no effect on the risk of mortality
Adverse events related to drugs	Relative risk: 1.17 (CI 95% 0.4 - 3.45) Based on data from 749 participants in 1 study	36 per 1000	42 per 1000	Low Due to serious risk of bias, serious imprecision ³	Baloxavir may have little or no difference on the incidence of adverse events related to drugs
		Difference: 6 more per 1000 (CI 95% 22 fewer - 88 more)			
Serious adverse events	Risk difference (CI 95% not calculable) Based on data from 749 participants in 1 study	Difference: 3.0 fewer (CI 95% 10.0 fewer - 5.0 more)		Moderate Due to serious risk of bias ⁴	Baloxavir probably not increase the risk of serious adverse events.

1. *Imprecision: serious.*

2. *Imprecision: serious. Wide confidence intervals;*

3. *Risk of bias: serious. Imprecision: serious. Wide confidence intervals;*

4. *Risk of bias: serious.*

References [66]

9.1.2 Laninamivir in persons exposed to seasonal influenza

Conditional recommendation for

For asymptomatic persons, who are at extremely high risk of severe illness if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 2 days, we **suggest administering laninamivir** (conditional recommendation, moderate quality evidence).

- Antiviral post-exposure prophylaxis does not replace influenza vaccination.
- Extremely high-risk patients are considered those patients over 85 years old with or without risk factors for severe disease or younger patients with multiple risk factors.

9.1.2.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

For asymptomatic persons, regardless of risk of severe disease if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 48 hours, laninamivir treatment probably reduces the risk of developing laboratory-confirmed symptomatic influenza by about 5%. The magnitude of risk reduction in the incidence of severe disease with laninamivir is, however, very small as laninamivir probably has little or no impact on mortality. There is no information from the available evidence on whether laninamivir leads to a reduction in hospitalization.

Laninamivir may have little or no effect on risk of serious adverse events.

Certainty of the evidence

Moderate

The certainty of evidence was rated as moderate for prevention of laboratory-confirmed symptomatic influenza. The certainty of evidence that laninamivir did not prevent mortality was assessed as moderate. There were no data available on whether laninamivir prevented hospital admission.

The certainty of evidence on severe adverse events was rated low.

Values and preferences	No substantial variability expected
<p>Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed extremely high-risk patients, exposed to seasonal influenza viruses in the previous 48 hours would choose to use laninamivir.</p>	
<p>The panel considered that most patients at high risk of severe disease if they develop influenza would consider a 5% absolute reduction (from 8% to 3%) in the probability of developing symptomatic influenza important. This is the case despite the likely very small reduction in the occurrence of severe influenza.</p>	
Resources and other considerations	Important issues, or potential issues not investigated
<p>Laninamivir is delivered by inhalation for 2 days.</p>	
<p><i>Access to treatment</i></p>	<p>Laninamivir is not widely available. Due to cost and availability, barriers to access in LMICs may prove formidable. Those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing and treatments, and thus less access to the interventions. If advantaged patients in these settings receive the intervention, this may exacerbate health inequity. It is important that countries integrate the influenza prevention clinical care pathway in the parts of the health system that provide care for patients with extremely high-risk patients (i.e., primary care, nursing homes).</p>
<p>The recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention. Individual countries may formulate their guidelines considering available resources and prioritize therapeutic options accordingly.</p>	

9.1.2.2 Justification

The GDG inferred that the threshold for use of laninamivir for the prevention of laboratory-confirmed symptomatic influenza infection in persons who are at extremely high risk of severe illness would be a 5% absolute reduction. That is, typical patients, at extremely high risk of severe disease if they develop influenza, would consider an effect over 5% as important and under 5% unimportant. This is despite

the fact that this 5% reduction would result in only extremely small reductions in the incidence of severe infection.

The absolute effect estimate was 44 per 1000 (4.4%) with a 95% CI between 2.9% and 5.5%. Thus, the point estimate is at the border of importance and the 95% CI includes both important and unimportant effects. There is moderate certainty evidence that laninamivir has little or no effect on adverse events.

The GDG also took into consideration that laninamivir is not widely available and is delivered via inhalation. These considerations, and the very low reduction in severe infections, are reasons for the conditional recommendation.

9.1.2.3 Practical info

Laninamivir has limited geographical availability. Clinicians should check with their national regulatory agency regarding the approved patient age groups and recommended treatment dose.

9.1.2.3.1 Route, dosage and duration

Laninamivir is given inhaled dry powder as a **single dose**, based on body weight, as below.

Table 9.4 Dosing of laninamivir for post-exposure prophylaxis of seasonal influenza

Age group	Dose of laninamivir for post-exposure prophylaxis of seasonal influenza
Adults	20 mg once daily for 2 days
Children < 10 years	20 mg single dose
Children ≥ 10 years up to 18 years	20 mg once daily for 2 days

Treatment should be administered as early as possible, and within 2 days of symptom onset.

9.1.2.3.2 Other considerations

Pregnancy: There are insufficient data available on use in pregnancy to inform a risk assessment for use.

Lactation: There are insufficient data available on use in pregnancy to inform a risk assessment for use.

The available application for pharmaceutical licensing by the Pharmaceuticals and Medical Devices Agency of Japan contains additional detail on animal studies and pharmacokinetics, adverse events, and drug interactions[31].

9.1.2.4 Summary

The NMA for laninamivir was informed by three RCTs, which enrolled 2593 participants exposed to seasonal influenza (studies provided direct comparisons for any outcomes of interest). All trials assessed antivirals for post-exposure prophylaxis against seasonal or pandemic influenza. Study characteristics, risk of bias ratings, and effect estimates by outcome for laninamivir used here have been published [65, 67].

For participants exposed to seasonal influenza, the GRADE Summary of Findings table shows the relative and absolute effects of laninamivir compared with placebo for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Six pre-specified subgroup analyses were requested by the GDG:

- Influenza virus type: pandemic influenza versus seasonal influenza versus zoonotic influenza;
- Age: young children (< 2 years) versus children (2-12 years) versus older adults (≥ 65 years);
- Exposure status: unprotected vs. protected exposure (wearing versus no masks);
- Exposure to the source of infection: exposure to human vs. animal source;
- Vaccination status: vaccinated versus unvaccinated;
- Patients at increased risk of severe disease vs. not
 - Women who are pregnant or up to 2 weeks post-partum;
 - Obesity (BMI > 40);
 - Patients with underlying health conditions – including chronic respiratory, cardiovascular disease
 - Patients who are immunosuppressed.

Sufficient data were unavailable to inform any of the pre-specified subgroup analyses.

Table 9.5 Summary of findings for laninamivir vs. placebo in asymptomatic persons, who are at extremely high risk of severe illness and are exposed to seasonal influenza viruses

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo	Laninamivir		
Lab-confirmed symptomatic influenza	Relative risk: 0.43 (CI 95% 0.3 - 0.63) Based on data from 2593 participants in 3 studies	78 per 1000	34 per 1000	Moderate Due to serious imprecision ¹	Laninamivir probably reduces lab-confirmed symptomatic influenza
		Difference: 44 fewer per 1000 (CI 95% 55 fewer - 29 fewer)			
Admission to hospital	No RCT data (CI 95% not calculable)				Laninamivir has little or no effect on admission to hospital due to the baseline risk being lower than the minimal important difference.
Mortality	Risk difference: 0.0 (CI 95% -0.01 - 0.01) Based on data from 341 participants in 1 study	Difference: 0.0 fewer per 1000 (CI 95% 11.0 fewer - 11.0 more)		Moderate Due to serious imprecision ²	Laninamivir probably has little or no impact on mortality.
Adverse events related to drugs	Relative risk: 1.4 (CI 95% 0.84 - 2.35) Based on data from 2806 participants in 3 studies	36 per 1000	50 per 1000	Moderate Due to serious imprecision ³	Laninamivir probably increases the incidence of adverse events related to drugs
Serious adverse events	Risk difference (CI 95% not calculable) Based on data from 341 participants in 1 study	Difference: 0 fewer per 1000 (CI 95% 11 fewer - 11 more)		Low Due to serious risk of bias, serious imprecision ⁴	Laninamivir may have little or no effect on the risk of serious adverse events

1. *Imprecision: serious.*

2. *Imprecision: serious.*

3. *Imprecision: serious. Wide confidence intervals;*

4. *Risk of bias: serious. Inadequate/ lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: serious.*

References [68-70]

Laninamivir in persons not at extremely high risk of severe illness exposed to seasonal influenza

Conditional recommendation against

For asymptomatic persons, who are NOT at extremely high risk of severe illness if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 2 days, we **suggest not administering laninamivir** (conditional recommendation, moderate quality evidence).

- Antiviral post-exposure prophylaxis does not replace influenza vaccination.
- Extremely high-risk patients are considered those patients over 85 years old with or without risk factors for severe disease or younger patients with multiple risk factors.

9.1.2.5 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

For asymptomatic persons, who are not at extremely high risk of severe disease if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 48 hours, laninamivir treatment probably reduces the risk of developing laboratory-confirmed symptomatic influenza by approximately 5%. There is no evidence that laninamivir will reduce mortality. There are no data available on the prevention hospitalization with the use of laninamivir. Laninamivir may have little or no effect on serious adverse events.

Certainty of the evidence

Moderate

Certainty of evidence was rated as moderate for prevention of laboratory-confirmed symptomatic influenza and for prevention of mortality, and low for severe adverse events.

Values and preferences

No substantial variability expected

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed patients who are exposed to seasonal

influenza virus in the previous 48 hours and not at extremely high risk of developing severe disease would choose not to use laninamivir.

As any consequent reduction in the occurrence of serious influenza would be extremely small, the panel considered that most patients not at extremely high risk of severe disease if they develop influenza infection would consider a 5% absolute reduction (8% to 3%) in incidence of influenza unimportant.

Resources and other considerations

Important issues, or potential issues not investigated

Laninamivir is administered by inhalation daily for 2 days.

Laninamivir is not widely available.

9.1.2.6 Justification

The GDG inferred that the threshold for use of laninamivir for the prevention of laboratory-confirmed symptomatic influenza infection in patients **at extremely high risk** would be a 5% absolute reduction. However, the panel considered that most patients not at extremely high risk of severe disease if they developed influenza would consider a 5% absolute reduction (8% to 3%) in incidence of influenza unimportant as any consequent reduction in the occurrence of serious influenza would be extremely small. Consistent with this inference, we have moderate certainty evidence that laninamivir does not reduce the risk of death to a degree that typical patients would consider important. That is the reason for the suggestion against using the medication in this group of patients.

However, particularly considering that we have moderate certainty evidence that laninamivir has little or no effect on adverse events, there may be some patients who consider an extremely small reduction in serious influenza important. That is the reason for the conditional recommendation.

9.1.2.7 Summary

The NMA for laninamivir was informed by three RCTs, which enrolled 2593 participants exposed to seasonal influenza (studies provided direct comparisons for any outcomes of interest). All trials assessed antivirals for post-exposure prophylaxis against seasonal or pandemic influenza. Study characteristics, risk of bias ratings, and effect estimates by outcome for laninamivir used here have been published [65].

For participants exposed to seasonal influenza, the GRADE Summary of Findings table shows the relative and absolute effects of Iaininamivir compared with placebo for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Six pre-specified subgroup analyses were requested by the GDG:

- Influenza virus type: pandemic influenza versus seasonal influenza versus zoonotic influenza;
- Age: young children (< 2 years) versus children (2-12 years) versus older adults (≥ 65 years);
- Exposure status: unprotected vs. protected exposure (wearing versus no masks);
- Exposure to the source of infection: exposure to human vs. animal source;
- Vaccination status: vaccinated versus unvaccinated;
- Patients at increased risk of severe disease vs. not
 - Women who are pregnant or up to 2 weeks postpartum;
 - Obesity (BMI > 40);
 - Patients with underlying health conditions – including chronic respiratory, cardiovascular disease
 - Patients who are immunosuppressed.

Sufficient data were unavailable to inform any of the pre-specified subgroup analyses.

Table 9.6 Summary of findings for laninamivir vs. placebo in asymptomatic persons, who are NOT at extremely high risk of severe illness and exposed to seasonal influenza viruses

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo	Laninamivir		
Lab-confirmed symptomatic influenza	Relative risk: 0.43 (CI 95% 0.3 - 0.63) Based on data from 2593 participants in 3 studies	78 per 1000	34 per 1000	Moderate Due to serious imprecision ¹	Laninamivir probably reduces lab-confirmed symptomatic influenza
		Difference: 44 fewer per 1000 (CI 95% 55 fewer - 29 fewer)			
Admission to hospital	No RCT data (CI 95% not calculable)				Laninamivir has little or no effect on admission to hospital due to the baseline risk being lower than the minimal important difference.
Mortality	Risk difference: 0.0 (CI 95% -0.01 - 0.01) Based on data from 341 participants in 1 study	Difference: 0.0 fewer per 1000 (CI 95% 11.0 fewer - 11.0 more)		Moderate Due to serious imprecision ²	Laninamivir probably has little or no impact on mortality.
Adverse events related to drugs	Relative risk: 1.4 (CI 95% 0.84 - 2.35) Based on data from 2806 participants in 3 studies	36 per 1000	50 per 1000	Moderate Due to serious imprecision ³	Laninamivir probably increases the incidence of adverse events related to drugs
Serious adverse events	Risk difference (CI 95% not calculable) Based on data from 341 participants in 1 study	Difference: 0 fewer per 1000 (CI 95% 11 fewer - 11 more)		Low Due to serious risk of bias, serious imprecision ⁴	Laninamivir may have little or no effect on the risk of serious adverse events

1. *Imprecision: serious.*

2. *Imprecision: serious.*

3. *Imprecision: serious. Wide confidence intervals;*

4. *Risk of bias: serious. Inadequate/ lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: serious.*

References [68-70]

9.1.3 Oseltamivir for persons exposed to seasonal influenza

Conditional recommendation for

For asymptomatic persons, who are at **extremely high risk** of severe illness if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 2 days, we **suggest administering oseltamivir** (conditional recommendation, moderate quality evidence).

- Antiviral post-exposure prophylaxis does not replace influenza vaccination.
- Extremely high-risk patients are considered those patients over 85 years old with or without risk factors for severe disease (see Sections 5.1 and 5.2) or younger patients with multiple risk factors.

9.1.3.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

For asymptomatic persons, regardless of their risk of severe disease if they develop influenza and those who are exposed to **seasonal influenza viruses** in the prior 48 hours, oseltamivir treatment probably reduces the risk of developing laboratory-confirmed symptomatic influenza by about 5%. The magnitude of risk reduction in the incidence of severe disease with oseltamivir is, however, very small; the evidence provided no demonstrable reduction in either hospitalization or mortality. Oseltamivir probably little or no effect on the risk of adverse events.

Certainty of the evidence

High

The certainty of evidence was rated as high for prevention of laboratory-confirmed symptomatic influenza, prevention of hospital admission and mortality. The certainty was assessed as moderate for serious adverse events.

Values and preferences

No substantial variability expected

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed extremely high-risk patients, exposed to seasonal influenza viruses in the previous 48 hours would choose to use oseltamivir.

Resources and other considerations

No important issues with the recommended alternative

Acceptability and feasibility

The usual course of oseltamivir for the prevention of seasonal influenza in adults and adolescents is 75 mg given orally once daily for 10 days, and in many of the clinical trials assessed for this recommendation this was the dose administered.

Such a long course may be difficult for some patients to complete.

Access to treatment

Oseltamivir is widely available, primarily in generic formulations, and has a low probability of causing adverse drug reactions. Nevertheless, availability and other barriers to access in LMICs may prove formidable. Those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing and treatments, and thus less access to the interventions. If advantaged patients in these settings receive the intervention, this may exacerbate health inequity. It is important that countries integrate the clinical care pathway in the parts of the health system that provide care for patients with extremely high-risk patients (i.e., primary care, nursing homes).

The recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention. Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly.

9.1.3.2 Justification

The panel considered that most patients at extremely high risk of severe disease if they developed influenza would consider a 5% absolute reduction (from 8% to 3%) in the probability of developing symptomatic influenza important. This is the case despite the likely very small reduction in the occurrence of severe influenza. The GDG inferred that a typical patient, **at extremely high risk of** severe disease if they developed influenza, would consider an effect over 5% as important and under 5% unimportant.

The absolute effect estimate was 47 per 1000 (4.7%) with a 95% CI between 3% and 5.8%. Thus, the point estimate is at the border of importance and the CI includes both

important and unimportant effects. This, along with no demonstrable effect on mortality or hospitalization and the fact that oseltamivir is widely available, primarily in generic formulations, and has a low probability of causing adverse drug reactions, is the reason for the conditional recommendation.

9.1.3.2.1 Applicability

Use in **extremely high-risk persons** exposed to seasonal influenza can be considered in planning health services in settings where high-risk persons may get exposed, such as nursing homes or in primary care services caring for patients above the age of 85 years and/ or persons with multiple chronic conditions.

9.1.3.3 Practical info

9.1.3.3.1 Route, dosage and duration – post-exposure prophylaxis of seasonal influenza

Oseltamivir is given orally as at a dose based on age and body weight, as below. It is available as capsules of 30 mg, 45 mg and 75 mg, and as oral powder for reconstitution.

Table 9.7 Dosing of oseltamivir for post-exposure prophylaxis of seasonal influenza

Age	Body weight	Dose of oseltamivir for post-exposure prophylaxis of seasonal influenza
Adults and those 13 years and over	> 40 kg	75 mg once daily for 10 days
Children from 1 year up to 13 years	10 kg to 15 kg	30 mg once daily for 10 days
	> 15 kg to 23 kg	45 mg once daily for 10 days
	> 23 kg to 40 kg	60 mg once daily for 10 days
	> 40 kg	75 mg once daily for 10 days
Children under 1 year		3 mg/kg once daily for 10 days

Prophylaxis should be administered as early as possible, and within 2 days of exposure.

9.1.3.3.2 Dose adjustment – post-exposure prophylaxis of seasonal influenza

Dose adjustment is recommended for adults and those 13 years and over who have moderate or severe renal impairment, as below:

Table 9.8 Dosing of oseltamivir for post-exposure prophylaxis of seasonal influenza in patients with renal impairment

Creatinine clearance (mL/min)	Dose of oseltamivir for post-exposure prophylaxis of seasonal influenza
> 60	75 mg once daily
> 30 to 60	30 mg once daily
> 10 to 30	30 mg every second day
≤ 10	Not recommended. No data available
Haemodialysis patients	30 mg after every second haemodialysis session
Peritoneal dialysis patients	30 mg once weekly

There are insufficient clinical data available in those under 13 years of age with renal impairment to be able to make any dosing recommendation.

9.1.3.3 Other considerations

Pregnancy: Observational studies of oseltamivir use during pregnancy (more than 1000 exposed outcomes during the first trimester) indicate that it is safe during pregnancy with no malformative nor fetal/ neonatal toxicity. Pregnant women can be offered oseltamivir when the potential benefits of using the drug are more likely than the potential risk of harm to the woman or their baby [34].

Lactation: Limited information is available. The manufacturer advises administration of oseltamivir may be considered where there are clear potential benefits to breastfeeding mothers.

Oseltamivir can be administered enterically by orogastric or nasogastric tube to intubated patients and is well absorbed, but is contraindicated in patients with malabsorption, gastric stasis, ileus or gastrointestinal bleeding.

The manufacturer's summary of product characteristics contains additional details on animal studies and pharmacokinetics, adverse events and drug interactions [37].

9.1.3.4 Summary

The NMA for oseltamivir was informed by six RCTs, which enrolled 3856 participants exposed to seasonal influenza (studies provided direct comparisons for any outcomes of interest). Two RCTs assessed antivirals for post-exposure prophylaxis against seasonal or pandemic influenza (e.g., close contact with patients with laboratory-confirmed influenza or influenza-like illness), four assessed antiviral prophylaxis for populations with an unclear definition of exposure status or pre-exposure prophylaxis

against influenza. Study characteristics, risk of bias ratings, and effect estimates by outcome for oseltamivir used here have been published [65].

For participants exposed to seasonal influenza, the GRADE Summary of Findings table shows the relative and absolute effects of oseltamivir compared with placebo for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Six pre-specified subgroup analyses were requested by the GDG:

- Influenza virus type: pandemic influenza versus seasonal influenza versus zoonotic influenza;
- Age: young children (< 2 years) versus children (2-12 years) versus older adults (≥ 65 years);
- Exposure status: unprotected vs. protected exposure (wearing versus no masks);
- Exposure to the source of infection: exposure to human vs. animal source;
- Vaccination status: vaccinated versus unvaccinated;
- Patients at increased risk of severe disease vs. not
 - Women who are pregnant or up to 2 weeks postpartum;
 - Obesity (BMI > 40);
 - Patients with underlying health conditions – including chronic respiratory, cardiovascular disease
 - Patients who are immunosuppressed.

Sufficient data were unavailable to inform any of the pre-specified subgroup analyses. All studies included seasonal influenza. Studies did not enrol children or report their exposure status, exposure to the source of infection, or vaccination status. Studies did not enrol patients with severe or critical illnesses.

Table 9.9 Summary of findings for oseltamivir vs. placebo in asymptomatic persons, who are at extremely high risk of severe illness and exposed to seasonal influenza viruses

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo	Oseltamivir		
Lab-confirmed	Relative risk: 0.4 (CI 95% 0.26 - 0.62)	78 per 1000	31 per 1000	High	Oseltamivir reduces lab-confirmed

symptom- matic influenza	Based on data from 3742 participants in 5 studies	Difference: 47 fewer per 1000 (CI 95% 58 fewer - 30 fewer)		symptomatic influenza
Admission to hospital	Relative risk: 1.11 (CI 95% 0.66 - 1.86) Based on data from 3434 participants in 4 studies	3 per 1000 Difference: 0 fewer per 1000 (CI 95% 1 fewer - 3 more)	3 per 1000 High 1	Oseltamivir has little or no effect on the risk of admission to hospital.
Mortality	Risk difference: 0.0 (CI 95% 0.0 - 0.0) Based on data from 3515 participants in 5 studies	Difference: 0 fewer per 1000 (CI 95% 2 fewer - 2 more)	High	Oseltamivir has little or no impact on mortality.
Adverse events related to drugs	No RCT data (CI 95% not calculable)			Whether oseltamivir increases adverse events related to drugs is very uncertain.
Serious adverse events²	Risk difference: 0.0 (CI 95% 0.0 - 0.0) Based on data from 3742 participants in 5 studies	Difference: 3.0 more (CI 95% 2.0 fewer - 7.0 more)	Moderate Due to serious imprecision ³	Oseltamivir has little or no effect on the risk of adverse events related to drugs

1. *Imprecision: serious. Wide confidence intervals; 2. Undefined; 3. Imprecision: serious.*

References [71-75]

Oseltamivir for persons at extremely high risk of severe illness exposed to seasonal influenza

Conditional recommendation against

For asymptomatic persons, who are NOT at extremely high risk of severe illness if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 2 days, we **suggest not administering oseltamivir** (conditional recommendation, moderate quality evidence).

- Antiviral post-exposure prophylaxis does not replace vaccination.
- Extremely high-risk patients are considered those patients over 85 years old with or without risk factors for severe disease or younger patients with multiple risk factors.

9.1.3.5 Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives
For asymptomatic persons, regardless of their risk of severe disease, if they develop influenza and those who are exposed to seasonal influenza viruses in the prior 48 hours, oseltamivir probably reduces the risk of developing laboratory-confirmed influenza by approximately 5%. Oseltamivir has little or no effect on the risk of admission to hospital or mortality and likely has little or no increase in serious adverse effects.	
Certainty of the evidence	Moderate
The certainty of evidence was rated as high for prevention of laboratory-confirmed symptomatic influenza, prevention of hospital admission and mortality. The certainty was assessed as moderate for serious adverse events.	
Values and preferences	No substantial variability expected
Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed patients who are not extremely high risk for influenza exposed to seasonal influenza virus infection in the previous 48 hours would choose not to use oseltamivir.	
As any consequent reduction in the occurrence of serious influenza would be extremely small, the panel considered that most patients not at extremely high risk of severe disease if they develop influenza would consider a 5% absolute reduction (8% to 3%) in incidence of influenza unimportant.	
Resources and other considerations	No important issues with the recommended alternative
The usual course of oseltamivir for the prevention of influenza is 75 mg administered orally once daily for 10 days, and in many of the clinical trials assessed for this recommendation this was the dose given to patients.	
Oseltamivir is widely available, primarily in generic formulations, and has a low probability of causing adverse drug reactions.	

9.1.3.6 Justification

The GDG inferred that the threshold for use of oseltamivir for the prevention of laboratory confirmed symptomatic influenza infection in extremely risk patients would be a 5% absolute reduction. On the contrary, the panel considered that most patients not at extremely high risk of severe disease if they developed influenza would consider a 5% absolute reduction (8% to 3%) in incidence of influenza unimportant as any consequent reduction in the occurrence of serious influenza would be extremely small,

Given that it is likely that oseltamivir has little or no effect on adverse events, and that there can be variability in values and preferences and some patients may value even an extremely small reduction in the risk of developing severe influenza. This is the reason for the conditional recommendation.

9.1.3.7 Summary

The NMA for oseltamivir was informed by six RCTs, which enrolled 3856 participants exposed to seasonal influenza (studies provided direct comparisons for any outcomes of interest). Two RCTs assessed antivirals for post-exposure prophylaxis against seasonal or pandemic influenza (e.g., close contact with patients with laboratory-confirmed influenza or influenza-like illness), four assessed antiviral prophylaxis for populations with an unclear definition of exposure status or pre-exposure prophylaxis against influenza. Study characteristics, risk of bias ratings, and effect estimates by outcome for oseltamivir used here have been published [65].

For participants exposed to seasonal influenza, the GRADE Summary of Findings table shows the relative and absolute effects of oseltamivir compared with placebo for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Six pre-specified subgroup analyses were requested by the GDG:

- Influenza virus type: pandemic influenza versus seasonal influenza versus zoonotic influenza;
- Age: young children (< 2 years) versus children (2-12 years) versus older adults (≥ 65 years);
- Exposure status: unprotected vs. protected exposure (wearing versus no masks);
- Exposure to the source of infection: exposure to human vs. animal source;
- Vaccination status: vaccinated versus unvaccinated;
- Patients at increased risk of severe disease vs. not
 - Women who are pregnant or up to 2 weeks postpartum;
 - Obesity (BMI > 40);
 - Patients with underlying health conditions – including chronic respiratory, cardiovascular disease
 - Patients who are immunosuppressed.

Sufficient data were unavailable to inform any of the pre-specified subgroup analyses. All studies included seasonal influenza. Studies did not enrol children or report their exposure status, exposure to the source of infection, or vaccination status. Studies did not enrol patients with severe or critical illnesses.

Table 9.10 Summary of findings for oseltamivir vs. placebo in asymptomatic persons, who are NOT at extremely high risk of severe illness and exposed to seasonal influenza viruses

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo	Oseltamivir		
Lab-confirmed symptomatic influenza	Relative risk: 0.4 (CI 95% 0.26 - 0.62) Based on data from 3742 participants in 5 studies	78 per 1000	31 per 1000	High	Oseltamivir reduces lab-confirmed symptomatic influenza
		Difference: 47 fewer per 1000 (CI 95% 58 fewer - 30 fewer)			
Admission to hospital	Relative risk: 1.11 (CI 95% 0.66 - 1.86) Based on data from 3434 participants in 4 studies	3 per 1000	3 per 1000	High ¹	Oseltamivir has little or no effect on the risk of admission to hospital.
		Difference: 0 fewer per 1000 (CI 95% 1 fewer - 3 more)			
Mortality	Risk difference: 0.0 (CI 95% 0.0 - 0.0) Based on data from 3515 participants in 5 studies	Difference: 0 fewer per 1000 (CI 95% 2 fewer - 2 more)		High	Oseltamivir has little or no impact on mortality.
AE related to drugs	No RCT data (CI 95% not calculable)				Whether oseltamivir increases AE related to drugs is very uncertain.
Serious adverse events	Risk difference: 0.0 (CI 95% 0.0 - 0.0) Based on data from 3742 participants in 5 studies	Difference: 3.0 more (CI 95% 2.0 fewer - 7.0 more)		Moderate Due to serious imprecision	Oseltamivir has little or no effect on the risk of adverse events related to drugs

1. *Imprecision: serious. Wide confidence intervals; References [71-75]*

9.1.4 Zanamivir for persons exposed to seasonal influenza

Conditional recommendation for

For asymptomatic persons, who are at extremely high risk of severe illness if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 2 days, we **suggest administering zanamivir** (conditional recommendation, moderate quality evidence).

- Antiviral post-exposure prophylaxis does not replace influenza vaccination.
- Extremely high-risk patients are considered those patients over 85 years old with or without risk factors for severe disease or younger patients with multiple risk factors.

9.1.4.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

For asymptomatic persons, who are at extremely high risk of severe disease if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 48 hours, zanamivir probably reduces the risk of developing laboratory-confirmed symptomatic influenza by about 5%. The magnitude of risk reduction in the incidence of severe disease with zanamivir is, however, very small as there was no demonstrable reduction in mortality. There is no information from the available evidence on whether zanamivir leads to a reduction in hospitalization.

Zanamivir has little or no effect on adverse events.

Certainty of the evidence

Moderate

Certainty of evidence was rated as moderate for prevention of laboratory-confirmed symptomatic influenza. The certainty of evidence that zanamivir did not prevent mortality was assessed as high; there were no data in the available evidence on whether zanamivir prevented hospital admission.

The evidence was rated as high for severe adverse events.

Values and preferences

No substantial variability expected

Applying the agreed upon values and preferences (Section 11.2), the GDG inferred that the majority of extremely high-risk well-informed patients exposed to seasonal influenza virus infection in the previous 48 hours would choose to use zanamivir.

The GDG inferred that most patients who are at extremely high risk of developing severe disease if they develop influenza would consider a 5% absolute reduction (8% to 3%) in the probability of developing symptomatic influenza important. This is despite the fact that any reduction in the likelihood of developing severe influenza would be very small.

Resources and other considerations

No important issues with the recommended alternative

Zanamivir is administered by inhalation. The dose is 10 mg by inhalation daily for 10 days. This was the dose used in the majority of the clinical trials investigating zanamivir for prevention of influenza.

Zanamivir is not available in all jurisdictions. Availability and other barriers to access in LMICs may prove formidable. Those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing and treatments, and thus less access to the interventions. If advantaged patients in these settings receive the intervention, this may exacerbate health inequity. It is important that countries integrate the clinical care pathway in the parts of the health system that provide care for patients with extremely high-risk patients (i.e., primary care, nursing homes).

9.1.4.2 Justification

The GDG inferred that the threshold for use of zanamivir for the prevention of laboratory-confirmed symptomatic influenza infection in patients at extremely high risk of severe disease would be a 5% absolute reduction. That is, typical patients, at extremely high risk of severe disease if they develop influenza, would consider an effect over 5% as important and under 5% unimportant. This is despite the fact that this 5% reduction would result in only extremely small reductions in the incidence of severe infection. The absolute effect estimate was 51 per 1000 (5.1%) with a 95% CI between 3.9% and 5.8%. The 95% CI thus includes both important and unimportant effects. There is high certainty evidence that zanamivir has little or no effect on serious adverse events.

The GDG also took into consideration that zanamivir is not widely available and is delivered via inhalation. These considerations, and the extremely low reduction in severe infection, are reasons for the conditional recommendation.

9.1.4.3 Practical info

9.1.4.3.1 Route, dosage and duration

Zanamivir is given as a dry powder inhaler. The dose for adults and children over 5 years is 10 mg once daily (that is two 5 mg inhalations) for 10 days.

Prophylaxis should be administered as early as possible, and within 2 days of exposure.

9.1.4.3.2 Other considerations

Pregnancy: Observational studies of zanamivir use during pregnancy (from less than 300 known outcomes) suggest that it is safe during pregnancy. Systemic exposure to zanamivir is low following administration by inhalation. However, there is no information on placental transfer of zanamivir in humans. Pregnant women can and should be offered zanamivir when the potential benefits of using the drug are more likely than the potential risk of harm to the woman or their baby.

Lactation: Systemic exposure to zanamivir is low following administration by inhalation; however, there is no information on secretion of zanamivir into human breastmilk. A risk to the breastfed child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/ abstain from zanamivir therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

9.1.4.4 Summary

The NMA for zanamivir was informed by ten RCTs, which enrolled 8156 participants exposed to seasonal influenza (studies provided direct comparisons for any outcomes of interest). Five RCTs assessed antivirals for post-exposure prophylaxis against seasonal or pandemic influenza, and five assessed antiviral prophylaxis for populations with unclear definitions of exposure status or pre-exposure prophylaxis against influenza. Study characteristics, risk of bias ratings, and effect estimates by outcome for zanamivir used here have been published [65].

For participants exposed to seasonal influenza, the GRADE summary of findings table shows the relative and absolute effects of zanamivir compared with placebo/

standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Six pre-specified subgroup analyses were requested by the GDG:

- Influenza virus type: pandemic influenza versus seasonal influenza versus zoonotic influenza;
- Age: young children (< 2 years) versus children (2-12 years) versus older adults (≥ 65 years);
- Exposure status: unprotected vs. protected exposure (wearing versus no masks);
- Exposure to the source of infection: exposure to human vs. animal source;
- Vaccination status: vaccinated versus unvaccinated;
- Patients at increased risk of severe disease vs. not
 - Women who are pregnant or up to 2 weeks postpartum;
 - Obesity (BMI > 40);
 - Patients with underlying health conditions – including chronic respiratory, cardiovascular disease
 - Patients who are immunosuppressed.

Two within-trial subgroup analyses (age and vaccination status) were conducted to assess the effect of zanamivir for the outcome of lab-confirmed symptomatic influenza. There were no statistically significant subgroup effects found between different age groups and influenza vaccine status on the outcome of lab-confirmed symptomatic influenza (interaction $p > 0.10$). All studies included seasonal influenza. Studies did not report the exposure status or the exposure to the source of infection. Studies did not enrol patients with severe or critical illnesses.

Table 9.11 Summary of findings for zanamivir vs. placebo in asymptomatic persons, who are at extremely high risk of severe illness if they develop influenza and who are exposed to seasonal influenza viruses

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo/ standard of care	Zanamivir		
Lab-confirmed symptomatic influenza	Relative risk: 0.35 (CI 95% 0.25 - 0.5) Based on data from 8104 participants in 9 studies	78 per 1000	27 per 1000	Moderate Due to serious imprecision ¹	Zanamivir probably reduces lab-confirmed symptomatic influenza
Admission to hospital	No RCT data (CI 95% not calculable)				Zanamivir has little or no effect on admission to hospital due to the baseline risk being lower than the minimal important difference.
Mortality²	Risk difference: 0.0 (CI 95% 0.0 - 0.0) Based on data from 4767 participants in 6 studies		Difference: 1 more per 1000 (CI 95% 1 fewer - 2 more)	High	Zanamivir has little or no effect on the incidence of mortality
Adverse events related to drugs	Relative risk: 1.07 (CI 95% 0.83 - 1.38) Based on data from 6814 participants in 8 studies	36 per 1000	39 per 1000	Moderate Due to serious imprecision ³	Zanamivir probably has little or no effect on the risk of adverse events related to drugs.
Serious adverse events	Risk difference: 0.0 (CI 95% 0.0 - 0.0) Based on data from 6708 participants in 8 studies		Difference: 0 fewer per 1000 (CI 95% 3 fewer - 4 more)	High	Zanamivir has little or no effect on the risk of serious adverse events

1. *Imprecision: serious. CI crosses threshold;*

2. *undefined*

3. *Imprecision: serious. Wide confidence intervals;*

References [76-84]

Zanamivir for persons not at extremely high risk of severe illness exposed to seasonal influenza

Conditional recommendation against

For asymptomatic persons, who are NOT at extremely high risk of severe illness if they develop influenza and who are exposed to **seasonal influenza viruses** in the prior 2 days, we **suggest not administering zanamivir** (conditional recommendation, moderate quality evidence).

- Antiviral post-exposure prophylaxis does not replace influenza vaccination.
- Extremely high-risk patients are considered those patients over 85 years old with or without risk factors for severe disease or younger patients with multiple risk factors.

9.1.4.5 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

For asymptomatic persons, regardless of their risk of severe disease if they develop influenza and those who are exposed to **seasonal influenza viruses** in the prior 48 hours, zanamivir treatment probably reduces the risk of developing laboratory-confirmed influenza by approximately 5%. Zanamivir has little or no effect on mortality but there were no data on preventing admission to hospital. Zanamivir has little or no increase in serious adverse effects.

Certainty of the evidence

Moderate

The certainty of evidence was rated as moderate for zanamivir preventing laboratory-confirmed symptomatic influenza. The certainty of evidence for prevention mortality was assessed as high. There were no data in the available evidence on whether zanamivir prevented hospital admission.

The evidence was rated as high for severe adverse events.

Values and preferences

No substantial variability expected

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of low-risk well-informed patients exposed to seasonal influenza virus infection in the previous 48 hours would choose to not use zanamivir.

As any consequent reduction in the occurrence of serious influenza would be extremely small, the panel considered that most patients not at extremely high risk of severe disease if they develop influenza infection would consider a 5% absolute reduction (8% to 3%) in incidence of influenza unimportant.

Resources and other considerations

No important issues with the recommended alternative

Zanamivir is administered by inhalation. The dose is 10 mg by inhalation daily for 10 days. This was the dose used in the majority of the clinical trials investing zanamivir for prevention of influenza.

Zanamivir is not available in all jurisdictions.

9.1.4.6 Justification

The GDG inferred that the threshold for use of zanamivir for the prevention of laboratory-confirmed symptomatic influenza infection in extremely high-risk patients would be a 5% absolute reduction. On the contrary, the panel considered that most patients not at extremely high risk of severe disease if they developed influenza would consider a 5% absolute reduction (8% to 3%) in incidence of influenza unimportant as any consequent reduction in the occurrence of serious influenza would be extremely small. Consistent with this inference, we have high certainty evidence that zanamivir does not reduce the risk of death to a degree that typical patients would consider important. That is the reason for the suggestion against using the zanamivir in this group of patients.

However, considering that we have moderate certainty evidence that zanamivir has little or no effect on adverse events, and that there may be variability in values and preferences, some patients may consider an extremely small reduction in serious influenza important. That is the reason for the conditional recommendation.

9.1.4.7 Summary

The NMA for zanamivir was informed by ten RCTs, which enrolled 8156 participants exposed to seasonal influenza (studies provided direct comparisons for any outcomes

of interest). Five RCTs assessed antivirals for post-exposure prophylaxis against seasonal or pandemic influenza, and five assessed antiviral prophylaxis for populations with unclear definitions of exposure status or pre-exposure prophylaxis against influenza. Study characteristics, risk of bias ratings, and effect estimates by outcome for zanamivir used here have been published [65].

For participants exposed to seasonal influenza, the GRADE summary of findings table shows the relative and absolute effects of zanamivir compared with placebo/standard care for the outcomes of interest, with certainty ratings, informed by the NMA.

Subgroup analysis

Six pre-specified subgroup analyses were requested by the GDG:

- Influenza virus type: pandemic influenza versus seasonal influenza versus zoonotic influenza;
- Age: young children (< 2 years) versus children (2-12 years) versus older adults (≥ 65 years);
- Exposure status: unprotected vs. protected exposure (wearing versus no masks);
- Exposure to the source of infection: exposure to human vs. animal source;
- Vaccination status: vaccinated versus unvaccinated;
- Patients at increased risk of severe disease vs. not
- Women who are pregnant or up to 2 weeks postpartum;
 - Obesity (BMI > 40);
 - Patients with underlying health conditions – including chronic respiratory, cardiovascular disease
 - Patients who are immunosuppressed.

Two within-trial subgroup analyses (age and vaccination status) were conducted to assess the effect of zanamivir for the outcome of lab-confirmed symptomatic influenza. There were no statistically significant subgroup effects found between different age groups and influenza vaccine status on the outcome of lab-confirmed symptomatic influenza (interaction $p > 0.10$). All studies included seasonal influenza. Studies did not report the exposure status or the exposure to the source of infection. Studies did not enrol patients with severe or critical illnesses.

Table 9.12 Summary of findings for zanamivir vs. placebo/ standard of care in asymptomatic persons, who are NOT at extremely high risk of severe illness if they develop influenza and who are exposed to seasonal influenza viruses

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo/standard of care	Zanamivir		
Lab-confirmed symptomatic influenza	Relative risk: 0.35 (CI 95% 0.25 - 0.5) Based on data from 8104 participants in 9 studies	78 per 1000	27 per 1000	Moderate Due to serious imprecision ¹	Zanamivir probably reduces lab-confirmed symptomatic influenza
Admission to hospital (No data from RCT)	No RCT data (CI 95% not calculable)				Zanamivir has little or no effect on admission to hospital due to the baseline risk being lower than the minimal important difference.
Mortality²	Risk difference: 0.0 (CI 95% 0.0 - 0.0) Based on data from 4767 participants in 6 studies	Difference: 1 more per 1000 (CI 95% 1 fewer - 2 more)	High		Zanamivir has little or no effect on the incidence of mortality
Adverse events related to drugs	Relative risk: 1.07 (CI 95% 0.83 - 1.38) Based on data from 6814 participants in 8 studies	36 per 1000	39 per 1000	Moderate Due to serious imprecision ³	Zanamivir probably has little or no effect on the risk of adverse events related to drugs.
Serious adverse events	Risk difference: 0.0 (CI 95% 0.0 - 0.0) Based on data from 6708 participants in 8 studies	Difference: 0 fewer per 1000 (CI 95% 3 fewer - 4 more)	High		Zanamivir has little or no effect on the risk of serious adverse events

1. *Imprecision: serious. CI crosses threshold;*

2. *undefined*

3. *Imprecision: serious. Wide confidence intervals;*

References [76-84]

9.2 Person exposed to zoonotic influenza virus associated with high mortality or unknown risk of severe disease

9.2.1 Baloxavir

Conditional recommendation for

For asymptomatic persons exposed to **zoonotic influenza viruses associated with high mortality in humans or with an unknown risk of causing severe disease** in the prior 2 days, we **suggest administering baloxavir** (conditional recommendation, low-quality evidence).

- Zoonotic influenza A viruses that have been associated with high mortality in humans when they become infected, include HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9).
- It is likely there will be uncertainty with any novel influenza A virus as to the potential clinical consequences or virulence.
- It is likely that there is variable susceptibility of antiviral medications to novel influenza A viruses so *in vitro* and clinical studies will remain necessary.

9.2.1.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Due to the small number of cases and episodic, unpredictable nature of the disease, there are no clinical trials of post-exposure baloxavir prophylaxis of zoonotic influenza. There are data from clinical trials of post-exposure baloxavir prophylaxis of seasonal influenza demonstrating efficacy when baloxavir is initiated within 48 hours of exposure. Therefore, baloxavir may reduce symptomatic laboratory-confirmed influenza and it is very uncertain if baloxavir reduces hospitalization and death.

Due to the episodic and unpredictable nature of these infections, direct RCT data are absent and we are very uncertain about effects on both transmission and patient-important outcomes.

Certainty of the evidence Low

Due to the small number of cases and episodic unpredictable nature of the disease, there are no clinical trials of post-exposure baloxavir prophylaxis of zoonotic influenza A. There are data from clinical trials of post-exposure baloxavir prophylaxis of seasonal influenza demonstrating efficacy when it is initiated within 48 hours of exposure.

Therefore the evidence was assessed as low certainty that baloxavir will prevent symptomatic laboratory-confirmed influenza and very low certainty that it will prevent hospitalization and death. The absolute risk reduction of 15 per 1000 for hospitalization and 3 per 1000 in mortality was modelled using assumptions of a high incidence of severe zoonotic infections in those infected, resulting in an appreciable impact on the outcomes of interest, i.e., admission to hospital and mortality. The assumptions in the model are, however, based on very low certainty evidence.

Values and preferences No substantial variability expected

Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed patients exposed to zoonotic influenza virus infection in the last 48 hours would choose to use baloxavir.

The panel considered that most patients exposed to zoonotic influenza that may have a high risk of death would consider a potential reduction in the risk of mortality important even if the benefit is uncertain given the lack of evidence in the area.

Resources and other considerations Important issues, or potential issues not investigated

Feasibility and acceptability

Baloxavir for prevention of influenza virus infection is a single oral dose, which provides an advantage for compliance compared with antivirals with longer duration of administration.

Baloxavir has limited availability worldwide.

Implementation of this recommendation will depend on clinicians and health and care settings, including occupational health settings, that may care for persons at risk for exposure (i.e., poultry or wild bird farms and markets) having in place clear protocols for use to ensure early access to this medicine.

9.2.1.2 Justification

The GDG were cognizant of the potential for high mortality with zoonotic influenza A virus infections (i.e., HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9)) and that well-informed patients would favour taking a treatment to prevent infection in this scenario, even if the evidence for the treatment is lacking.

Novel influenza viruses also introduce uncertainty regarding the effectiveness of antiviral medications, and this was also taken into account by the GDG. Due to the episodic and unpredictable nature of these infections, RCT data are limited.

Stemming from the potential high mortality of these infections, the evidence of antiviral prophylaxis against seasonal influenza viruses and that probably there is little or no effect on risk of adverse events related to baloxavir, the GDG recommend the use of baloxavir despite low certainty of evidence for zoonotic influenza A. The conditional recommendation is based on the very low certainty of evidence available.

9.2.1.2.1 Applicability

Pregnant and postpartum women exposed to zoonotic influenza A virus infection might consider using medication that reduces the risk of disease progression. However, baloxavir was not formally tested in pregnancy, and concerns regarding undesirable effects in both pregnant individuals and fetuses immediately arise. Thus the GDG concluded baloxavir should not be given to pregnant or postpartum women until more evidence on safety is available. In this use case, other alternatives for this subpopulation are available, such as NAIs.

Adolescents were enrolled in some of the trials, and thus those exposed to zoonotic influenza A virus infection could consider prophylactic treatment with baloxavir. Note, younger children and infants were not enrolled in baloxavir trials. In this case, other alternatives for this subpopulation are available such as NAIs.

9.2.1.3 Practical info

9.2.1.3.1 Route, dosage and duration

Baloxavir is given orally as a **single dose**, based on body weight, see *Table 9.13*. This dose is used for seasonal influenza; there are no specific data on dosing for zoonotic influenza.

Table 9.13 Dosing of baloxavir for pro-exposure prophylaxis of zoonotic influenza

Body weight	Dose of baloxavir
< 20 kg	2 mg/kg (as suspension)
20 kg to 79 kg	40 mg (tablet)
80 kg and over	80 mg (tablet)

Prophylaxis should be administered as early as possible, and within 2 days of exposure.

Children: Baloxavir marboxil has been studied in treatment trials in patients > 5 years of age with adverse events similar to those reported in adults [27]. However, limited data are available for patients ≤ 5 years of age [28]. The pharmacokinetics of baloxavir in paediatric patients below 1 year of age have not been established [25].

9.2.1.3.2 Other considerations

Pregnancy: Due to lack of safety and efficacy data for treatment of pregnant and postpartum women, baloxavir is currently not recommended for use in pregnant people [26].

Immunocompromised patients: Baloxavir may increase the risk of antiviral resistance emerging, and its use in immunocompromised patients is therefore cautioned.

9.2.1.4 Summary

No RCTs were identified for antiviral post-exposure prophylaxis of persons exposed to symptomatic persons or to infected animals with novel influenza A viruses (zoonotic influenza). The NMA considered indirect evidence from trials of antiviral post-exposure prophylaxis for seasonal influenza. The panel infers that when using antivirals for post-exposure prophylaxis against zoonotic influenza, the adverse events are similar to those when using antivirals for post-exposure prophylaxis against seasonal influenza. The systematic review used here has been published [65].

For participants exposed to zoonotic influenza, the GRADE Summary of Findings table shows the relative and absolute effects of baloxavir compared with placebo for the outcomes of interest, with certainty ratings informed by the NMA.

Table 9.14 Summary of findings for baloxavir vs. placebo in asymptomatic persons exposed to zoonotic influenza viruses associated with high mortality in humans or with an unknown risk of causing severe disease

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo	Baloxavir		
Lab-confirmed symptomatic influenza	Relative risk: 0.43 (CI 95% 0.23 - 0.79) Based on data from 749 participants in 1 study	30 per 1000	13 per 1000	Low Due to very serious indirectness ¹	Baloxavir may reduce lab-confirmed symptomatic influenza
		Difference: 17 fewer per 1000 (CI 95% 23 fewer - 6 fewer)			
Admission to hospital (model)	(CI 95% not calculable)	24 per 1000	10 per 1000	Very low Due to very serious indirectness, serious imprecision ²	Whether baloxavir reduces admission to hospital is very uncertain.
		Difference: 14 fewer per 1000 (CI 95% 18 fewer - 5 fewer)			
Mortality (model)	(CI 95% not calculable)	5 per 1000	2 per 1000	Very low Due to serious imprecision, very serious indirectness ³	Whether baloxavir reduces mortality is very uncertain.
		Difference: 3 fewer per 1000 (CI 95% 4 fewer - 1 fewer)			
Adverse events related to drugs	Relative risk: 1.17 (CI 95% 0.4 - 3.45) Based on data from 749 participants in 1 study	36 per 1000	42 per 1000	Low Due to serious risk of bias, serious imprecision ⁴	Baloxavir may have little or no difference on the incidence of adverse events related to drugs
		Difference: 6 more per 1000 (CI 95% 22 fewer - 88 more)			
Serious adverse events	Risk difference (CI 95% not calculable) Based on data from 749 participants in 1 study	Difference: 3.0 fewer (CI 95% 10.0 fewer - 5.0 more)		Moderate Due to serious risk of bias ⁵	Baloxavir probably not increase the risk of serious adverse events.

1. Indirectness: very serious.

2. Indirectness: very serious. Imprecision: serious.

3. Indirectness: very serious. Imprecision: serious. Wide confidence intervals;

4. Risk of bias: serious. Imprecision: serious. Wide confidence intervals;

5. Risk of bias: serious.

Reference [66]

9.2.2 Laninamivir

Conditional recommendation for

For asymptomatic persons exposed to **zoonotic influenza viruses associated with high mortality in humans or with an unknown risk of causing severe disease** in the prior 2 days, **we suggest administering laninamivir** (conditional recommendation, low-quality evidence).

- Avian influenza A viruses that have been associated with high mortality in humans when they become infected, include HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9).
- It is likely there will be uncertainty with any novel influenza virus as to the potential clinical consequences or virulence.
- It is likely that there is variable susceptibility of antiviral medications to novel influenza A viruses so *in vitro* and clinical studies will remain necessary.

9.2.2.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Due to the small number of cases and episodic, unpredictable nature of the disease, there are no clinical trials of post-exposure laninamivir prophylaxis of zoonotic influenza A. There are data from clinical trials of post-exposure laninamivir prophylaxis of seasonal influenza demonstrating efficacy when laninamivir is initiated within 48 hours of exposure. Therefore, laninamivir may reduce symptomatic laboratory-confirmed influenza and it is very uncertain if laninamivir reduces hospitalization and death.

Due to the episodic and unpredictable nature of these infections, direct RCT data are absent and we are very uncertain about effects on both transmission and patient-important outcomes.

Certainty of the evidence

Low

Due to the small number of cases and episodic unpredictable nature of the disease, there are no clinical trials of post-exposure laninamivir prophylaxis of zoonotic

influenza. There are data from clinical trials of post-exposure laninamivir prophylaxis of seasonal influenza demonstrating efficacy when it is initiated within 48 hours of exposure.

Therefore the evidence was assessed of low certainty that laninamivir will prevent symptomatic laboratory-confirmed influenza and very low certainty that it will prevent hospitalization and death. The absolute risk reduction of 15 per 1000 for hospitalization and 3 per 1000 in mortality was modelled using assumptions of a high incidence of severe zoonotic infections in those infected, resulting in an appreciable impact on the outcomes of interest, i.e., admission to hospital and mortality. The assumptions in the model are, however, based on very low certainty evidence.

Values and preferences	No substantial variability expected
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Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed patients exposed to zoonotic influenza A virus infection in the last 48 hours would choose to use laninamivir.

The panel considered that most patients exposed to zoonotic influenza A associated with high mortality would consider a potential reduction in the risk of mortality important even if the benefit is uncertain given the lack of evidence in the area.

Resources and other considerations	Important issues, or potential issues not investigated
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The usual course of laninamivir is delivered by inhalation daily for 2 days.

Laninamivir is not widely available.

Implementation of this recommendation will depend on clinicians and health care settings that may care for persons at risk for exposure (i.e., poultry or wild bird farms and markets) having in place clear protocols for use to ensure early access to this medicine.

9.2.2.2 Justification

The GDG were cognisant of the potential for high mortality with zoonotic influenza A virus infections (i.e., HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9))

and that well-informed patients would favour taking a treatment to prevent the infection in this scenario, even if the evidence for the treatment is lacking.

Novel influenza viruses also introduce uncertainty of the effectiveness of antiviral medications, and this was also taken into account by the GDG. Due to the episodic and unpredictable nature of these infections, RCT data are limited. Stemming from the potential high mortality of such infections, the evidence of antiviral prophylaxis against seasonal influenza viruses and that probably there is little or no effect on risk of adverse events related to laninamivir, the GDG recommend the use of laninamivir despite low certainty of evidence for zoonotic influenza. The conditional recommendation is based on the very low certainty evidence available.

9.2.2.3 Practical info

Laninamivir has limited geographical availability. Clinicians should check with their national regulatory agency regarding the approved patient age groups and recommended treatment dose.

9.2.2.3.1 Route, dosage and duration

Laninamivir is given inhaled dry powder as a **single dose**, based on body weight, see *Table 9.15*.

Table 9.15 Dosing of laninamivir for post-exposure prophylaxis of zoonotic influenza

Age group	Dose of laninamivir for post-exposure prophylaxis
Adults	20 mg once daily for 2 days
Children < 10 years	20 mg single dose
Children ≥ 10 years up to 18 years	20 mg once daily for 2 days

Prophylaxis should be administered as early as possible, and within 2 days of exposure.

9.2.2.3.2 Other considerations

Pregnancy: There are insufficient data available on use in pregnancy to inform a risk assessment for use.

Lactation: There are insufficient data available on use in pregnancy to inform a risk assessment for use.

The available application for pharmaceutical licensing by the Pharmaceuticals and Medical Devices Agency of Japan contains additional details on animal studies and pharmacokinetics, adverse events and drug interactions [31].

9.2.2.4 Summary

No RCTs were identified for antiviral post-exposure prophylaxis of persons exposed to symptomatic persons or to infected animals with novel influenza A viruses (zoonotic influenza). The NMA considered indirect evidence from trials of antiviral post-exposure prophylaxis for seasonal influenza. The panel infers that when using antivirals for post-exposure prophylaxis against zoonotic influenza, the adverse events are similar to those when using antivirals for post-exposure prophylaxis against seasonal influenza. The systematic review used here has been published [65].

For participants exposed to zoonotic influenza, the GRADE Summary of Findings table shows the relative and absolute effects of laninamivir compared with placebo for the outcomes of interest, with certainty ratings, informed by the NMA.

Table 9.16 Summary of findings for laninamivir vs. placebo in asymptomatic persons exposed to zoonotic influenza viruses associated with high mortality in humans or with an unknown risk of causing severe disease

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo	Laninamivir		
Lab-confirmed symptomatic influenza	Relative risk: 0.43 (CI 95% 0.3 - 0.63) Based on data from 2593 participants in 3 studies	30 per 1000	13 per 1000	Low Due to very serious indirectness ¹	Laninamivir may reduce lab-confirmed symptomatic influenza
Admission to hospital (model)	(CI 95% not calculable)	24 per 1000	10 per 1000	Very low Due to very serious indirectness, serious imprecision ²	Whether laninamivir reduces admission to hospital is very uncertain.
Mortality (model)	(CI 95% not calculable)	5 per 1000	2 per 1000	Very low Due to serious imprecision, very serious indirectness. ³	Whether laninamivir reduces mortality is very uncertain.

Adverse events related to drugs	Relative risk: 1.4 (CI 95% 0.84 - 2.35) Based on data from 2806 participants in 3 studies	36 per 1000	50 per 1000	Moderate Due to serious imprecision ⁴	Laninamivir probably increases the incidence of adverse events related to drugs
Serious adverse events	Risk difference (CI 95% not calculable) Based on data from 341 participants in 1 study	Difference: 0 fewer per 1000 (CI 95% 11 fewer - 11 more)	Low Due to serious risk of bias, serious imprecision ⁵	Laninamivir may have little or no effect on the risk of serious adverse events	

1. *Indirectness: very serious.*
2. *Indirectness: very serious. Imprecision: serious.*
3. *Indirectness: very serious. Imprecision: serious.*
4. *Imprecision: serious. Wide confidence intervals;*
5. *Risk of bias: serious. Inadequate/ lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: serious.*

References [68-70]

9.2.3 Oseltamivir

Conditional recommendation for

For asymptomatic persons exposed to **zoonotic influenza viruses associated with high mortality in humans or with an unknown risk of causing severe disease** in the prior 2 days, we **suggest administering oseltamivir** (conditional recommendation, low-quality evidence).

- Avian influenza A viruses that have been associated with high mortality in humans when they become infected, include HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9).
- It is likely there will be uncertainty with any novel influenza virus as to the potential clinical consequences or virulence.
- It is likely that there is variable susceptibility of antiviral medications to novel influenza A viruses so in vitro and clinical studies will remain necessary.

9.2.3.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Zoonotic influenza A viruses that have caused disease in humans have a heterogenous, wide spectrum of clinical manifestations. However, there are a few that have been associated with high mortality in humans when they become infected, such as HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9) and a novel zoonotic influenza virus may emerge in the future that may also cause severe disease in humans.

Oseltamivir may reduce laboratory-confirmed symptomatic influenza virus infection. Whether oseltamivir reduces hospitalization and mortality is uncertain.

Oseltamivir has little or no effect on severe adverse events.

Certainty of the evidence

Very low

Due to the small number of cases and episodic, unpredictable nature of the disease, there are no clinical trials of post-exposure oseltamivir prophylaxis of zoonotic influenza. There are data from clinical trials of post-exposure oseltamivir

prophylaxis of seasonal influenza demonstrating efficacy when oseltamivir is initiated within 48 hours of exposure.

Therefore the evidence was assessed as low certainty that oseltamivir will prevent symptomatic laboratory-confirmed influenza and very low certainty that it will prevent hospitalization and death. The absolute risk reduction of 15 per 1000 for hospitalization and 3 per 1000 in mortality was modelled using assumptions of a high incidence of severe zoonotic infections in those infected, resulting in an appreciable impact on the outcomes of interest, i.e., admission to hospital and mortality. The assumptions in the model are, however, based on very low certainty evidence.

Values and preferences

No substantial variability
expected

Applying the agreed upon values and preferences (see *Section 11.2*), the GDG inferred that the majority of well-informed patients exposed to zoonotic influenza A virus infection associated with high mortality in humans in the previous 48 hours would choose to use oseltamivir.

The panel considered that most patients exposed to zoonotic influenza virus A that is associated with high mortality in humans would consider a potential reduction in the risk of mortality important even if the benefit is very uncertain.

Resources and other considerations

Important issues, or potential
issues not investigated

Acceptability and feasibility

Oseltamivir is widely available, primarily in generic formulations, and has a low probability of causing adverse drug reactions. Oseltamivir is approved for treatment of influenza virus infection in different age groups and in pregnant and postpartum women.

The relatively long course for prophylaxis in asymptomatic individuals may make it difficult for some patients to complete.

Implementation of this recommendation will depend on clinicians and health and care settings, such as occupational health, that may care for persons at risk for exposure (i.e., poultry or wild bird farms and markets) having in place clear protocols for use to ensure early access to this medicine.

9.2.3.2 Justification

The GDG were cognizant of the potential for high mortality with some zoonotic influenza virus infections (i.e., HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9)) and thus inferred that well-informed patients would favour taking a treatment to prevent the infection even though the evidence for the treatment is indirect and of very low certainty.

Novel influenza viruses also introduce uncertainty regarding the effectiveness of antiviral medications, and this was also taken into account by the GDG. Due to the episodic and unpredictable nature of these infections, RCT data are limited.

Stemming from the potential high mortality of such infections, the evidence of antiviral prophylaxis against seasonal influenza viruses and that probably there is little or no effect on risk of adverse events related to oseltamivir, the GDG recommend the use of oseltamivir despite low certainty of evidence for prevention of zoonotic influenza. The conditional recommendation is based on the very low certainty evidence available.

9.2.3.3 Practical info

9.2.3.3.1 Route, dosage and duration – post-exposure prophylaxis of zoonotic influenza associated with high mortality in humans

Oseltamivir is given orally at a dose based on age and body weight, as below. It is available as capsules of 30 mg, 45 mg and 75 mg, and as oral powder for reconstitution.

For post-exposure prophylaxis after unprotected exposures to novel influenza A viruses associated with high mortality in infected humans the appropriate dose and duration are uncertain. Prophylaxis dose for seasonal influenza is 75mg once daily, but for prophylaxis for novel influenza A virus exposure, treatment doses (75 mg twice daily) have been advocated for 10-14 days. The rationale for this, in the absence of human studies of prophylaxis efficacy in novel influenza A viruses, is supportive animal data [85], and an aim to reduce the likelihood of resistance emerging while receiving once daily chemoprophylaxis.

Table 9.17 Dosing of oseltamivir for post-exposure prophylaxis of zoonotic influenza

Age	Body weight	Dose of oseltamivir for post-exposure prophylaxis for novel influenza A virus exposure
Adults and those 13 years and over	> 40 kg	75 mg twice daily for 10–14 days

Children from 1 year up to 13 years	10 kg to 15 kg > 15 kg to 23 kg > 23 kg to 40 kg > 40 kg	30 mg twice daily for 10–14 days 45 mg twice daily for 10–14 days 60 mg twice daily for 10–14 days 75 mg twice daily for 10–14 days
Children under 1 year	3 mg/kg twice daily for 10–14 days	

Prophylaxis should be administered as early as possible, and within 2 days of exposure.

9.2.3.3.2 Dose adjustment – post-exposure prophylaxis of influenza

Dose adjustment is recommended for adults and those 13 years and over who have moderate or severe renal impairment, see *Table 9.18*.

Table 9.18 Dosing of oseltamivir for post-exposure prophylaxis of zoonotic influenza in patients with renal impairment

Creatinine clearance (mL/min)	Dose of oseltamivir for post-exposure prophylaxis for novel influenza A virus exposure
> 60	75 mg twice daily
> 30 to 60	30 mg twice daily
> 10 to 30	30 mg once daily
≤ 10	Not recommended. No data available
Haemodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients	30 mg single dose

There are insufficient clinical data available in those under 13 years of age with renal impairment to be able to make any dosing recommendation.

9.2.3.3.3 Other considerations

Pregnancy: Observational studies of oseltamivir use during pregnancy (more than 1000 exposed outcomes during the first trimester) indicate that it is safe during pregnancy with no malformative nor fetal/ neonatal toxicity. Pregnant women can be offered oseltamivir when the potential benefits of using the drug are more likely than the potential risk of harm to the woman or their baby [34].

Lactation: Limited information is available. The manufacturer advises administration of oseltamivir may be considered where there are clear potential benefits to breastfeeding mothers.

Oseltamivir can be administered enterically via orogastric or nasogastric tube to intubated patients and is well-absorbed, but is contraindicated in patients with malabsorption, gastric stasis, ileus or gastrointestinal bleeding.

The manufacturer's summary of product characteristics contains additional details on animal studies and pharmacokinetics, adverse events and drug interactions [34].

9.2.3.4 Summary

No RCTs were identified for antiviral post-exposure prophylaxis of persons exposed to symptomatic persons or to infected animals with novel influenza A viruses (zoonotic influenza). The NMA considered indirect evidence from trials of antiviral post-exposure prophylaxis for seasonal influenza. The NMA infer that when using antivirals for post-exposure prophylaxis against zoonotic influenza, the adverse events are similar to those when using antivirals for post-exposure prophylaxis of seasonal influenza. The systematic review used here has been published [65].

For participants exposed to zoonotic influenza, the GRADE Summary of Findings table shows the relative and absolute effects of oseltamivir compared with placebo for the outcomes of interest, with certainty ratings, informed by the NMA.

Table 9.19 Summary of findings for oseltamivir vs. placebo in asymptomatic persons exposed to zoonotic influenza viruses associated with high mortality in humans or with an unknown risk of causing severe disease

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo	Oseltamivir		
Lab-confirmed symptomatic influenza	Relative risk: 0.4 (CI 95% 0.26 - 0.62) Based on data from 3742 participants in 5 studies	30 per 1000	12 per 1000	Low Due to very serious indirectness ¹	Oseltamivir may reduce lab-confirmed symptomatic influenza
		Difference: 18 fewer per 1000 (CI 95% 22 fewer - 11 fewer)			
Admission to hospital (model)	(CI 95% not calculable)	24 per 1000	9 per 1000	Very low Due to very serious indirectness, serious imprecision. ²	Whether oseltamivir reduces admission to hospital is very uncertain.
		Difference: 15 fewer per 1000 (CI 95% 18 fewer - 9 more)			
Mortality (model)	(CI 95% not calculable)	5 per 1000	2 per 1000	Very low	

	Difference: 3 fewer per 1000 (CI 95% 4 fewer - 2 more)	Due to very serious indirectness, serious imprecision ³	Whether oseltamivir reduces mortality is very uncertain.	
Adverse events related to drugs	No RCT data (CI 95% not calculable)		Whether oseltamivir increases adverse events related to drugs is very uncertain.	
Serious adverse events⁴	Risk difference: 0.0 (CI 95% 0.0 - 0.0) Based on data from 3742 participants in 5 studies	Difference: 3.0 more (CI 95% 2.0 fewer - 7.0 more)	Moderate Due to serious imprecision ⁵	Oseltamivir has little or no effect on the risk of serious adverse events

1. *Indirectness: very serious.*
2. *Indirectness: very serious. Imprecision: serious. Wide confidence intervals;*
3. *Indirectness: very serious. Imprecision: serious.*
4. *undefined*
5. *Imprecision: serious.*

References [71-75]

9.2.4 Zanamivir

Conditional recommendation for

For asymptomatic persons exposed to **zoonotic influenza viruses associated with high mortality in humans or with an unknown risk of causing severe disease** in the prior 2 days, we **suggest administering zanamivir** (conditional recommendation, low-quality evidence).

- Avian influenza A viruses that have been associated with high mortality in humans when they become infected include HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9).
- It is likely there will be uncertainty with any novel influenza A virus as to the potential clinical consequences or virulence.
- It is likely that there is variable susceptibility of antiviral medications to novel influenza A viruses so in vitro and clinical studies will remain necessary.

9.2.4.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Due to the small number of cases and episodic, unpredictable nature of the disease, there are no clinical trials of post-exposure zanamivir prophylaxis of zoonotic influenza. There are data from clinical trials of post-exposure zanamivir prophylaxis of seasonal influenza demonstrating efficacy when zanamivir is initiated within 48 hours of exposure. Therefore, zanamivir may reduce symptomatic laboratory-confirmed influenza and it is very uncertain if zanamivir reduces hospitalization and death.

Due to the episodic and unpredictable nature of these infections, direct RCT data are absent and we are very uncertain about effects on both transmission and patient-important outcomes.

Certainty of the evidence

Low

Due to the small number of cases and episodic unpredictable nature of the disease, there are no clinical trials of post-exposure zanamivir prophylaxis of zoonotic

influenza. There are data from clinical trials of post-exposure zanamivir prophylaxis of seasonal influenza demonstrating efficacy when it is initiated within 48 hours of exposure. Therefore, the evidence was assessed of low certainty that zanamivir will prevent symptomatic laboratory-confirmed influenza and very low certainty that it will prevent hospitalization and death.

The absolute risk reduction of 15 per 1000 for hospitalization and 3 per 1000 in mortality was modelled using assumptions of a high incidence of severe zoonotic infections in those infected, resulting in an appreciable impact on the outcomes of interest, i.e., admission to hospital and mortality. The assumptions in the model are, however, based on very low certainty evidence.

Values and preferences

No substantial variability
expected

Applying the agreed upon values and preferences (see *Section 11.2*), the GDG inferred that the majority of high-risk well-informed patients exposed to zoonotic influenza virus infection in the previous 48 hours would choose to use zanamivir.

The panel considered that most patients exposed to zoonotic influenza A that is associated with high mortality would consider a potential reduction in the risk of mortality important even if the benefit is uncertain given the lack of evidence in the area.

Resources and other considerations

Important issues, or potential
issues not investigated

Acceptability and feasibility

Zanamivir is administered by inhalation. This was the mode of administration used in the majority of the clinical trials investigating zanamivir for prevention of seasonal influenza.

Zanamivir is not available in all jurisdictions.

9.2.4.2 Justification

The GDG were cognizant of the potential for high mortality with certain zoonotic influenza virus infections (i.e., HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9)) and thus inferred that well-informed patients would favour taking a

treatment to prevent the infection even though the evidence for the treatment is indirect and of very low certainty.

Novel influenza viruses also introduce uncertainty of the effectiveness of antiviral medications, and this was also taken into account by the GDG. Due to the episodic and unpredictable nature of these infections, RCT data are limited. Stemming from the potential high mortality of such infection, the evidence of antiviral prophylaxis against seasonal influenza viruses and that probably there is little or no effect on risk of adverse events related to zanamivir, the GDG recommend the use of zanamivir despite low certainty of evidence for zoonotic influenza. The conditional recommendation is based on the very low certainty evidence available.

The GDG also noted that zanamivir is not universally available and is administered by inhalation.

9.2.4.3 Practical info

9.2.4.3.1 Route, dosage and duration

Zanamivir is given as a dry powder inhaler. The dose for adults and children over 5 years is 10mg once daily (that is two 5mg inhalations) for 10 days.

Prophylaxis should be administered as early as possible, and within 2 days of exposure.

9.2.4.3.2 Other considerations

Pregnancy: Observational studies of zanamivir use during pregnancy (from less than 300 known outcomes) suggest that it is safe during pregnancy. Systemic exposure to zanamivir is low following administration by inhalation. However, there is no information on placental transfer of zanamivir in humans. Pregnant women can and should be offered zanamivir when the potential benefits of using the drug are more likely than the potential risk of harm to the woman or their baby.

Lactation: Systemic exposure to zanamivir is low following administration by inhalation; however, there is no information on secretion of zanamivir into human breast milk. A risk to the breastfed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/ abstain from zanamivir therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

9.2.4.4 Summary

No RCTs were identified for antiviral post-exposure prophylaxis of persons exposed to symptomatic persons or to infected animals with novel influenza A viruses (zoonotic influenza). The NMA considered indirect evidence from trials of antiviral post-exposure prophylaxis for seasonal influenza. The NMA infer that when using antivirals for post-exposure prophylaxis against zoonotic influenza, the adverse events are similar to those when using antivirals for post-exposure prophylaxis of seasonal influenza. The systematic review used here has been published [65].

For participants exposed to zoonotic influenza, the GRADE Summary of Findings table shows the relative and absolute effects of zanamivir compared with placebo for the outcomes of interest, with certainty ratings, informed by the NMA.

Table 9.20 Summary of findings for zanamivir vs. placebo/ standard of care in asymptomatic persons exposed to zoonotic influenza viruses associated with high mortality in humans or with an unknown risk of causing severe disease

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence	Summary
		Placebo/ standard of care	Zanamivir		
Lab-confirmed symptomatic influenza	Relative risk: 0.35 (CI 95% 0.25 - 0.5) Based on data from 8104 participants in 9 studies	30 per 1000	11 per 1000	Low Due to very serious indirectness ¹	Zanamivir may reduce lab-confirmed symptomatic influenza
Admission to hospital (model)	(CI 95% not calculable)	24 per 1000	9 per 1000	Very low Due to very serious indirectness, serious imprecision ²	Whether zanamivir reduces admission to hospital is very uncertain.
Mortality (model)³	(CI 95% not calculable)	5 per 1000	2 per 1000	Very low Due to very serious indirectness, serious imprecision ⁴	Whether zanamivir reduces mortality is very uncertain.
Adverse events related to drugs	Relative risk: 1.07 (CI 95% 0.83 - 1.38) Based on data from 6814 participants in 8 studies	36 per 1000	39 per 1000	Moderate Due to serious imprecision ⁵	Zanamivir probably has little or no effect on the risk of adverse events related to drugs.
	Risk difference: 0.0 (CI 95% 0.0 - 0.0)	per 1000	per 1000	High	Zanamivir has little or no effect on the risk

Serious adverse events	Based on data from 6708 participants in 8 studies	Difference: 0 fewer per 1000 (CI 95% 3 fewer - 4 more)	of serious adverse events
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1. *Indirectness: very serious.*
2. *Indirectness: very serious. Imprecision: serious.*
3. *undefined*
4. *Indirectness: very serious. Imprecision: serious.*
5. *Imprecision: serious. Wide confidence intervals;*

References [76-84]

10. Recommendations for diagnostic testing strategies in patients with suspected influenza

When a patient with an influenza like illness presents to primary care or to the emergency department (or equivalent acute assessment facility) the recommended influenza testing strategy will depend on the characteristics of the diagnostic test and the expected delay until results will be available. Therefore, to support a decision analysis of influenza testing in clinical settings, a systematic review was performed to identify a meta-analyses of the sensitivity and specificity of various assays that are available to use in clinical settings to detect influenza viral antigens (antigen detection assays) or influenza viral RNA (NAATs, including RT-PCR) in respiratory specimens (online [here](#)) [86].

For non-severe influenza (for patients at high risk for severe influenza) and for patients with severe influenza, a decision analysis was performed for different diagnostic testing strategies and subsequent treatment with the antiviral baloxavir. This analysis then determined the potential reduction in time to alleviation of symptoms and development of adverse events. The QALDs gained were compared across the various treatment strategies.

The following diagnostic testing strategies for diagnosing influenza in persons with suspected influenza presenting to primary care or to emergency departments were evaluated using decision analytic model [86]:

1. No test, and do not treat patients with suspected influenza with an antiviral ("Treat none");
2. No test and treat patients with suspected influenza with an antiviral ("Treat all");
3. Test all patients with suspected influenza with a rapid point-of-care test and treat those with a positive test with an antiviral ("rapid test – treat");
4. Test all patients with suspected influenza with a molecular assay and treat with an antiviral until results become available at 24 hours ("PCR-treat");
5. Test all patients with suspected influenza with a molecular assay, but do not treat with an antiviral until results are available ("PCR-wait").

Outcomes: Modelled QALDs; symptom-free days; adverse events; proportions of patients with and without influenza treated appropriately.

Given no reported hospitalization or mortality benefit associated with treatment (baloxavir or oseltamivir), the results reflected a compromise between the shorter time to symptom alleviation and the risk of adverse events associated with treatment. Considering that all diagnostic tests exhibited high (> 97%) specificity, test sensitivity was the key factor in accurately identifying patients with influenza. Therefore, diagnostic test strategies with higher sensitivity such as "PCR", "NAAT" led to the highest number of individuals appropriately treated for influenza and resulted in the highest number of QALDs.

10.1 Non-severe influenza

10.1.1 Type of influenza testing in non-severe infection

Conditional recommendation for

In patients with suspected non-severe influenza virus infection who are at high risk of progression to severe influenza, we **suggest using point-of-care influenza NAATs (molecular assays) or influenza digital immunoassays** and treating all patients who are positive with a WHO-recommended antiviral agent (conditional recommendation, low-quality evidence).

- The GDG noted the importance of understanding the prevalence in the community and therefore the pre-test probability. With a lower prevalence in the community, testing is likely to be more impactful on implementing appropriate treatment for patients.
- Patients with non-severe influenza but at high risk of progression to severe disease include the following (see *Section 5.1*):
 - Patients 65 years and older;
 - Patients with one or more major risk factors for developing severe influenza.

10.1.1.1 Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives
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Point-of-care influenza NAATs, are molecular assays that detect influenza virus nucleic acids in respiratory specimens. NAATs have high sensitivity and high specificity to detect influenza virus nucleic acids in upper respiratory tract specimens when collected within 3-4 days of symptom onset. Point-of-care influenza DIAs detect influenza virus antigens in respiratory specimens. Influenza DIAs have moderate to moderately high sensitivity and high specificity to detect influenza virus antigens in upper respiratory tract specimens when collected within 3-4 days of symptom onset.

The decision analysis provided low-quality evidence of differences between testing strategies on outcomes of interest but compelling evidence that differences

between strategies in outcomes of interest were likely to be very small. The treatment strategies "DIA", "NAAT" and "PCR-treat" had highest QALDs associated.

Certainty of the evidence

Low

These recommendations are derived from a decision analysis model with input parameters for diagnostic test characteristics, illness epidemiology, treatment effects and utilities, many of which are based on relatively low-quality evidence. The evidence is also limited in terms of directness for low-income countries in that the data predominately come from high-income countries. The GDG also were aware that the analysis did not formally include a cost-benefit analysis.

Values and preferences

No substantial variability expected

The recommendation reflects the panel placing a high value on small reductions in duration of illness and on avoiding unnecessary antiviral treatment. The panel also placed a high value on making expeditious decisions regarding patient management.

Resources and other considerations

Important issues, or potential issues not investigated

Influenza NAATs and other influenza molecular assays may not be available in many clinical settings due to their cost. Influenza DIAs are less expensive than NAATs but require a reader device and again may not be widely available in all resource settings due to cost.

Obstacles to access in LMICs may prove formidable due to cost and availability. Those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing, thus less access to the interventions. Therefore lack of access to investigations and testing could exacerbate inequity, with patients not having access to treatment as their illness, such as influenza, is not diagnosed. The GDG recognized this and encourage jurisdictions to improve access to diagnostic testing for patients at high risk of progression to severe influenza.

In addition, there is now one WHO recommended medicine for non-severe influenza, baloxavir, and it needs to be given within 48 hours of symptom onset. Thus, accurate testing must be linked to treatment care pathways in health care settings. As this recommendation involves ideally administering treatment with baloxavir within 2 days of symptom onset, increasing access and ensuring

appropriate use of diagnostic tests is essential for implementation. Thus, availability and use of appropriate influenza diagnostic tests is needed to improve access to medications, especially in targeting the early phase of disease. Health care systems must, however, gain expertise in choosing and implementing diagnostic tests, and choosing those most applicable to their settings. See Recommendation on diagnostics (see Section 10).

10.1.1.2 Justification

It is important to recognize the influence of community prevalence of influenza viruses on diagnostic testing. When influenza viruses are circulating at high prevalence in a community, most patients with positive NAATs will have influenza but a number with negative results will also have influenza. When influenza viruses are circulating at low prevalence or not circulating among people in a community, most patients with a negative test result will not have influenza but a small number with a positive test will also not have influenza. The same is true of influenza DIAs.

Alternatives to consider, such as conducting PCR testing and waiting to treat or not treat depending on results, will entail considerable feasibility and acceptability limitations. Treating all patients without testing will mean a substantial proportion of individuals will be treated unnecessarily, particularly in low-prevalence situations. The GDG noted that this would lead to inappropriate use of scarce resource (i.e., in this case baloxavir, the WHO recommended treatment), overuse of treatment that may increase the risk of antimicrobial resistance and exposing patients unnecessarily to adverse events. Treating no patients will mean individuals with influenza will experience slightly longer duration of illness, and this will constitute a substantial proportion of the population in high-prevalence situations.

The conditional recommendation reflects low certainty evidence of the relative impact of testing strategies on patient-important outcomes and likely very small difference in such outcomes across strategies. The GDG did note, however, if more effective treatments were available, the impact on QALDs may be affected.

This recommendation is preferred over the alternatives of treating all patients in this scenario or treating no patients or undertaking PCR testing and waiting on the result of the test to determine if antiviral treatment will be recommended.

10.1.1.3 Practical info

Interpretation of tests should take into account the prevalence of influenza viruses circulating in the community (high or low prevalence) as part of the pre-testing probability of disease.

Influenza NAATs and DIAs are most accurate when upper respiratory tract specimens are collected within 3-4 days of symptom onset. Collection of a good quality upper respiratory tract specimen from a patient with suspected influenza is very important. The highest yield for influenza viruses is from testing nasopharyngeal specimens, either nasopharyngeal swab or aspirate specimens. High yield for influenza viruses can also be achieved by testing a combined nasal swab and throat swab specimen (collected separately and placed together in the same sterile specimen container). Proper interpretation of test results, particularly negative results by influenza DIA because of the potential for a false negative result during high influenza prevalence in patients with suspected non-severe influenza who are at high risk for progression to severe influenza, is important.

10.1.1.4 Summary

Assumptions: Older adult patients (i.e., those at high risk of severe influenza sequelae) with non-severe influenza like illness (with a seasonal pre-test probability of influenza of 24.3%), testing positive for influenza would receive treatment with a single dose of baloxavir, and experience a shorter symptom duration (1.02 fewer days) and a 10% higher rate of adverse events relative to untreated individuals. Additionally, no hospitalization or mortality benefits associated with the treatment were considered, based on the WHO systematic review.

The overall preferred strategy in terms of quality adjusted life days (QALDs) was “PCR-wait” followed by “NAAT”, “DIA” (

Table 10.1). Compared to the “Treat none” strategy, “PCR-wait” strategy offered 23 337 symptom-free days per 100 000 population, and was associated with an additional 501 adverse events per 100 000 population. That translated into an overall gain of 4529 QALDs per 100,000 population (

Table 10.1, Figure 10.1). The “Treat all” strategy resulted in outcomes worse than “Treat none”, as it inappropriately treated a large proportion of individuals (

Table 10.1, Figure 10.1) and was associated with the highest number of adverse events. The “PCR-treat” strategy mirrored the result of “Treat all” considering that a

full regimen of baloxavir (a single dose) was administered prior to receiving test results.

Table 10.1 Outcomes for strategies examined for patients with non-severe influenza-like illness.

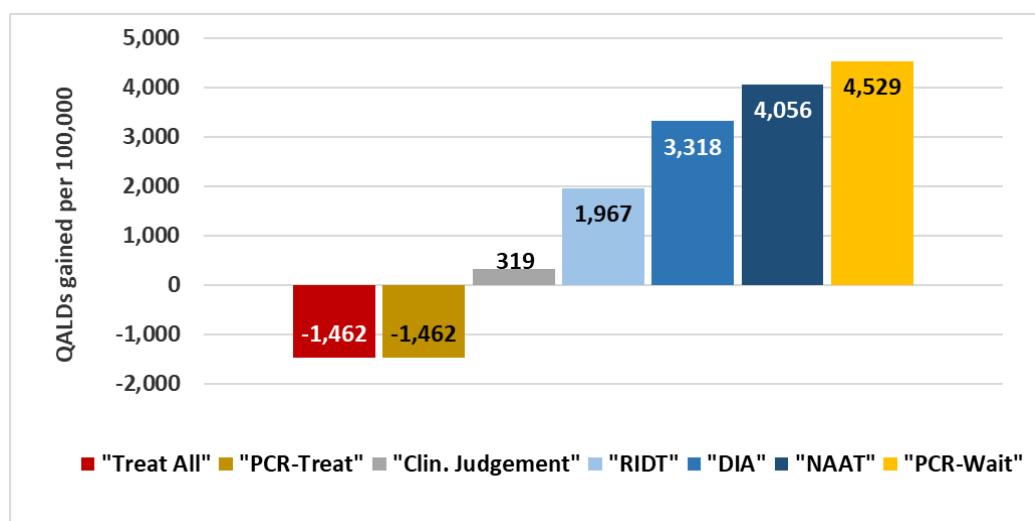
Strategy	Appropriate of treatment (proportion)	Inappropriate (influenza, receives treatment)	Inappropriate (influenza, does not receive treatment)	Inappropriate (no influenza, receives treatment)	Adverse events	Symptom-free days gain	QALD gain/ loss
Treat all	0.242	0.000	0.758	13 376	24 660	-1462	
PCR-treat	0.242	0.000	0.758	13 376	24 660	-1462	
Treat none	0.000	0.242	0.000	2 930	0	0	
Clinical judgement	0.087	0.155	0.167	5 338	8846	319	
RIDT	0.098	0.144	0.003	3089	9958	1967	
DIA	0.172	0.070	0.022	3451	17 565	3318	
NAAT	0.205	0.037	0.014	3374	20 881	4056	
PCT-wait	0.229	0.013	0.016	3431	23 337	4529	

DIA, digital immunoassay tests; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction;

QALDs, quality-adjusted life days; RIDT, rapid influenza diagnostic tests.

Symptom-free days and quality-adjusted days gain were calculated relative to "Treat none" strategy.

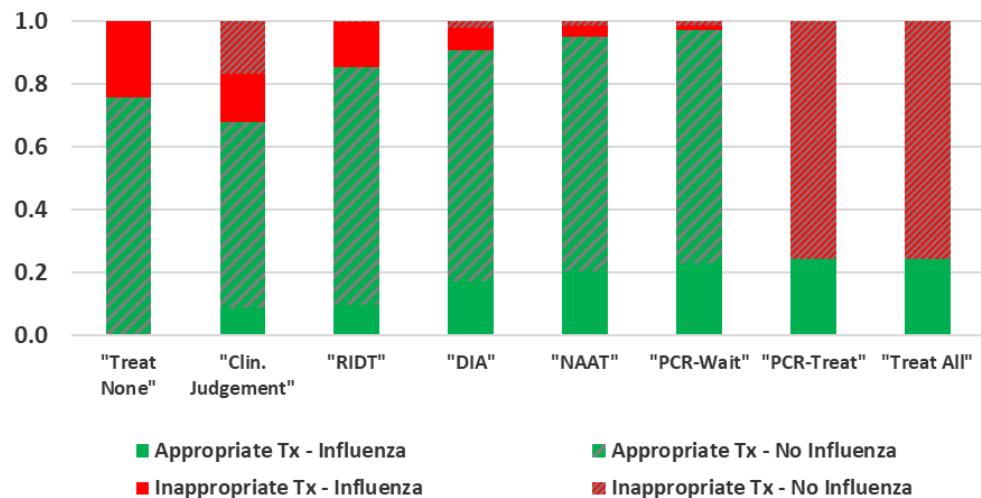
Figure 10.1 Quality-adjusted life days gained relative to the "Treat none" strategy per 100,000 population with non-severe influenza-like illness



DIA, digital immunoassay; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; QALD, quality-adjusted life days; RIDT, rapid influenza diagnostic test

Note: The "PCR-treat" strategy (treating everyone up-front and discontinuing treatment after 24 hours upon negative test results) mirrored the outcomes of the "Treat-All" strategy because the full treatment regimen of baloxavir was administered upfront as a single dose. Thus, all patients with "PCR-treat" strategy received a full course of treatment similar to the "Treat all" strategy. Both strategies were associated with a QALD loss compared to the "Treat none" strategy due to the highest number of adverse events.

Figure 10.2 Treatment appropriateness (proportion of patients with non-severe influenza-like illness who are appropriately treated and proportion of patients without influenza who are inappropriately treated) under the strategies examined.



Note: Green bars indicate influenza patients who received treatment, striped green bars are patients without influenza and with no treatment, while red bars represent untreated patients with influenza and red-striped bars show patients without influenza who received treatment.

10.2 Severe influenza

Older adult patients with severe influenza-like illness (with a seasonal pre-test probability of influenza of 36.5%), testing positive for influenza would receive treatment with oseltamivir (5-day course), and experience a shorter length of in-hospital stay (1.63 fewer days), and a 23% higher rate of adverse events relative to untreated individuals. No mortality benefit associated with this treatment was considered, based on the WHO systematic review.

The overall preferred strategy in terms of QALDs was “PCR-wait” followed by “PCR-treat”, “NAAT” (Table 11.2). Relative to the “Treat none” strategy, the “PCR-wait” strategy reduced the in-hospital stay by 56 212 days per 100 000 population and was associated with an additional 1202 adverse events per 100 000. That translated into an overall gain of 12 370 QALDs per 100 000 population (Table 10.2, Figure 10.3).

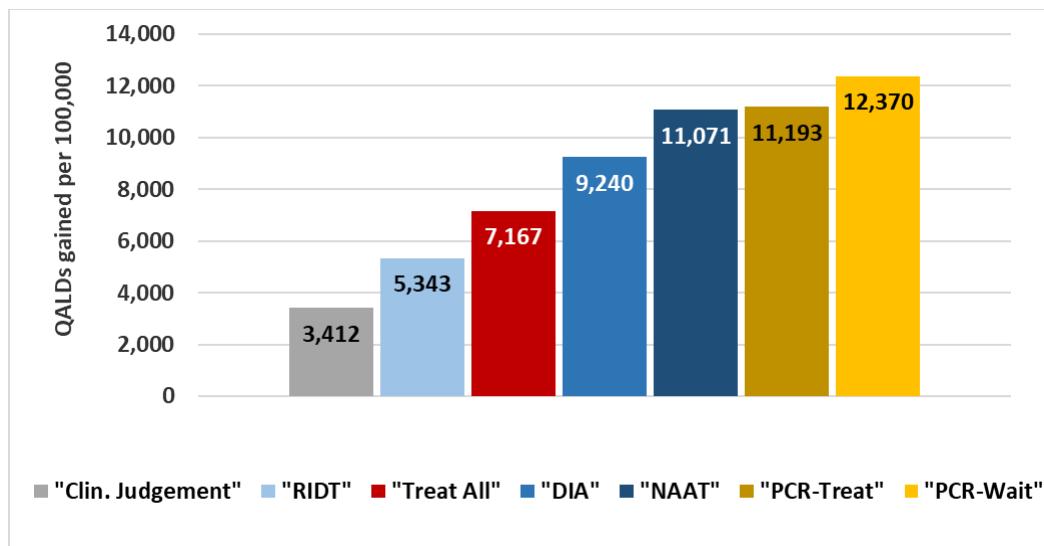
Table 10.2 Outcomes for strategies examined for patients with severe influenza-like illness

Strategy	Appropriate of treatment (proportion)			Health outcomes (per 100 000)		
	Appropriate (influenza, receives treatment)	Inappropriate (influenza, does not receive treatment)	Inappropriate (no influenza, receives treatment)	Adverse events	Symptom-free days gain	QALD gain/loss
Treat all	0.000	0.364	0.000	4431	0	0
PCR-treat	0.131	0.233	0.139	6935	21 348	3412
Treat none	0.148	0.216	0.003	4887	24 093	5343
Clinical judgement	0.364	0.000	0.636	15 042	59 311	7167
RIDT	0.260	0.104	0.018	5475	42 385	9240
DIA	0.309	0.055	0.011	5515	50 331	11 071
NAAT	0.345	0.019	0.013	7501	56 212	11 193
PCT-wait	0.345	0.019	0.013	5633	56 212	12 370

Notes: DIA - digital immunoassay tests; NAAT - nucleic acid amplification test; PCR - polymerase chain reaction; QALDs - quality-adjusted life days; RIDT - rapid influenza diagnostic tests.

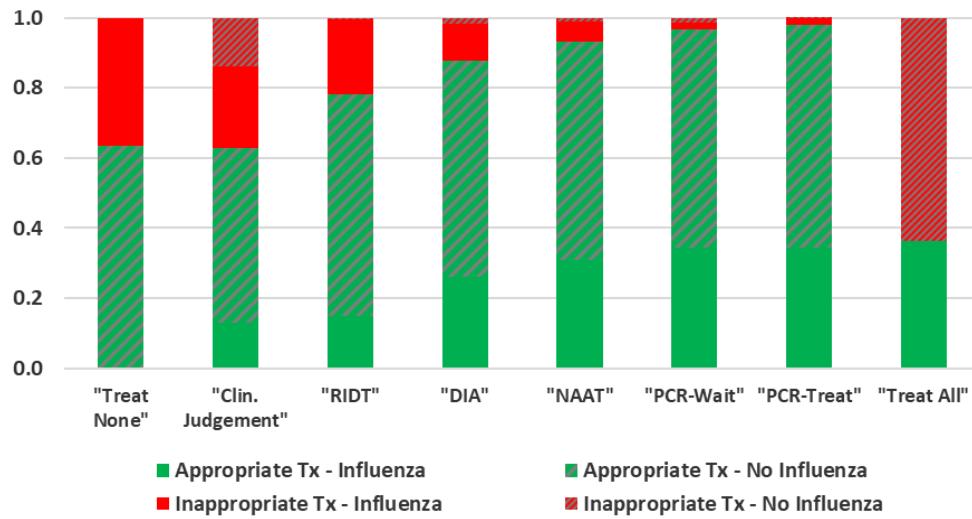
Symptom-free days and QALDs gain were calculated relative to “Treat none” strategy.

Figure 10.3 Quality-adjusted life days gained relative to the "Treat none" strategy per 100 000 population with severe influenza-like illness



Notes: DIA - digital immunoassay; NAAT - nucleic acid amplification test; PCR - polymerase chain reaction; QALDs - quality-adjusted life days; RIDT - rapid influenza diagnostic test.

Figure 10.4 Treatment appropriateness (proportion of patients with severe influenza-like illness appropriately treated and proportion of patients without influenza inappropriately treated) under the strategies examined



Note: Green bars indicate influenza patients who received treatment, striped green bars are patients without influenza and with no treatment, while red bars represent untreated patients with influenza and red-striped bars show patients without influenza who received treatment.

10.2.1 Type of influenza testing in severe disease

Conditional recommendation for

In patients with suspected severe influenza virus infection, we **suggest using high sensitivity and high specificity tests (NAAT or PCR)** for the diagnosis of influenza and treating all patients who are positive with a WHO recommended antiviral agent.

If high sensitivity and specificity tests are available but results will be delayed for more than 24 hours then we recommend starting treatment with a WHO-recommended antiviral agent and ceasing the treatment if the test is negative (conditional recommendation, low-quality evidence).

- If NAAT testing is available and results are rapidly available then this is the preferred approach.
- If PCR testing is available and results are available within 24 hours then “PCR-wait” is a reasonable approach.
- If PCR testing is available and results are not available within 24 hours then “PCR-treat” may be a reasonable approach, provided that that treatment is stopped if the test is negative.

10.2.1.1 Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Nucleic acid amplification tests (NAATs), including RT-PCR, are molecular assays that detect influenza virus nucleic acids in respiratory specimens. NAATs have high sensitivity and high specificity to detect influenza virus nucleic acids in respiratory specimens.

NAATs in inpatient setting may be associated with a small increase in QALDs. Currently, the only antiviral with a recommendation for use in severe influenza patients is oseltamivir. Its effect is uncertain in regard to mortality and admission to ICU and possible reduction in days of hospitalization, the difference in QALDs is very small. A strategy of treating all also had a very small increase in QALDs but, importantly, overall differences between all options were very small.

Certainty of the evidence	Low
These recommendations are conditional as they are not derived from RCTs of testing strategies. They are derived from a decision analysis model with input parameters for diagnostic test characteristics, illness epidemiology, treatment effects and utilities, many of which are based on relatively low-quality index. The decision analysis used data from high-income countries and did not formally incorporate costs.	
Values and preferences	No substantial variability expected
Applying the agreed upon values and preferences (see Section 11.2), the GDG inferred that the majority of well-informed patients with severe influenza virus infection would choose to use influenza NAATs (molecular assays).	
Resources and other considerations	Important issues, or potential issues not investigated

Feasibility and acceptability

Influenza NAATs and other influenza molecular assays may not be available in many clinical settings due to their cost.

Access to influenza diagnostics

Targeted treatments for viral pneumonias, such as influenza or COVID-19 requires accurate testing to guide decision-making. This includes ensuring diagnostic results are available and can give results within a time frame to guide treatment. As this recommendation involves administering treatment with oseltamivir as soon as practical, ensuring appropriate use of diagnostic tests is essential for implementation.

10.2.1.2 Justification

When influenza A or B viruses are circulating at high prevalence among people in a community, NAATs have high positive predictive values to detect influenza viruses in upper respiratory specimens within 3-4 days of illness onset. When influenza A or B viruses are circulating at low prevalence or not circulating among people in a community, NAATs have high negative predictive values to detect influenza viruses in upper respiratory specimens within 3-4 days of illness onset. In patients with severe influenza virus infection and lower respiratory disease, influenza virus infection of the

upper respiratory tract may have been cleared, but influenza virus replication may be occurring in the lower respiratory tract; therefore, collection of lower respiratory specimens for influenza NAAT or PCR can help inform clinical management of patients with suspected influenza without a diagnosis.

The GDG inferred that the marginal increase in QALDs for the “NAAT” strategy and “PCR-treat” was preferable compared with a “Treat all” strategy, as more targeted clinical treatment would be preferable to avoid wasting resources, overuse of antivirals that is contrary to antimicrobial stewardship strategies and exposing patients unnecessarily to adverse events. The GDG also noted that if there was a more effective antiviral in future, this would impact the model's output on QALDs.

10.2.1.3 Practical info

Interpretation of tests should take into account the prevalence of influenza viruses circulating in the community (high or low prevalence) as part of the pre-testing probably of disease.

Influenza NAATs are most accurate when upper respiratory tract specimens are collected within 3-4 days of symptom onset. Collection of a good quality upper respiratory tract specimen from a patient with suspected influenza is very important. The highest yield for influenza viruses is from testing nasopharyngeal specimens, either nasopharyngeal swab or aspirate specimens. High yield for influenza viruses can also be achieved by testing a combined nasal swab and throat swab specimen (collected separately and placed together in the same sterile specimen container). Patients who test negative in upper respiratory tract specimens by influenza NAAT and who have lower respiratory tract disease may have influenza virus replication in the lower respiratory tract. Therefore, in patients with lower respiratory tract disease and suspected influenza virus infection without a diagnosis, collection of lower respiratory tract specimens (e.g., sputum, endotracheal aspirates from intubated patients, bronchoalveolar lavage fluid) can be tested by influenza NAAT.

10.2.1.4 Summary

Assumptions: Older adult patients (i.e., those at high risk of severe influenza sequelae) with non-severe influenza like illness (with a seasonal pre-test probability of influenza of 24.3%), testing positive for influenza would receive treatment with a single dose of baloxavir, and experience a shorter symptom duration (1.02 fewer days) and a 10% higher rate of adverse events relative to untreated individuals. Additionally, no

hospitalization or mortality benefits associated with the treatment were considered, based on the WHO systematic review.

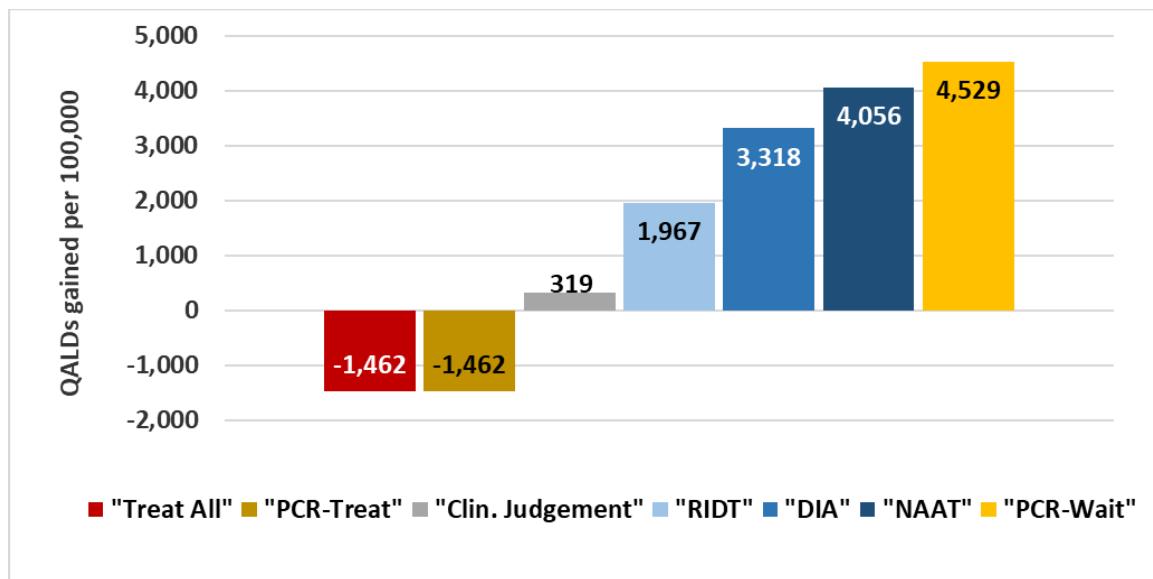
The overall preferred strategy in terms of quality adjusted life days (QALDs) was "PCR-wait" followed by "NAAT", "DIA" (Table 10.3). Compared to the "Treat none" strategy, "PCR-wait" strategy offered 23 337 symptom-free days per 100 000 population, and was associated with an additional 501 adverse events per 100 000 population. That translated into an overall gain of 4529 QALDs per 100,000 population (*Table 10.3, Figure 10.5*). The "Treat all" strategy resulted in outcomes worse than "Treat none", as it inappropriately treated a large proportion of individuals (*Table 10.3, Table 10.3*) and was associated with the highest number of adverse events. The "PCR-treat" strategy mirrored the result of "Treat all" considering that a full regimen of baloxavir (a single dose) was administered prior to receiving test results.

Table 10.3 Outcomes for strategies examined for patients with non-severe influenza-like illness.

Strategy	Appropriate of treatment (proportion)			Health outcomes (per 100 000)		
	Appropriate (influenza, receives treatment)	Inappropriate (influenza, does not receive treatment)	Inappropriate (no influenza, receives treatment)	Adverse events	Symptom-free days gain	QALD gain/loss
Treat all	0.242	0.000	0.758	13 376	24 660	-1462
PCR-treat	0.242	0.000	0.758	13 376	24 660	-1462
Treat none	0.000	0.242	0.000	2 930	0	0
Clinical judgement	0.087	0.155	0.167	5 338	8846	319
RIDT	0.098	0.144	0.003	3089	9958	1967
DIA	0.172	0.070	0.022	3451	17 565	3318
NAAT	0.205	0.037	0.014	3374	20 881	4056
PCT-wait	0.229	0.013	0.016	3431	23 337	4529

DIA, digital immunoassay tests; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; QALDs, quality-adjusted life days; RIDT, rapid influenza diagnostic tests.
Symptom-free days and quality-adjusted days gain were calculated relative to "Treat none" strategy.

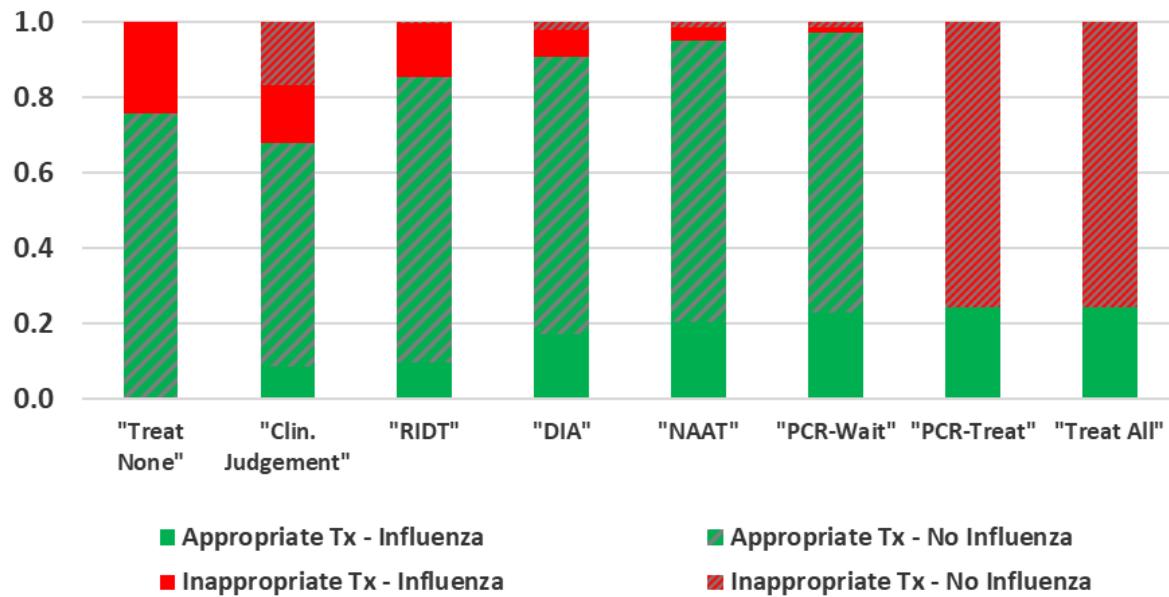
Figure 10.5 Quality-adjusted life days gained relative to the "Treat none" strategy per 100,000 population with non-severe influenza-like illness



DIA, digital immunoassay; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; QALD, quality-adjusted life days; RIDT, rapid influenza diagnostic test

Note: The "PCR-treat" strategy (treating everyone up-front and discontinuing treatment after 24 hours upon negative test results) mirrored the outcomes of the "Treat-all" strategy because the full treatment regimen of baloxavir was administered upfront as a single dose. Thus, all patients with "PCR-treat" strategy received a full course of treatment similar to the "Treat all" strategy. Both strategies were associated with a QALD loss compared to the "Treat none" strategy due to the highest number of adverse events.

Figure 10.6 Treatment appropriateness (proportion of patients with non-severe influenza-like illness who are appropriately treated and proportion of patients without influenza who are inappropriately treated) under the strategies examined.



Note: Green bars indicate influenza patients who received treatment, striped green bars are patients without influenza and with no treatment, while red bars represent untreated patients with influenza and red-striped bars show patients without influenza who received treatment.

11. How was this guideline created

11.1 Guideline development process

11.1.1 Introduction

The development of these guidelines adheres to standards for trustworthy guidelines, including those of the United States Institute of Medicine [87], WHO [1] and Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [88, 89].

11.1.2 Timelines

In 2022 WHO published guidelines for the clinical management of severe illness from influenza virus infections. The process for the development of this previous guideline had commenced in 2016 and was delayed due to the COVID-19 pandemic. As this previous guideline had been commenced over 7 years previously and the scope did not include non-severe influenza, the WHO guideline steering committee identified the need for an updated guideline and planning for this commenced in late 2022.

In early 2023 a WHO steering committee group was assembled (see *Section 11.1*) and gaps in the previously published guideline were identified. In May 2023 a planning document was submitted to the WHO Guidelines Review Committee for approval; this was approved after two additional revisions in January 2024.

In 2023 the WHO selected and convened the influenza GDG (see *Section 11.1*). The GDG is a multidisciplinary group comprised of individuals from all WHO regions, including technical experts in influenza, researchers, frontline clinicians, patient representatives and other stakeholders. For this update of the guideline the GDG also included an expert in health ethics, equity and justice, recognizing the challenges of providing recommendations that take into account varying global access to influenza therapeutics and diagnostics. WHO also ensured that the GDG was balanced for gender and representation from all WHO regions.

The initial meeting of the GDG was held on 2 October 2023. At this initial meeting it was confirmed that this update of the guideline would be an update of the guideline published in 2022 with the addition of the treatment of non-severe disease and the use of antivirals as prophylaxis for influenza. PICO questions were formulated using the following parameters.

11.1.3 PICOs

The **population of interest** included persons with suspected or confirmed influenza virus infection including seasonal influenza, pandemic influenza and zoonotic influenza. The following subgroups were pre-specified:

- Influenza type: seasonal, zoonotic, pandemic influenza viruses;
- Confirmed or suspected infection;
- Age: children < 2 years; or children; or adults and adolescents; or older adults (≥ 65 years).
- Patients at increased risk of poor outcomes vs. not including:
 - People who are pregnant or up to 2 weeks postpartum
 - Obesity (BMI > 40)
 - Patients with underlying health conditions – including chronic respiratory, cardiovascular disease
 - Patients who are immunosuppressed.

Outcomes of critical interest were also identified as the following:

- Mortality;
- Admission to hospital;
- Duration of hospitalization;
- Admission to ICU;
- Progression to mechanical ventilation;
- Duration of symptoms;
- Emergence of antiviral resistance;
- Adverse events related to therapeutic interventions.

11.1.4 Evidence synthesis

In 2023 evidence reviews were externally commissioned from four independent, academic groups as follows:

Dr Qiukui Hao and colleagues at McMaster University, Canada, undertook a systematic review of randomized controlled studies on antivirals in severe influenza. The systematic review team analysed RCTs in all major databases from database inception to 20 September 2023 that enrolled hospitalized patients with suspected or laboratory-confirmed influenza and compared direct acting antivirals against placebo, standard care or another antiviral.

Dr Hao and colleagues also completed a systematic review of antivirals in non-severe influenza. Again the team searched and analysed RCTs published between database inception and 20 September 2023 that compared direct-acting antiviral drugs. These included but was not limited to baloxavir, favipiravir, laninamivir, oseltamivir, peramivir, umifenovir and zanamivir compared with no intervention, placebo, standard care or another antiviral drug.

Dr Hao and colleagues also completed a systematic review of antiviral therapies for prophylaxis against influenza. As a new section of this guideline it involved a complete search of all relevant databases up until September 2023 for RCTs examining the efficacy and safety of direct-acting influenza antivirals compared with another antiviral or placebo, standard care or no treatment as prophylaxis against influenza. Dr Hao was a presenter at the GDG meeting in December 2023.

Dr Barnaby Young and colleagues at Nanyang Technological University, Singapore, and the National University of Singapore had undertaken a systematic review of adjunctive immunomodulatory therapies for severe influenza for the previous guideline published 2022. The systematic review team then updated that previous search, undertaken in January 2019, and so the search for this review was limited to 2019 to 2023. As there were no specific RCTs identified investigating corticosteroids in severe influenza, a number of other sources of indirect evidence were analysed. A 2023 systematic review had identified 16 RCTs of corticosteroids as adjunctive therapy for community-acquired pneumonia [90]. In addition, a Cochrane review that had investigated observational studies of the impact of corticosteroids on influenza was used to inform the evidence for this guideline [53]. As this Cochrane review had been published in 2020, Embase/ MEDLINE was then searched, using the same search strategy as the Cochrane review, for the period of 2020 to 2023. Four observational studies were identified, and these observational data were provided to the GDG as part of the summary of findings tables. Dr Young attended the GDG meeting in December 2023 virtually.

Ms Shannon Kelly and colleagues of University of Ottawa Heart Institute undertook a systematic review and meta-analysis of antibiotic use in patients with non-confirmed symptomatic influenza who had a low risk of bacterial co-infection. The search included MEDLINE, Embase and Cochrane for the period of database inception until 14 October 2023. Ms Kelly presented at the GDG meeting in December 2023 virtually.

As per the previous guideline, the steering committee and the GDG identified the need to review influenza diagnostic testing strategies for influenza in the population

of interest. The GDG noted that, using the GRADE approach, estimates of the impact of alternative testing approaches on patient-important outcomes are required for making recommendations. The GDG anticipated finding no observational studies or RCTs directly comparing influenza testing strategies and therefore recommended a modelling approach. Yeva Sahakyan and Dr Beate Sander from Toronto Health Economics and Technology Assessment Collaborative, University Health Network, developed a decision-analytic model based on data from recent relevant meta-analysis to assess the optimal testing strategy for patients with influenza-like illness to inform treatment with antivirals in regard to QALDs. The reference case for the decision tool was a 65-year-old patient presenting with a) non-severe influenza-like illness presenting to an outpatient setting; or b) severe influenza-like illness presenting to an inpatient setting. For each reference case six strategies were assessed:

1. No test, and do not treat anyone with ILI ("Treat none");
2. No test and treat everyone ("Treat all");
3. No test and treat individuals based on clinical judgement ("Clinical judgement");
4. Rapid test for all patients and treat if tested positive for influenza;
5. PCR test, and treat everyone until results become available ("PCR-treat");
6. PCR test, but don't treat until results are available ("PCR-wait");

Ms Sahakyan and Dr Sander presented at the December 2023 GDG meeting.

From the previous guideline the steering committee had identified a need to determine both the baseline risk of patients with non-severe influenza requiring hospitalization, i.e., progressing to severe influenza. In addition, the steering committee requested an analysis of observational data to determine what risk factors were important in determining the risk of an individual patient progressing from non-severe influenza to severe influenza.

Dr Qiukui Hao and colleagues at McMaster University were commissioned to systematically review available observational data to determine the prognosis of influenza patients, both severe and non-severe, and determine the risk factors for disease progression. Major databases, including MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature and Global Health were searched from database inception to 26 October 2023.

Studies were included with patients with laboratory-confirmed influenza virus infections reporting hospitalization and/ or mortality among the influenza patients (available online [here](#))[86].

11.1.5 GDG meeting; GRADE - considerations for evidence to decision in the making of recommendations

In December 2023, a hybrid (face-to-face and virtual) GDG meeting was held to review the results of the systematic review from the systematic review teams and formulate recommendations. At this meeting GRADE methodology was used to assess the overall quality of evidence, which could not be higher than the lowest quality rating for any outcome considered critical to informing a recommendation. Standard approaches to lowering or raising the level of quality or confidence were used, including risk of bias, inconsistency, indirectness, imprecision, publication bias, confounding bias, dose response or large effect.

The review of observational data to determine the baseline risk of patients with influenza was not available at the time of the GDG meeting so baseline risks were estimated from a small number of high-quality observational studies and from the data in the RCTs used in the systematic reviews on the effectiveness of antivirals. The review of baseline risks was completed in March 2024 and the results made available to the GDG at this time. Reassuringly, there was minimal difference in the estimates of baseline risk made prior to the GDG review and those found in the systematic review.

The GDG decided a priori not to consider costs in determining the strength and direction of recommendations as cost-effectiveness analyses were not performed. Nonetheless, the cost of interventions and the resources required for the application of the guidelines were discussed by the GDG members and feasibility is an important component of the evidence to decision framework. Specifically, some GDG members were concerned that conditional recommendations in favour of a specific intervention may be less likely to be able to be feasibly applied in resource-limited settings. However, there was consensus on the determinants of the strength of recommendations and that the interpretation of a conditional recommendation was aligned with standard GRADE guidance. In other words, a conditional recommendation in favour of an intervention is a recommendation to "administer the intervention to most persons" with suspected or confirmed influenza virus infection.

11.1.6 GDG decision-making

In making recommendations, the GDG considered the magnitude of benefits and harms, the quality of evidence (very low to high) supporting estimates of the magnitude of benefits and harms, and their belief regarding values and preferences of stakeholders (in particular, patients infected by influenza virus). Interpretations of strong and conditional recommendations from the perspectives of patients, clinicians and policymakers appear in Table 12.1.

Table 11.1 Strength of recommendations

Implications for...	Strong recommendation "We recommend..."	Conditional recommendation "We suggest..."
Patients	Most people in this situation will want the recommended course of action and only a few will not.	The majority of people in the situation would want the recommended course of action, but a substantial minority would not.
Clinicians	Most patients should receive the recommended course of action.	Different choices will be appropriate for different patients. Patients will need help to arrive at a management decision consistent with their values and preferences.
Policymakers	The recommendation could be adopted as policy.	There is a need for substantial debate and involvement of stakeholders.

It was determined that if consensus was not reached in regard to recommendations then voting would be undertaken to finalize recommendations with a majority (80%) vote required for a strong recommendation to be adopted. A conditional recommendation could be made by the approval > 50% of the panel.

Consistent with recent advice to guideline panels, the GDG attempted to make recommendations even when there was insufficient evidence, so as to support clinicians and patients in the face of uncertainty and to encourage further research. In doing so, the GDG considered the totality of available evidence pertaining to critical outcomes. The GDG avoided making strong recommendations when evidence was of low or very low-quality. Discussions on rationale, feasibility and accessibility, equity implications (if any) and implementation considerations were also documented. Equity implications included qualitative discussions of feasibility implications of any recommendations in favour of an intervention for constrained health care systems, and in the context of other health care needs (such as supportive care) for the population of interest.

The GDG achieved consensus on all recommendations and formal voting was not required.

11.1.7 Minimally important difference

We did not provide the GDG with an evidence-based description of the MID, defined as the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, either beneficial or harmful, and which would lead the patient or clinician to consider a change in management of the patient [91]. The GDG therefore relied on their own judgement of what well-informed patients would consider as the MID for the outcomes of interest. This included a survey of the GDG to specifically investigate the preferred MID for duration of symptoms in non-severe influenza.

Table 11.2 Minimally important differences for outcomes of interest

MID	
Admission to hospital	15 per 1000
Mortality	3 per 1000
Mechanical ventilation	10 per 1000
Adverse events	10 per 1000
Length of hospital stay	1 day
Time to symptom resolution	1 day

11.1.8 Peer review

In March 2023 a separate peer review was undertaken to evaluate the usability and clarity of the guidance document (see *Section 11.1* for the members of the external review group).

11.2 Values and preferences

We did not provide the GDG with an evidence-based description of patient experiences or values and preferences regarding treatment decisions for the clinical management of influenza.

The GDG, therefore, relied on their own judgements of what well-informed patients would value after carefully balancing the benefits, harms and burdens of treatment. There were patient representatives on the GDG who actively contributed to the

deliberations. The GDG agreed that the following values and preferences would be typical of well-informed patients:

- “Most patients would choose to use a medication that had a small but important effect on outcomes they consider important, provided that there is a low likelihood of adverse effects, and that adverse effects when they do occur are mild.”
- “Most patients would be reluctant to use a medication in which there was considerable uncertainty regarding its benefits and would only do so if the low certainty evidence suggested a benefit, there was a low likelihood of adverse effects, and that adverse effects when they did occur are mild.”

Key to the decision-making was the threshold of importance that the panel inferred for each outcome of importance. To provide an example, the GDG inferred that the threshold for the use of baloxavir treatment of patients with non-severe influenza at high risk of progression to severe disease would be a reduction in hospitalization of 15 per 1000.

In addition to these considerations, the panel also inferred that convenience versus burden were important to patients. For instance, with respect to baloxavir, the panel noted that the drug is given as a single oral dose. This is convenient for patients and increases the appeal of this intervention.

In addition to taking an individual patient perspective, the GDG also considered a population perspective in which feasibility, acceptability, equity and cost were important considerations. Specific deliberations on values and preferences and associated feasibility and resource related considerations are presented for each recommendation.

11.3 Managing declaration of interests

The co-chairs and all members of the GDG and external expert reviewers each submitted a declaration of interest (DOI) prior to or at the beginning of each meeting and were given the opportunity to update their DOI at the beginning of each meeting. These were reviewed and cleared by the responsible technical officer and discussed with the WHO Compliance, Risk Management and Ethics Department.

Potential conflicts of interest were declared by two of the GDG.

The three GDG co-chairs, with Professor Guyatt also serving as the methodologist, did not have any financial or intellectual conflicts of interest. GDG members did not

perform the systematic reviews, develop the GRADE evidence profiles or write the final document.

An adviser with expertise in pharmacology (Professor Andrew Owen) participated in the guideline development process, but was a non-voting member.

Andy Gray: Is a member of three advisory committees at the South African Health Products Regulatory Authority: Names and Scheduling Committee (Chair), Pharmacovigilance Committee, Legal Committee. Mr Gray is a member of the South African National Essential Medicines List Committee and Chair of its Paediatric Expert Review Committee. He is Co-Director of the WHO Collaborating Centre for Pharmaceutical Policy and Evidence Based Practice, located in the Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal. **No action required.**

Nida Qadir: Is the site principal investigator for the Investigating Respiratory Viruses in the Acutely Ill Network. This is an observational, prospective, public health surveillance activity conducted by the United States Centers for Disease Control and Prevention (CDC) to evaluate influenza and COVID-19 vaccine effectiveness. All funding is provided by the CDC and used for the conduct of the study. There are no commercial or for-profit entities involved. This is expected to continue through 2023.

No action required.

11.4 Financial support

This guideline was developed with the financial support of the Office of Global Affairs, United States Department of Health and Human Services.

12. How to access and use this guideline

12.1 How to access the guideline

- [WHO website in PDF format](#);
- [MAGIC platform online](#).

12.2 How to navigate this guideline

End-users will need to understand what is meant by strong and conditional recommendations (see below) and certainty of evidence (the extent to which the estimates of effect from research represent true effects from treatment).

For each recommendation additional information is available online through the following tabs:

Research evidence: Readers can find details about the research evidence underpinning the recommendations as GRADE summary of findings tables and narrative evidence summaries.

Evidence to decision: The absolute benefits and harms are summarized, along with other factors such as the values and preferences of patients, practical issues around delivering the treatment as well as considerations concerning resources, applicability, feasibility, equity and human rights. These latter factors are particularly important for those needing to adapt the guidelines for national or local contexts.

Justification: Explanation of how the GDG considered and integrated evidence to decision factors when creating the recommendations, focusing on controversial and challenging issues.

Practical information: For example, dosing, duration and administration of medications, or how to apply tests to identify patients in practice.

Decision aids: Tools for shared decision-making in clinical encounters.

12.3 Additional educational modules and implementation tools for health workers

- [WHO Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation](#) provides algorithms and practical tools for clinicians working in acute care hospitals managing adult and paediatric patients with acute respiratory infection, including severe pneumonia, ARDS, sepsis, and septic shock. This includes information on screening, testing, monitoring and treatments.
- [WHO Global Clinical Platform for SARI](#).
- [OpenWHO training modules on seasonal influenza](#).

This WHO guideline is also used to inform the activities of the [WHO Prequalification of Medicinal Products](#).

13. Uncertainties and future research

There is an urgent need for a better evidence-based understanding of patients' values and preferences.

Other important uncertainties and deficits in our clinical toolkit were identified by the GDG. Key areas for evidence generation were:

13.1 Seasonal influenza

- Accurate clinical tools for seasonal influenza, especially to predict hospitalization and mortality (establishing the relative and absolute risks associated with patient and viral factors);
- High certainty efficacy data for new and existing antiviral therapies in patients with non-severe disease and high risk for progression (to prevent hospitalization and improve the disease course);
 - High certainty efficacy data for new and existing antiviral therapies in patients with severe disease (to reduce severe outcomes including mortality). The optimal dose of antivirals in severe disease also requires further urgent investigation. The estimates of effects in high-risk patients are much less certain than those at low risk – this is a priority. The estimates of effects in high-risk patients are much less certain than those at low risk – this is a priority;
 - High certainty efficacy data for adjuvant therapies in patients with severe disease (including corticosteroids and newer immunomodulators);
 - An urgent need for large, adaptive randomised controlled trials that investigate the impact of combination therapy with antivirals and immunomodulatory therapy in severe disease.
- Understanding of longer-term outcomes of influenza, including functional status for patients with non-severe and severe disease;
- High certainty efficacy data for new and existing antiviral therapies in patients exposed to influenza (post-exposure prophylaxis).

13.2 Novel influenza A associated with high mortality in humans

- Understanding of hospitalization and mortality (establishing the relative and absolute risks associated with patient and viral factors);
- High certainty efficacy data for new and existing antiviral therapies in patients with novel influenza A;
- High certainty efficacy data for new and existing antiviral therapies in patients exposed to novel influenza A (post-exposure prophylaxis), including those at high risk of occupational transmission.

It was noted that evidence generation should be inclusive of all patient populations including those frequently excluded from trials (children, immunocompromised, pregnant women). Safety data for baloxavir are an important priority.

Research networks should adopt efficient designs for generating evidence, including the use of always-on platforms, particularly for severe disease, and maximizing the harmonization of protocols to allow patient-level data to be meta-analysed appropriately.

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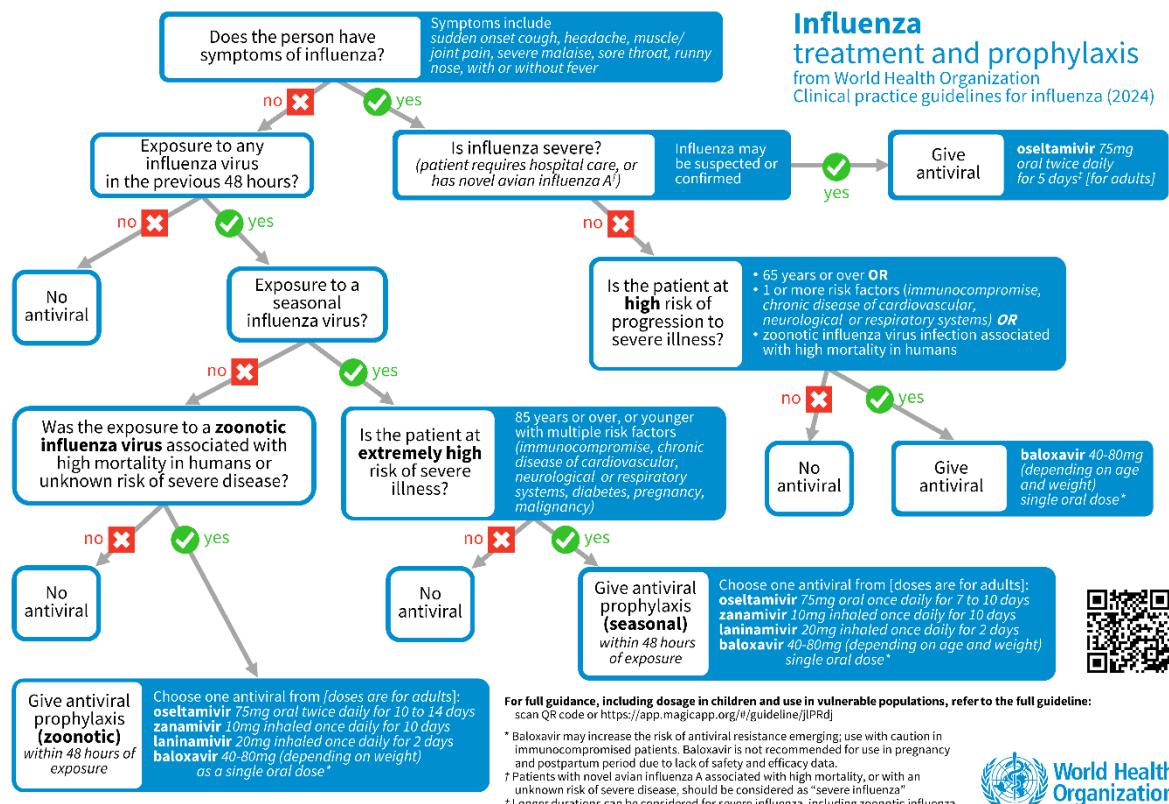
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Annex 1. Tools associated with the guideline

Complete flowchart

(PDF and Powerpoint versions in reference [4, 5])

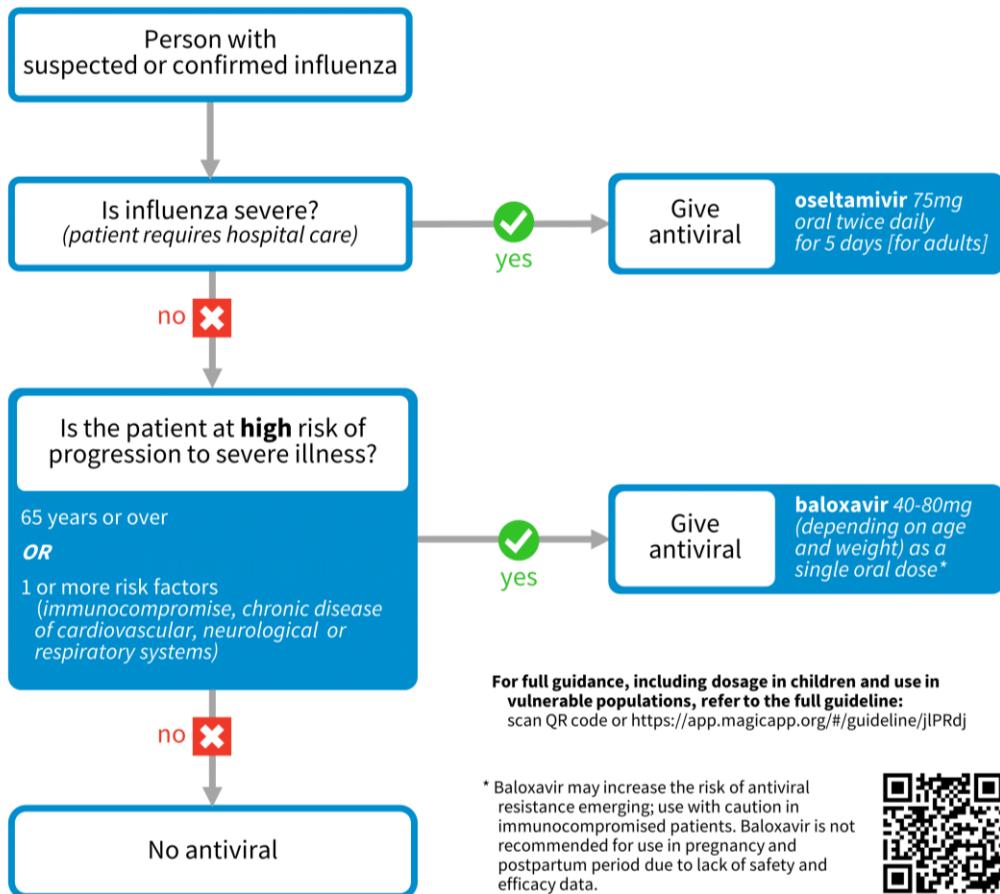


Treatment for seasonal influenza

(PDF and Powerpoint versions in reference [2, 3])

Influenza treatment (seasonal flu)

from World Health Organization
Clinical practice guidelines for influenza (2024)

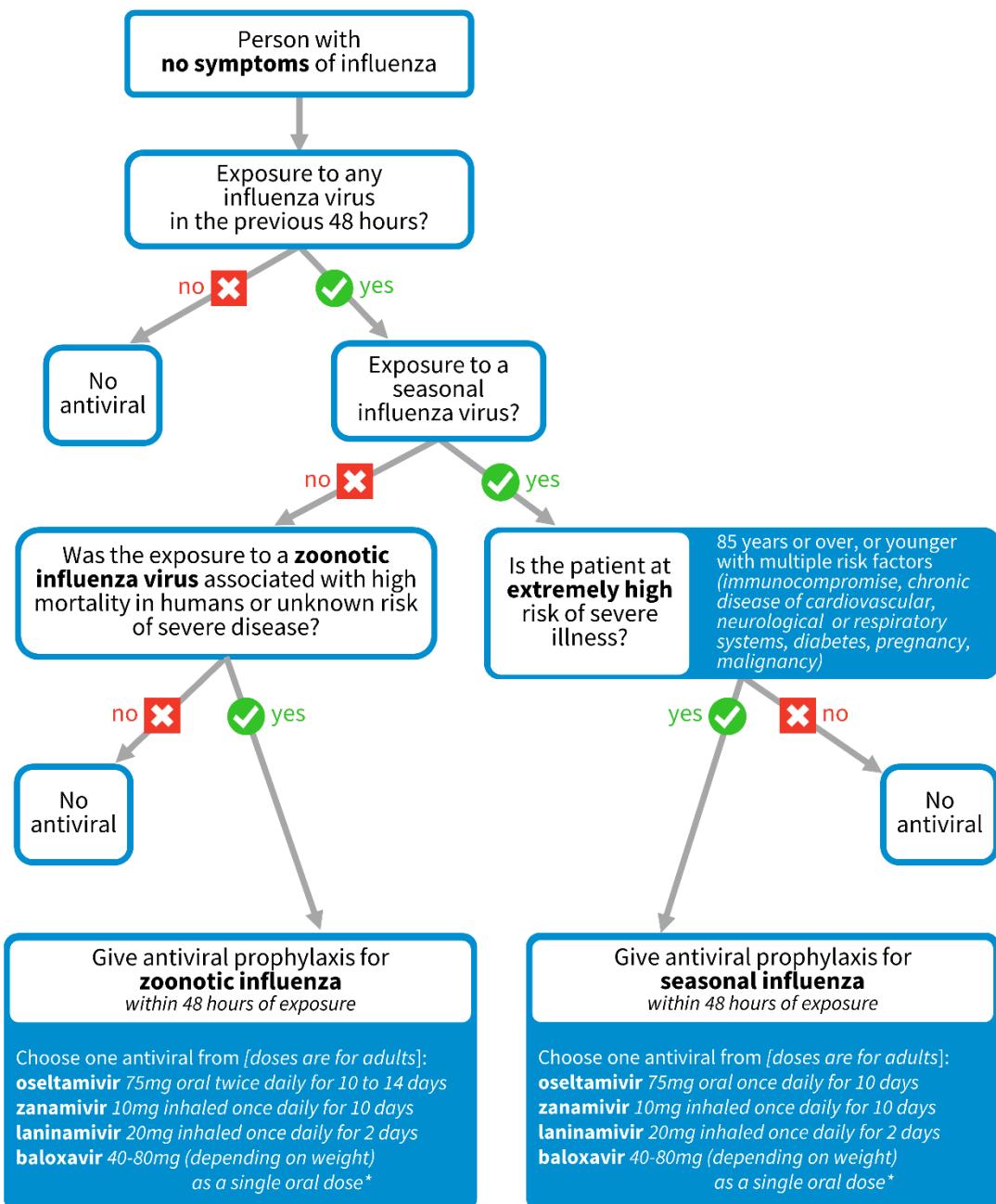


Prophylaxis for influenza

(PDF and Powerpoint versions in reference [2, 3])

Influenza prophylaxis

from World Health Organization
Clinical practice guidelines for influenza (2024)



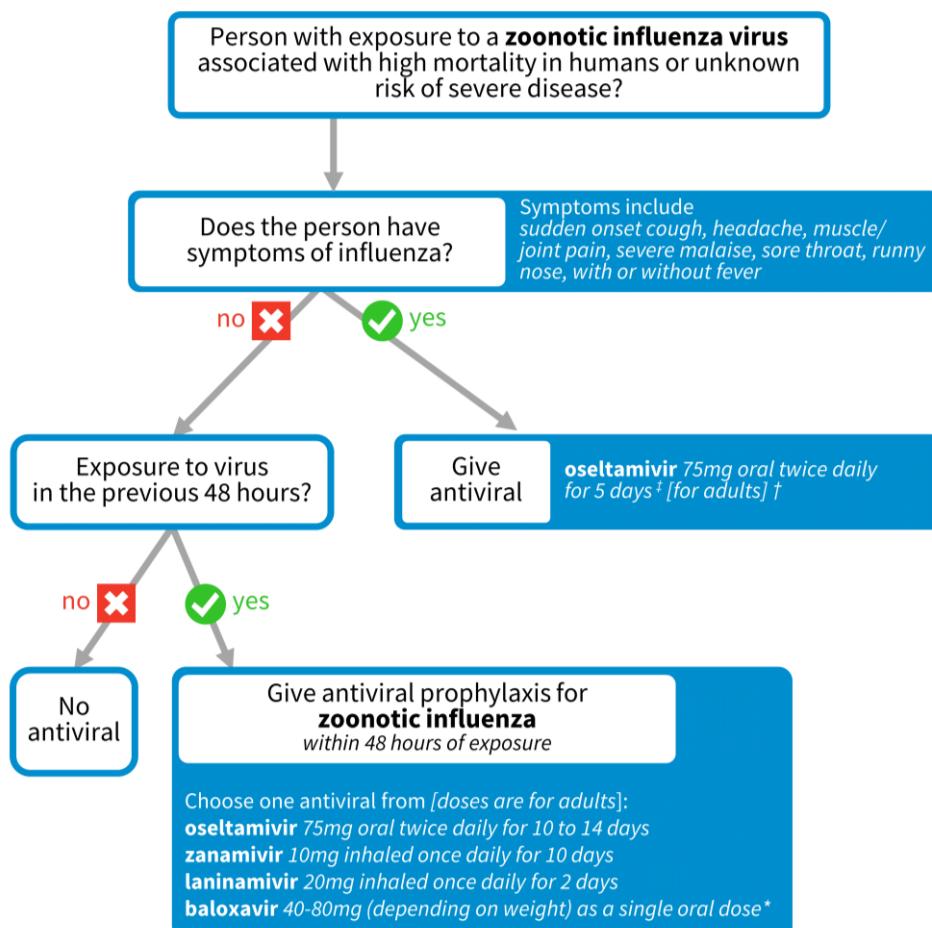
For full guidance, including dosage in children and use in vulnerable populations, refer to the full guideline:
scan QR code or <https://app.magicapp.org/#/guideline/jlPRdj>



* Baloxavir may increase the risk of antiviral resistance emerging; use with caution in immunocompromised patients.
Baloxavir is not recommended for use in pregnancy and postpartum period due to lack of safety and efficacy data.

Zoonotic influenza associated with high mortality in humans

(PDF and Powerpoint versions in reference [2, 3])



For full guidance, including dosage in children and use in vulnerable populations, refer to the full guideline:
scan QR code or <https://app.magicapp.org/#/guideline/JlPRdj>



* Baloxavir may increase the risk of antiviral resistance emerging; use with caution in immunocompromised patients.

Baloxavir is not recommended for use in pregnancy and postpartum period due to lack of safety and efficacy data.

† Baloxavir might be considered as an alternative to oseltamivir where oseltamivir is not available

‡ Longer durations can be considered for zoonotic influenza

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