World Health Organization

Guidelines for the clinical management of severe illness from influenza virus infections

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ABBREVIATIONS

aOR	adjusted odds ratio
ARDS	acute respiratory distress syndrome
BMI	body mass index
CDC	Centers for Disease Control and Prevention (USA)
COPD	chronic obstructive pulmonary disease
DIA	digital immunoassay
DOI	declaration of interest
DSMB	Data Safety and Monitoring Board
GDG	Guideline Development Group (WHO)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guideline Review Committee (WHO)
HA	haemagglutinin
HDU	high dependency unit
ICU	intensive care unit
ILI	influenza-like illness
IOM	Institute of Medicine (USA)
NA	neuraminidase
NAAT	nucleic acid amplification test
NAI	neuraminidase inhibitor
NRS	non-randomized studies
NSAIDs	non-steroidal anti-inflammatory drugs
PICO	Population, Intervention (or Exposure), Comparator, Outcomes
QALY	quality-adjusted life year
RCT	randomized controlled trial
RIDT	rapid influenza diagnostic test
RR	risk ratio
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
WHO	World Health Organization

EXECUTIVE SUMMARY

Of the four types of influenza viruses, A, B, C and D, all but D viruses infect humans. Seasonal influenza A and B viruses circulate among humans worldwide causing epidemics of acute respiratory disease that are estimated to result in 3 to 5 million cases of severe illness and 290 000 to 650 000 respiratory deaths globally each year *(1, 2)*. Infection with zoonotic influenza A viruses can cause severe illness and contribute to the emergence of pandemic strains.

The purpose of this document is to guide clinicians in the care of patients with or at risk of severe illness from influenza virus infection, including those caused by seasonal influenza viruses, pandemic influenza viruses and zoonotic (novel influenza A) viruses. To this end, the World Health Organization (WHO) established a Guideline Development Group (GDG) whose members convened November 2017, March 2019 and September 2019. Guided by the GDG, WHO commissioned three independent academic groups to conduct systematic reviews, two on pharmacologic interventions (neuraminidase inhibitors, adjunctive therapies) and one on diagnostic testing strategies. The GDG developed the questions according to the PICO (Population, Intervention or Exposure, Comparator, Outcomes) structure, reviewed the results of the commissioned systematic reviews, evaluated the quality of evidence (also known as confidence in estimates of effect) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, and formulated recommendations. The guideline was then reviewed by an external review group and approved by the WHO Guideline Review Committee (GRC).

This guideline provides recommendations on the following:

- Treatment with antivirals, specifically neuraminidase inhibitors.

- Treatment with adjunctive therapies, specifically corticosteroids, macrolides and passive immune therapy.

- Use of diagnostic testing strategies to guide treatment of patients with or at risk of severe influenza virus infection.

The recommendations apply to persons with suspected or confirmed influenza virus infection with or at risk of severe illness (i.e. including seasonal influenza, pandemic influenza and zoonotic influenza).

Note: Clinical management of otherwise healthy persons with mild influenza-like illness (ILI) and use of antivirals for post-exposure chemoprophylaxis is not within the scope of this guidance.

Recommendations on antivirals – neuraminidase inhibitors	
1	**We suggest administering oseltamivir as soon as possible (vs not administering oseltamivir).** Conditional recommendation, low-quality evidence. Implementation: when the decision to use oseltamivir is made, it should be administered as soon as possible.
2	**We suggest not administering inhaled zanamivir (vs administering inhaled zanamivir).** Conditional recommendation, very low-quality evidence.
3	**We suggest not administering inhaled laninamivir (vs administering inhaled laninamivir).** Conditional recommendation, very low-quality evidence.
4	**We suggest not administering intravenous peramivir (vs administering intravenous peramivir).** Conditional recommendation, very low-quality evidence.

Recommendations on adjunctive therapies	
5	**We suggest not administering corticosteroids (vs administering corticosteroids).** Conditional recommendation, very low-quality evidence.
6	**We suggest not administering passive immune therapy (vs administering passive immune therapy).** Conditional recommendation, very low-quality evidence.
7	**We suggest not administering a macrolide antibiotic for treatment of influenza (vs administering a macrolide).** Conditional recommendation, very low-quality evidence.

Recommendations for influenza diagnostic testing strategy When seasonal influenza A and B viruses are suspected or known to be circulating in the community, in patients presenting to the emergency department (or equivalent area for assessment of acutely ill patients) with signs and symptoms suggestive of influenza (suspected influenza), with or at risk for severe illness, the recommended testing strategy depends on the diagnostic test characteristic and expected timing of results.	
8	**In settings where batch reverse transcription polymerase chain reaction (RT-PCR) or other rapid molecular influenza assays (with similar high sensitivity and high specificity) are available and results expected within 24 hours, we suggest a strategy of testing for influenza, treating with oseltamivir as soon as possible, and re-evaluating treatment when the test result is available.** Conditional recommendation, low-quality evidence.
9	**In settings where batch RT-PCR or other rapid molecular influenza assays (with similar high sensitivity and high specificity) are not available to provide results within 24 hours, we suggest a strategy of not testing for influenza and treating with oseltamivir as soon as possible.** Conditional recommendation, low-quality evidence.

The GDG acknowledged research gaps regarding the effectiveness of anti-influenza therapies that should be addressed given the large number of patients affected annually, predictability of yearly outbreaks, and global health burden. Priority areas for future study include:

- Randomized controlled trials (RCTs), including adaptive trials in patients with suspected or confirmed influenza and severe illness:
  – oseltamivir vs no oseltamivir
  – other neuraminidase inhibitor (peramivir, zanamivir or laninamivir) vs not
  – oseltamivir vs oseltamivir and adjunctive therapy
  – combination antivirals vs single antiviral
  – combination antivirals and immunomodulators vs single antiviral
  – optimal therapy in oseltamivir resistance.

- Development of a set of core outcomes, including other endpoints that would serve as a reliable surrogate for mortality.

- Treatment strategies in subgroups:
  – immunocompromised patients with influenza, focused on resource-limited settings with high prevalence of severe malnutrition and tuberculosis
  – influenza B.

- Linked diagnostic and treatment strategies for patients with suspected influenza:
  – treat all suspected cases early vs delayed treatment until diagnostic confirmation.

- Other interventions:
  – concurrent antibiotics in critically ill patients with influenza virus infection
  – optimizing supportive care and advanced organ support for critically ill patients with influenza virus infection.

1. Introduction

1. INTRODUCTION

Influenza is an acute respiratory viral infection caused by influenza viruses. Seasonal influenza A and B viruses circulate among humans worldwide. There are four types of influenza viruses: types A, B, C and D.

- **Influenza A viruses** are further classified into subtypes according to the combinations of the haemagglutinin (HA) and the neuraminidase (NA), the main glycoproteins on the surface of the virus. Currently circulating among humans are subtype A(H1N1)pdm09 and A(H3N2) influenza viruses. A(H1N1)pdm09 virus caused the 2009 pandemic and subsequently replaced the seasonal influenza A(H1N1) virus which had circulated among humans prior to 2009. A(H3N2) virus caused the 1968 pandemic and has continued to circulate as a seasonal influenza A virus. Only novel influenza type A viruses are known to have caused pandemics.

- **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.

- **Influenza C viruses** can infect both humans and pigs, and have been reported to cause sporadic illness, mostly in young children. Mild to severe illness has been reported in children and adults. Influenza C viruses are not typically captured by influenza surveillance *(3)*.

- **Influenza D viruses** primarily affect cattle and are not known to cause illness in humans.

1.1 Seasonal influenza

Seasonal influenza A and B viruses and pandemic influenza A viruses can spread readily from person to person, when an infected person coughs or sneezes and infectious droplets are dispersed into the air and deposited on the conjunctiva, mouth, nose, throat or pharyngeal mucosa of another susceptible person *(4)*. Although most large droplets travel a short distance (up to 1 m), smaller droplets may travel up to 2 m *(5)*. The virus can also be potentially spread by the hands or fomites contaminated with influenza virus with subsequent inoculation into the upper respiratory tract, and by aerosol transmission during aerosol-generating procedures *(4)*.

Uncomplicated seasonal influenza illness is characterized by a sudden onset of cough, headache, muscle and joint pain, severe malaise, sore throat and a runny nose, with or without fever. Most people recover from fever and other symptoms within a week, without requiring medical attention. But influenza can cause severe illness (such as sepsis, severe pneumonia, acute respiratory distress syndrome [ARDS], multiorgan failure, exacerbation of chronic medical conditions) or death, especially in people at high risk for complications from influenza virus infection.

Worldwide, annual seasonal influenza epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 290 000 to 650 000 respiratory deaths *(1, 2)*. The highest mortality rates have been estimated in sub-Saharan Africa (2.8–16.5 per 100 000 individuals), South-East Asia (3.5–9.2 per 100 000 individuals) and among people aged 75 years or older (51.3–99.4 per 100 000 individuals).

Table 1.1. People at greater risk for severe illness or complications

People with certain medical conditions *(6–8)*:
- chronic cardiac disease (such as coronary artery disease, congenital heart disease, congestive heart failure);
- asthma and chronic pulmonary disease (such as chronic obstructive pulmonary disease [COPD], cystic fibrosis);
- chronic renal disease;
- metabolic disorders;
- endocrine disorders (such as diabetes);
- neurologic and neurodevelopmental disorders;
- liver disease;
- haematologic diseases (such as sickle cell disease);
- individuals with immunosuppressive conditions (such as HIV/AIDS, receiving chemotherapy or systemic corticosteroids or malignancy).

Other persons at greater risk for severe disease include:
- pregnant women and women up to 2 weeks postpartum;
- children under 59 months, particularly younger than 2 years old;
- persons 65 years and older;
- people younger than 19 years of age on long-term aspirin- or salicylate-containing medications;
- people with a body mass index (BMI) of 40 or higher.

Health care workers are at high risk of acquiring influenza virus infection due to increased exposures during patient care and risk further spread, particularly when caring for vulnerable patients.

In children younger than 18 years of age, seasonal influenza is responsible for an estimated average of 10% of all respiratory hospitalizations; 6% of those < 1 year, 7% of those < 5 years and 16% of older children aged 5–17 years *(9)*. More than half of these estimated 870 000 influenza-related hospitalizations in children occur in Africa and South-East Asia. For 92 countries, among children < 5 years, 9243–105 690 influenza-associated respiratory deaths occur annually *(1)*. Although the effects of seasonal influenza epidemics in developing countries are not fully known, research suggests that 99% of deaths in children < 5 years of age with influenza-related lower respiratory tract infections are found in developing countries *(10)*. A recent study conducted in low- and middle-income countries found a low prevalence (< 5%) of influenza A or B virus infections in hospitalized patients with severe pneumonia, but the years of the study may have been low influenza virus circulation years *(2, 11)*.

1.2 Zoonotic influenza

Humans can also be infected sporadically with zoonotic influenza A viruses, 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) *(12)*. Human infections are primarily acquired through direct contact with infected animals or contaminated environments; these viruses have not acquired the ability of sustained transmission among humans. Human infection can range from asymptomatic to mild upper respiratory tract illness (cough with or without fever) to rapid progression to severe pneumonia, sepsis, ARDS, multiorgan failure, shock and even death *(13, 14)*. The case fatality proportion for A(H5N1), A(H5N6) and A(H7N9) subtype virus infections among humans is much higher than that for seasonal influenza A and B virus infections, whereas most human infections with avian influenza A(H7N7) and A(H9N2) viruses have typically resulted in mild illness to date.

1.3 Diagnosis

Clinical diagnosis of influenza is difficult because signs and symptoms can be non-specific (many respiratory pathogens can cause similar illness) and vary depending on virus type and 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, but RT-PCR requires testing at specialized public health laboratories, and the turnaround times for results may not be timely 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 analyser devices, and rapid nucleic acid amplification tests (NAATs or molecular assays) are available in clinical settings and can provide results within 30 minutes. A recent systematic review reported that the newer rapid antigen-detection tests (NAATs, DIAs) have higher sensitivities for detecting influenza A and B than RIDTs that do not utilize analyser devices in adults and children (91.6% vs 80% vs 54.4%, respectively) *(15)*. Rapid molecular assays with higher sensitivity than DIAs to detect influenza viruses in respiratory tract specimens are commercially available for point-of-care use in clinical settings, and a recent systematic review reported a pooled sensitivity of 90.9% *(16)*. Serology is not recommended for testing any patients for seasonal influenza A or B viruses because collection of paired acute and convalescent serum is required and results will not be timely to inform clinical management *(17)*.

Diagnostic test accuracy requires proper specimen collection, storage and transport. This includes factors such as: 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 recent publication *(17)* and summarized below:

- Nasopharyngeal or combined nasal and throat swabs are preferred for testing of seasonal influenza A and B viruses or zoonotic influenza A 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 tested negative for influenza viruses in upper respiratory tract specimens.

1.4 Antiviral treatment

The clinical management of patients with or at risk for severe influenza virus infection is to provide optimal intensive (supportive) care for severe clinical syndromes and administration of efficacious, influenza-specific antivirals as soon as possible. Neuraminidase inhibitors (NAIs) are both widely available and active against all currently circulating seasonal influenza A and B viruses and zoonotic influenza A viruses. Of the four NAIs that are commercially available (oral oseltamivir, inhaled zanamivir, inhaled laninamivir and intravenous peramivir), oseltamivir is the most widely studied and available. Others are available in certain jurisdictions, approved for certain age groups, vary by administration, dosing and duration of treatment, contraindications and adverse effects. No completed randomized placebo-controlled trials exist for NAIs in hospitalized influenza patients, although many observational studies of oseltamivir treatment in hospitalized influenza patients have been published along with systematic reviews *(18, 19)*. Baloxavir, a newer antiviral, with a different mechanisms of action (selective inhibitor of influenza cap-dependent endonuclease) than NAIs, has been approved for early treatment of adolescent and adult patients with uncomplicated influenza based on phase 2 and 3 studies *(20)*.

2. Methods

2. METHODS

2.1 Purpose of guidance

The purpose of this document is to guide clinicians in the care of **persons with suspected or confirmed influenza virus infection with or at risk of severe illness from influenza virus infection, including those with seasonal influenza viruses, pandemic influenza viruses and zoonotic influenza A viruses known to cause severe illness, such as A(H5N1), A(H5N6) and A(H7N9).**

Persons at risk for severe illness from influenza virus infection are described in Table 1.1.

Severe illness from influenza virus infection is defined by an illness that would lead to hospitalization. This includes patients with clinical syndromes such as:

- severe pneumonia, ARDS;
- sepsis, multiorgan failure or shock;
- exacerbation or complications associated with chronic diseases, such as diabetic crises, asthma attack, COPD exacerbation, acute heart failure or acute renal failure.

This guideline provides recommendations on the following:

- Treatment with antivirals, specifically **neuraminidase inhibitors**.
- Treatment with **adjunctive therapies**, specifically corticosteroids, macrolides and passive immune therapy.
- **Use of diagnostic testing strategies** to guide treatment of patients with, or at risk, of severe influenza virus infection.

Note: **Clinical management of otherwise healthy persons with mild influenza-like illness (ILI) and use of antivirals for post-exposure chemoprophylaxis is not within the scope of this guidance.**

2.2 Target audience

The guidelines are designed primarily for health care providers responsible for recognizing and managing patients with, or at high risk for, severe illness from influenza virus infection and can be applied at all levels of the health care system.

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

2.3 Guideline development process

Introduction

The development of these guidelines adheres to standards for trustworthy guidelines, including those of the United States Institute of Medicine (IOM) *(21)*, WHO *(22)* and Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group *(23, 24)*.

Timeline and PICO questions

In 2016, the development process began with a scoping assessment of research gaps since the last WHO guidance publication for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses *(25)*. A WHO steering group was assembled (see Annex 2) and the proposed guideline development was approved by the WHO GRC.

In November 2017, the WHO selected and convened the influenza Guideline Development Group (GDG) (see Annex 2 for GDG group members). The GDG is a multidisciplinary group composed of individuals from all WHO regions, including technical experts in influenza, researchers and frontline clinicians and other stakeholders. A limitation of the GDG was the absence of patient and health care decision-maker representation and a lack of members with explicit expertise in issues of gender, equity and human rights.

At this initial meeting, the PICO questions were formulated using the following parameters. The population of interest included **persons with suspected or confirmed influenza virus infection and with or at risk of severe illness, including seasonal influenza, pandemic influenza and zoonotic influenza.** The following subgroups were pre-specified:

- Hospitalized patients in wards vs critically ill patients.
- Confirmed vs suspected influenza virus infection.
- Age: infants (≤ 1 year), children vs adults and adolescents vs elderly (≥ 65 years).
- Patients with chronic co-morbidities (cardiovascular disease, respiratory disease, neurological disease, extreme obesity, immunocompromised patients) vs not.
- Women who are pregnant or up to 2 weeks postpartum.
- Resource-limited settings.
- Vulnerable populations such as displaced persons or refugees, indigenous persons.

The **interventions of interest** included:

- Treatment with specific NAI antiviral drugs compared with no treatment or compared with other NAIs.
- Adjunctive treatment with corticosteroids, macrolide antibiotics, passive immune therapy, as compared with antiviral therapy or supportive care alone.
- Diagnostic testing strategies.

At the initial GDG meeting, interventions of interest also included supportive care of patients with severe illness due to influenza virus infections, including the syndromes of hypoxaemia, lower respiratory tract infection, such as pneumonia, ARDS, sepsis and septic shock. However, because of limited resources available to the GDG and alternative professional society guidelines covering these topics, for example (*26, 27*), fully specified questions and evidence reviews were not developed or conducted, respectively, for these interventions.

The **outcomes of critical interest** were (see Annex 1):

- hospital mortality
- intensive care unit (ICU) mortality
- progression of disease severity to hospitalization
- progression of disease severity to ICU admission
- 28-day mortality
- progression to mechanical ventilation.

The GDG also 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 randomised trials directly comparing influenza testing strategies and therefore recommended a modelling approach.

Evidence reviews

Between November 2017 and March 2019, evidence reviews were externally commissioned from three independent, academic groups as follows:

Professor Holger Schunemann and Dr Nancy Santesso and colleagues at the Michael G DeGroote Cochrane Canada Centre, McMaster University, undertook an updated systematic review of observational and randomized controlled studies on neuraminidase antivirals in influenza up to March 2018, having previously published a meta-analysis of observational studies in 2012 *(19)*. Importantly, the commissioned review examined a previously published systematic review of NAIs for influenza *(18)* that included published randomized trials, clinical study reports from drug manufacturers and regulators, and observational studies in patients with influenza A(H1N1) pdm09 virus infection, particularly in hospitalized patients. This step was undertaken because that review *(18)* concluded that "treatment trials with oseltamivir or zanamivir do not settle the question of whether or not the complications of influenza (such as pneumonia) are reduced, because of a lack of diagnostic definitions" and that "insufficient evidence from 30 observational studies to support oseltamivir having a protective effect on 2009A/H1N1 influenza patients for mortality". Dr Schunemann was a presenter at the 2017 meeting, and Dr Santesso was a presenter at the 2019 meeting.

Dr Barnaby Young and colleagues at Nanyang Technological University, Singapore, and the National University of Singapore undertook a systematic review and meta-analysis of adjunctive immunotherapies in severe influenza of published data between 2007–2019; this review is now published *(28)*. Although initially commissioned to include non-steroidal anti-inflammatory drugs

(NSAIDs), statins and mTOR inhibitors; the lack of published data led to a decision to not proceed with these reviews. Dr Young was a presenter at the 2019 meeting.

Stephen Mac, Ryan O'Reilly and Dr Beate Sander undertook a decision analysis to assess the impact of point-of-care testing strategies on quality-adjusted life years (QALY) in patients presenting to an emergency department (or equivalent area for assessment of acutely ill patients) with suspected or confirmed influenza infection. The model incorporated data from a systematic review and meta-analysis of test characteristics and from the natural history of influenza and the effects of treatment *(15)*. Dr Sander was a presenter at the 2019 meeting.

Details of the methods of these reviews are included in the annexes.

GRADE: considerations for evidence to decision in the making of recommendations

In March 2019, a second GDG meeting was held (see Annex 2 for members) to review the results of the systematic review and formulate recommendations. Due to availability, some of the GDG members were new at the second meeting; this second panel assessed the evidence presented and agreed on 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 *(29)*. 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. Specifically, the GDG considered the randomized trials in the previously mentioned review *(18)* to be indirect evidence because the large majority of enrolled patients were outpatients and did not have severe illness with influenza virus infection. The observational studies in this review that did include such patients were included in the body of evidence, with appropriate downgrading for risk of bias. The GDG members made a distinction between studies conducted in persons with or at risk of severe illness from influenza virus infection and studies conducted in otherwise healthy patients with suspected or confirmed influenza (i.e. outpatients with mild disease). The GDG members determined that studies conducted in individuals who are otherwise healthy with mild disease provided indirect evidence for the current guidelines. Accordingly, the evidence from these studies was considered separately and downgraded for indirectness in the GRADE assessment of certainty of evidence.

The GDG was not resourced to conduct systematic reviews of the values and preferences of patients and substitute decision-makers regarding severe influenza infections or to consult with a breadth of patients and patient groups. Instead, GDG members from various WHO regions estimated these values and preferences based on their clinical interactions with patients.

The GDG decided *a priori* not to consider costs in determining the strength and direction of recommendations because resources were not available to commission cost-effectiveness analyses. Nonetheless, the cost of interventions and the resources required for the application of the guidelines were discussed by the GDG members. Specifically, some GDG members were concerned that conditional recommendations in favour of a specific intervention may be less likely to be applied in resource-limited settings. Nonetheless, 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 with or at risk of severe illness *(30, 31)*.

Table 2.1. Strength of recommendations

Implication 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.
Policy-makers	The recommendation could be adopted as policy.	There is a need for substantial debate and involvement of stakeholders.

Implementation considerations

Many recommendations are followed by contextualizing remarks labelled as "implementation considerations". Some remarks are ungraded best practice statements based on referenced sources; these are distinct from graded recommendations in that evidence reviews were not conducted. GDG members reviewed all text following each recommendation and had the opportunity to revise.

Voting

Voting was undertaken to finalize recommendations. Consensus was preferred, but when not attainable, a majority (80%) vote was required for a strong recommendation to be adopted. A conditional recommendation could be made by the approval > 50% of the panel. The GDG members voted on the direction (in favour or against) and the strength (strong or conditional) of each recommendation, based on their confidence that the desirable effects of the interventions outweighed their undesirable effects *(30, 31)*. 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 policy-makers appear in Table 2.1 *(31)*. Consistent with recent advice to guideline panels, the GDG attempted to make recommendations even with insufficient evidence, to support clinicians and patients in the face of uncertainty and to encourage further research *(32)*. 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.

In September 2019, a teleconference was held with GDG members to review additional requested modelling data for influenza diagnostic tests and clinical decision-making algorithm and to finalize recommendations.

The GDG achieved consensus on all recommendations, except for that related to diagnostic tests, where 12 voted yes and 9 did not vote (done by e-mail). Recommendations related to diagnostic tests were conditional based on the evidence reviews and considerations of values and preferences, acceptability and feasibility. Therefore, the strength of the recommendation did not change despite < 80% of panellists voting in favour.

Peer review

In December 2019, a separate peer review was undertaken to evaluate the usability and clarity of the guidance document (see Annex 2 for the members of the external review group).

2.4 Managing potential declarations of interest

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.

The three GDG co-chairs, who also served as methodologists, 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. Potential conflicts of interest were reported by four of the GDG members, two of the temporary advisors, and one of the four presenters. One of the three external reviewers reported a conflict of interest. See Table 2.2 for details and actions taken.

Temporary advisers with expertise in influenza virology (Dr Fred Hayden, Dr Mike Ison, Dr Aeron Hurt) participated in the two meetings, but were non-voting members. Dr Hayden helped to take notes at the 2017 meeting. Drs Hayden and Ison declared conflicts of interest (see Table 2.2).

Table 2.2. Declarations of interest

Four GDG members declared conflicts of interest; see below for details and action taken.
Tawee Chotpitayasunondh: Centers for Disease Control and Prevention (CDC) grant for "Influenza vaccine effectiveness in Thai children" project 2016–2019. Research honoraria on vaccine work totalling US$ 2900. Chairman of the Data Safety and Monitoring Board (DSMB) for influenza vaccine produced by the Government Pharmaceutical Organization of Thailand. Grant support for this influenza vaccine project by WHO 2017–2019. Honoraria US$ 100 per DSMB meeting. Tawee Chotpitayasunondh was allowed to participate as a full member of GDG as guidance was not about vaccines. No action.
Menno de Jong: Ad hoc member of scientific advisory boards relating to trial design for clinical development of new antivirals. Drugs included monoclonal antibodies (Crucell, MedImmune), pimodivir (Janssen) and baloxivir (Shionogi). Honoraria were €150–200 per hour and most memberships were a day. All honoraria paid to the Academic Medical Centre, University of Amsterdam. Menno de Jong was allowed to participate as full member as these drugs were not discussed at this GDG meeting as the new antivirals are either unlicensed in the world (therefore out of scope for this GDG) or licensed in a few countries but without sufficient evidence for consideration in this guidance. No action.
Andy Gray: Previous member of the South African Medicines Control Council (2015–2018), and two of its expert committees, now operating as advisory committees to the South African Health Products Regulatory Authority Legal Advisory Committee (since 2016) and Names and Scheduling Advisory Committee (since 2000). Member of the South African National Essential Medicines List Committee (since 2014). Member of the WHO Expert Panel on Drug Policies and Management (since 2007) and a member of the WHO Expert Committee on the Selection and Use of Essential Medicines at various times (most recently, 2011 and 2013). Past member of the WHO GRC (completed term in 2013). Andy Gray was allowed to participate fully as GDG member. No action.
Norio Sugaya: Consultation and technical advisor for evaluation of safety of oseltamivir, peramivir and baloxivir in children; ceased in 2017. Shionogi 300 000 yen (US$ 2800). Lecture fees (on influenza) joint meetings with Japanese Medical Association and pharma (Chugai, Daiichi, Sankyo, Merck, Astellas, Shionogi, Denka Seiken) to the value of 1 340 000 yen 2017 (US$ 12 600) and 1 250 000 yen 2018 (US$ 11 800). Norio Sugaya was allowed to participate as a full GDG member as his consultation for antiviral oseltamivir discussed in this guideline ended in 2017, and the 2018 honorarium was for newer antivirals that were not reviewed in this guideline. No action.

Table 2.2. *continued*

Two temporary advisors, non-voting members participated due to their expertise in virology, but conflict of interests led to the decision to restrict their participation.
Fred Hayden: Consulting payments from University of Alabama AD3C and WHO leading to over US$ 10 000 in personal reimbursement and donations to Ford Haitian Orphanage and School (Cidara, PREP BioPharma, resTORbio, ReViral, Sequiris, Shionogi) for consulting activities. Meeting travel support from Shionogi and Roche. Payments to the University of Virginia for DSMB service (GSK, Celltrion and Vaccitech) and for consulting (Singapore IID) totalling over US$ 10 000. Service on the Infectious Disease Society of America's Influenza Task Force that provides advice regarding influenza management and antivirals – updated guidance published in *Clinical Infectious Diseases* 2018. Unpaid consultant to multiple companies engaged in developing influenza and respiratory virus antivirals and vaccines (including CoCrystal, Crucell, Genetech/Roche, Gilead, GSK, Biocryst, FujiFilm/Toyama/Medivector, Alios/Janssen/JNJ, Regeneron, Sanford Applied Biotherapeutics, Vir, Visterra). Received personal honoraria for lectures on influenza (University of Tennessee, US$ 1000, 2018; 4th China Influenza Forum, US$ 3000, 2019); royalties from ASM Press for textbook *Clinical Virology* (US$ 1974, 2018); and engaged in certified continuing medical education activities (talks and publication) related to influenza clinical management organized by companies (Vindico, Practicing Clinicians Exchange) that made charitable donations to Ford Haitian Orphanage and School for his time. Participation restricted and not allowed to vote on recommendations.
Mike Ison: Research and consulting support from Genentech/Roche, Celltrion, Janssen, Viracor, Virbio, Aicuris, Chimerix, Emerging Bioscience, Gilead, Shire, DSMB service, GSK, Shionogi leading totalling over US$ 10 000 reimbursement. Participation restricted to non-voting member and not allowed to vote on recommendations.

One presenter had a conflict of interest and no action was taken.
Barnaby Young: On advisory board for Roche to discuss their strategy for baloxavir. The board met in January 2018 and was primarily concerned with prioritizing further research studies with baloxavir. He gave a talk in December 2018 for Roche about how severe influenza is managed in Singapore. Both engagements were one-off events, and honorarium of SGD 1500 for each was paid to his employer. His role was as presenter on adjunctive therapies, not antivirals. As presenter, he was a non-voting member. No action.

One external reviewer had a conflict of interest and no action was taken.
Nancy Bellei: Consultancy on influenza diagnostics with Abbott, received kit donation value < US$ 1000. Consulting advisor for baloxavir with Roche, received < US$ 1000, ceased in 2018. Speaker at Abbott sponsored symposium on point-of-care testing, received < US$ 1000, ceased 2019. Non-monetary support from Abbott for influenza point-of-care diagnostics, received US$ 6000 work of diagnostics, ongoing. Expert consultant for the Ministry of Health in Brazil, unpaid. Speaker at training for physicians before influenza season, sponsored by UNIMED insurance company, received US$ 1200, ceased 2019. No action.

The remaining GDG members, temporary advisors, presenters, and external reviewers had no conflict of interest.

2.5 Financial support

This guideline was funded by WHO.

2.6 Dissemination

The final document will be broadly disseminated by WHO in open-access format. This guideline will be submitted to a peer-reviewed journal. It will be presented at relevant conferences and posted on the appropriate websites. In addition, in keeping with recent recommendations on data sharing *(33)*, the steering committee will encourage other organizations to disseminate or endorse it, whether or not they choose to make modifications beforehand.

2.7 Previous guidelines and updating of the current guideline

This guideline supersedes the 2010 guideline entitled *WHO Guidelines for pharmacological management of pandemic influenza A(H1N1) and other influenza viruses*.

An updated guideline will include a broader GDG composition (including patient and health care decision-maker representatives), strategies to learn about patient values and preferences with respect to treatment decisions for influenza, and will consider indirect evidence related to adjunctive therapies of severely ill patients with COVID-19.

3. Recommendations on antivirals – neuraminidase inhibitors

3. RECOMMENDATIONS ON ANTIVIRALS – NEURAMINIDASE INHIBITORS

General remark: as shown for each recommendation, subgroup analyses were either not possible due to limitations of available evidence, or there were no credible subgroup effects.

3.1 Oseltamivir (oral)

RECOMMENDATION 1

In persons with suspected or confirmed influenza virus infection with or at risk of severe illness (i.e. including seasonal influenza, pandemic influenza and zoonotic influenza), **we suggest administering oseltamivir as soon as possible (vs not administering oseltamivir)** (conditional recommendation, low-quality evidence).

Rationale

The recommendation was based on low-quality evidence for critical outcomes. All RCT data included patients who did not have, or were not at risk of, severe illness and, generally, a mix of patients with suspected and confirmed influenza virus infection; most patients in non-randomized studies (NRS) were inpatients with confirmed influenza virus infection. Immortal time bias in NRS was discussed but was not concerning to GDG members due to timing of death in untreated patients beyond the time window for treatment of influenza.

Values and preferences/feasibility and accessibility/acceptability

The GDG was confident that there would be limited variability in the values and preferences of patients and their families with regard to the evidence presented, given that signals for the benefit of oseltamivir were concordant across outcomes and there were no signals of harm.

The GDG considered that the intervention was feasible and accessible in most clinical settings: administered orally; limited monitoring required other than dose adjustments for reduced renal function. For children unable to swallow capsules, if the liquid form is not available, it is possible to open the capsule and dilute its content in water. Cost was not perceived as a significant barrier by the GDG. The GDG agreed the intervention is acceptable to patients and clinicians.

Implementation considerations

In patients tested for influenza, oseltamivir should be stopped if a highly sensitive test (e.g. batch PCR or molecular influenza assay) shows no evidence of influenza virus infection in appropriately collected respiratory tract specimens. When the decision to use oseltamivir is made, it should be administered as soon as possible *(34, 35)*. Detailed considerations for administration are detailed by the U S Food and Drug Administration *(36)*.

In jurisdictions where oseltamivir is already on a formulary, a conditional recommendation is not intended to lead to its removal. In jurisdictions where oseltamivir is not on a formulary, a conditional recommendation suffices to support its inclusion.

Virologic considerations and other data suggest that oseltamivir will have no effect in patients without influenza and in patients with infections due to oseltamivir-resistant viruses, e.g. A(H1N1) pdm09 viruses with H275Y substitution in NA.

Summary of the evidence

P – Persons with suspected or confirmed influenza virus infection with or at risk of severe illness, including seasonal influenza, pandemic influenza and zoonotic influenza
I – Oseltamivir
C – No oseltamivir
O –Critical outcomes (see Table 3.1)

Table 3.1. Evidence summary for oseltamivir (up to March 2018)

Outcome	Direct	Indirect	Conclusion
Mortality	8 observational studies (n=4725), aOR 0.38 (95% CI 0.19–0.75), low-quality evidence.	No data	Oseltamivir therapy may reduce mortality in this patient population. Low confidence.
Hospitalization	2 observational studies (n=14 445), aOR 0.65 (95% CI 0.48–0.87), low-quality evidence.	12 RCTs (n=7765), RR 1.07 (95% CI 0.69–1.64), low-quality evidence.	Oseltamivir may reduce hospitalization in this patient population. Low confidence.
ICU admission/mechanical ventilation	4 observational studies (n=4074), aOR 1.07 (95% CI 0.54–2.13), low-quality evidence.	No data	Oseltamivir may have little to no effect on ICU admission/ mechanical ventilation in this patient population. Low confidence.
Complications: pneumonia	2 observational studies (n=14 445), aOR 0.80 (95% CI 0.62–1.04), low-quality evidence.	12 RCTs (n=6494), RR 0.76 (95% CI 0.53–1.09), low-quality evidence.	Oseltamivir therapy may lower the risk of pneumonia in this patient population. Low confidence.
Complications: cardiac events, including myocardial infarction, stroke, angina, heart failure, sudden cardiac death	1 observational study (n=37 482), aOR 0.41 (95% CI 0.34–0.49), low-quality evidence.	6 RCTs (n=3943), RR 0.49 (95% CI 0.25–0.97), low-quality evidence.	Oseltamivir therapy may lower risk of cardiac events in this patient population. Low confidence.
Complications: neuropsychiatric events, including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide	No data	8 RCTs (n=5616), RR 0.93 (95% CI 0.43–2.03), low-quality evidence and 3 observational studies (n=359 228), aOR 0.86 (95% CI 0.79–0.93), very low-quality evidence.	Oseltamivir may have little to no effect on the risk of neuropsychiatric events in this patient population. Low confidence.
Complications: serious adverse events (SAEs)	No data	13 RCTs (n=7324), RR 0.91 (95% CI 0.56–1.46), low-quality evidence.	Oseltamivir may have little to no effect on the risk of SAEs. Low confidence.
Persistent viral shedding	No data	4 observational studies (n=449), OR 0.51 (95% CI 0.21–1.23), very low-quality evidence.	It is uncertain whether oseltamivir has any effect on persistent viral shedding. Very low confidence.
Emergence of resistance	No data	6 observational studies (n=3549), OR 1.77 (95% CI 0.84–3.74), very low-quality evidence.	It is uncertain whether oseltamivir has any effect on emergence of resistance. Very low confidence.

Note: Subgroup considerations – there were no credible subgroup effects. Most analyses could not be conducted (ward vs ICU; pregnancy; chronic comorbidities; resource-limited settings; refugees and displaced persons).

3.2 Zanamivir (inhaled)

RECOMMENDATION 2

In persons with suspected or confirmed influenza virus infection with or at risk of severe illness (i.e. including seasonal influenza, pandemic influenza and zoonotic influenza), **we suggest not administering inhaled zanamivir (vs administering inhaled zanamivir)** (conditional recommendation, very low-quality evidence).

Rationale

The recommendation is based on the **very low certainty of benefit rather than on evidence of harm.** When moving from evidence to the conditional recommendation against the use of inhaled zanamivir for the population of interest, the GDG emphasized the very low certainty that zanamivir has any effect on critical outcomes of mortality, hospitalization, or ICU admission/ mechanical ventilation (see Table 3.2). Given the very low certainty evidence for these outcomes, the GDG concluded that the evidence did not prove that zanamivir has no benefit; rather, there was no evidence based on currently available data that it improves patient-important outcomes.

While the evidence summary reviewed by the GDG contained no information on adverse respiratory reactions to this inhaled therapy, GDG members were concerned by reports of bronchospasm that improved after zanamivir was stopped *(37, 38)* and expiratory filter obstruction leading to death in a mechanically ventilated patient *(39)*.

Values and preferences/feasibility and accessibility/acceptability

The GDG was confident that there would be limited variability in the values and preferences of patients and their families with regard to the evidence presented for the outcomes. The GDG inferred that most patients would be reluctant to use zanamivir given very low certainty of any beneficial effect on critical outcomes.

The GDG recognizes that in some jurisdictions, inhaled zanamivir is widely available, and is likely to continue to be used, in otherwise healthy outpatients with suspected or confirmed influenza. Zanamivir may be unavailable or judged too expensive in most jurisdictions.

Implementation considerations

The GDG recognizes that inhaled zanamivir is used in some jurisdictions; nonetheless, the evidence review shows very low certainty of benefit in the population of interest. The GDG emphasized that the recommendation does not apply to situations where the causative strain is known or at high risk of being resistant to oseltamivir and does not apply to intravenous zanamivir, which was not addressed in the systematic review.

Summary of the evidence

P – Persons with suspected or confirmed influenza virus infection with or at risk of severe illness, including seasonal influenza, pandemic influenza and zoonotic influenza
I – Inhaled zanamivir
C – No inhaled zanamivir
O – Critical outcomes (see Table 3.2)

Table 3.2. Evidence summary for inhaled zanamivir

Outcome	Direct	Indirect	Conclusion
Mortality	1 observational study (n=87), aOR 0.47 (95% CI 0.02–8.97), very low-quality evidence.	16 RCTs, incomplete data leading to inability to generate a pooled estimate for all-cause mortality.	It is uncertain whether inhaled zanamivir therapy has any effect on the risk of death in this patient population. Very low confidence.
Hospitalization	No data	1 observational study (n=4674), aOR 0.58 (95% CI 0.30–1.13), very low-quality evidence.	It is uncertain whether inhaled zanamivir therapy has any effect on the risk of hospitalization in this patient population. Very low confidence.
ICU admission/mechanical ventilation	No data	1 observational study (n=87), aOR 1.18 (95% CI 0.29–4.83), very low-quality evidence.	It is uncertain whether inhaled zanamivir therapy has any effect on the risk of ICU admission/mechanical ventilation in this patient population. Very low confidence.
Complications: pneumonia	No data	13 RCTs (n=6613), RR 0.87 (95% CI 0.57–1.32), low-quality evidence and 1 observational study (n=4674), OR 1.17 (95% CI 0.98–1.39), very low-quality evidence.	Inhaled zanamivir therapy may have little to no effect on the risk of pneumonia in this patient population. Low confidence.
Complications: cardiac events, including myocardial infarction, stroke, angina, heart failure, sudden cardiac death	No data	11 RCTs (n=5204), RR 0.98 (95% CI 0.50–1.91), low-quality evidence.	Inhaled zanamivir therapy may have little to no effect on the risk of cardiac events in this patient population. Low confidence.
Complications: neuropsychiatric events, including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide	No data	10 RCTs (n=4732), RR 1.16 (95% CI 0.57–2.38), low-quality evidence.	Inhaled zanamivir therapy may have little to no effect on the risk of neuropsychiatric events in this patient population. Low confidence.
Complications: serious adverse events (SAEs)	No data	10 RCTs (n=4388), RR 0.86 (95% CI 0.49–1.50), low-quality evidence.	Inhaled zanamivir therapy may have little to no effect on the risk of SAEs in this patient population. Low confidence.
Persistent viral shedding	No data	2 observational studies (n=236), proportion with shedding 19% (14–24%), low-quality evidence.	It is uncertain whether zanamivir has any effect on viral shedding. Very low confidence.
Emergence of resistance	No data	2 RCTs (n=508), no events of resistance with zanamivir compared with placebo.	It is uncertain whether zanamivir has any effect on viral resistance. Very low confidence.

Note: Subgroup considerations – subgroup analyses could not be conducted.

3.3 Inhaled laninamivir

RECOMMENDATION 3

In persons with suspected or confirmed influenza virus infection with or at risk of severe illness (i.e. including seasonal influenza, pandemic influenza and zoonotic influenza), **we suggest not administering inhaled laninamivir (vs administering inhaled laninamivir)** (conditional recommendation, very low-quality evidence).

Rationale

The **recommendation is based on very low certainty of benefit rather than evidence of harm**. When moving from evidence to the conditional recommendation against the use of inhaled laninamivir for the population of interest, the GDG emphasized the very low certainty that inhaled laninamivir has any effect on critical outcomes (see Table 3.3). For mortality, hospitalization, and progression to ICU admission/mechanical ventilation, no data were available. Given the very low certainty evidence for these outcomes, the GDG concluded that the evidence did not prove that inhaled laninamivir has no benefit; rather, there was no evidence based on currently available data that it improves patient-important outcomes.

Values and preferences/feasibility and accessibility/acceptability

The GDG was confident that there would be limited variability in the values and preferences of patients and their families with regard to the evidence presented. The GDG inferred that most patients would be reluctant to use inhaled laninamivir given very low certainty of any beneficial effect on critical outcomes.

Implementation considerations

The GDG recognizes that in some jurisdictions, inhaled laninamivir is widely available, and is likely to continue to be used in otherwise healthy outpatients with suspected or confirmed influenza. Nonetheless, the evidence review shows very low certainty of benefit of inhaled laninamivir in the population of interest.

The GDG emphasized that the recommendation does not apply to situations where the causative strain is at high risk of being resistant to oseltamivir *(40)*.

Summary of the evidence

P – Persons with suspected or confirmed influenza virus infection with or at risk of severe illness, including seasonal influenza, pandemic influenza and zoonotic influenza
I – Laninamivir
C – No laninamivir
O – Critical outcomes (see Table 3.3)

Table 3.3. Evidence summary for laninamivir

Outcome	Direct	Indirect	Conclusion
Mortality	No data	1 RCT (n=639), 0 deaths reported.	There is no evidence to inform a conclusion.
Hospitalization	No data	No data	There is no evidence to inform a conclusion.
ICU admission/mechanical ventilation	No data	No data	There is no evidence to inform a conclusion.
Complications: pneumonia	No data	1 RCT (n=434), risk difference 0% (95% CI -2%–1%), very low-quality evidence, and 1 observational study (n=69 697), aOR 0.27 (95% CI 0.12–0.63), very low-quality evidence.	It is uncertain whether laninamivir has an effect on the risk of pneumonia in this patient population. Very low confidence.
Complications: cardiac events, including myocardial infarction, stroke, angina, heart failure, sudden cardiac death	No data	No data	There is no evidence to inform a conclusion.
Complications: neuropsychiatric events, including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide	No data	1 observational study (n=69 697) reported identical percentages (0.02%) of serious neuropsychiatric adverse events among patients who received laninamivir and those who did not, very low-quality evidence.	It is uncertain whether laninamivir has an effect on the risk of neuropsychiatric events in this patient population. Very low confidence.
Complications: serious adverse events (SAEs)	No data	1 RCT (n=434), risk difference 0% (95% CI -1%–1%), very low-quality evidence, and 1 observational study (n=69 697), aOR 0.28 (95% CI 0.15–0.51), very low-quality evidence.	It is uncertain whether laninamivir has an effect on the risk of SAEs in this patient population. Very low confidence.
Persistent viral shedding	No data	No data	There is no evidence to inform a conclusion.

Note: Subgroup considerations – subgroup analyses could not be conducted.

3.4 Peramivir (intravenous)

RECOMMENDATION 4

In persons with suspected or confirmed influenza virus infection with or at risk of severe illness (i.e. including seasonal influenza, pandemic influenza and zoonotic influenza), **we suggest not administering intravenous peramivir (vs administering intravenous peramivir)** (conditional recommendation, very low-quality evidence).

Rationale

The recommendation is based on **very low certainty of benefit rather than evidence of harm**. When moving from evidence to the conditional recommendation against the use of intravenous peramivir for the population of interest, the GDG emphasized the very low certainty that intravenous peramivir has any effect on critical outcomes (see Table 3.4). For mortality, hospitalization, and progression to ICU admission/mechanical ventilation, no data were available. Given the very low certainty evidence for these outcomes, the GDG concluded that the evidence did not prove that intravenous peramivir has no benefit; rather, there was no evidence based on currently available data that it improves patient-important outcomes.

Values and preferences/feasibility and accessibility/acceptability

The GDG were confident that there would be limited variability in the values and preferences of patients and their families with regard to the evidence presented. The GDG inferred that most patients would be reluctant to use intravenous peramivir given very low certainty of any beneficial effect on critical outcomes.

Implementation considerations

The GDG recognizes that peramivir is administered intravenously and could be used instead of oral oseltamivir, inhaled zanamivir or inhaled laninamivir, when patients are not able to take oral or inhaled NAIs or an oral medication is contraindicated (such as ileus, malabsorption or gastric outlet obstruction). Nonetheless, the evidence review shows very low certainty of benefit of intravenous peramivir in the population of interest.

Summary of the evidence

P – Persons with suspected or confirmed influenza virus infection with or at risk of severe illness, including seasonal influenza, pandemic influenza and zoonotic influenza
I – Peramivir
C – No peramivir
O –Critical outcomes (see Table 3.4)

Table 3.4. Evidence summary for peramivir

Outcome	Direct	Indirect	Conclusion
Mortality	1 RCT (n=121), risk difference -5% (95% CI -12%–2%), very low-quality evidence.	No data	It is uncertain whether peramivir therapy has an effect on mortality in this patient population. Very low confidence.
Hospitalization	No data	No data	There is no evidence to inform a conclusion.
ICU admission/mechanical ventilation	No data	No data	There is no evidence to inform a conclusion.
Complications: pneumonia	1 RCT (n=121), RR 1.10 (95% CI 0.35–3.45), low-quality evidence.	No data	It is uncertain whether peramivir therapy has an effect on mortality in this patient population. Low confidence.
Complications: cardiac events, including myocardial infarction, stroke, angina, heart failure, sudden cardiac death	No data	No data	There is no evidence to inform a conclusion.
Complications: neuropsychiatric events, including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide	No data	No data	There is no evidence to inform a conclusion.
Complications: serious adverse events (SAEs)	No data	3 RCTs (n=1042), RR 0.48 (95% CI 0.17–1.38), very low-quality evidence.	It is uncertain whether peramivir therapy has an effect on the risk of SAEs in this patient population. Very low confidence.
Persistent viral shedding	No data	1 observational study (n=281), risk difference 0.5% (95% CI -1%–2%), very low-quality evidence.	It is uncertain whether peramivir therapy has an effect on the risk of viral shedding in this patient population. Very low confidence.
Emergence of resistance	No data	1 observational study (n=144), no resistance reported with peramivir or placebo, very low-quality evidence.	There is no evidence to inform a conclusion. Very low confidence.

Note: Subgroup considerations – subgroup analyses could not be conducted.

4. Recommendations on adjunctive therapies

4. RECOMMENDATIONS ON ADJUNCTIVE THERAPIES

General remark: as shown for each recommendation, subgroup analyses were either not possible due to limitations of available evidence, or there were no credible subgroup effects.

4.1 Corticosteroids

RECOMMENDATION 5

In persons with suspected or confirmed influenza virus infection with or at risk of severe illness (i.e. including seasonal influenza, pandemic influenza and zoonotic influenza), **we suggest not administering corticosteroids (vs administering corticosteroids)** (conditional recommendation, very low-quality evidence).

Rationale

There are no RCTs to inform this question. This recommendation, based on observational studies, **acknowledges the signal for increased risk of mortality with corticosteroids, although this finding is confounded by indication and time-dependent biases**. Thus, data from observational studies support the conditional recommendation against corticosteroids for the sole indication of suspected or confirmed influenza virus infection with or at risk of severe illness *(41, 42)*.

Values and preferences/feasibility and accessibility/acceptability

The GDG was confident that there would be limited variability in the values and preferences of patients and their families with regard to the evidence presented. The GDG inferred that most patients would be reluctant to use corticosteroids given very low certainty evidence suggesting harm. The GDG recognizes that corticosteroids are generally widely available and generally inexpensive

Implementation considerations

Clinicians should still consider administration of corticosteroids for other concurrent indications, when consistent with other recommendations. Examples include exacerbations of asthma *(43)* or COPD *(44)* and septic shock *(45)*.

Summary of the evidence

P – Persons with suspected or confirmed influenza virus infection with or at risk of severe illness, including seasonal influenza, pandemic influenza and zoonotic influenza
I – Corticosteroids
C – No corticosteroids
O –Critical outcomes (see Table 4.1)

Table 4.1. Evidence summary for corticosteroids

Outcome	Direct	Conclusion
Mortality	1. Crude mortality, 11 observational studies (n=8409), OR 2.84 (95% CI 2.12–3.80), very low-quality evidence. 2. Adjusted mortality, 6 observational studies (n=1277), aOR 2.46 (95% CI 1.49–4.06), low-quality evidence. 3. Adjusted mortality, 5 observational studies (n=7132), adjusted hazard ratio 1.32 (95% CI 0.95–1.85), low-quality evidence.	Corticosteroids may increase the risk of death in this patient population. Overall very low confidence considering all mortality analyses.
Hospitalization	1 observational study (n=2649), β 3.15 for corticosteroids (95% CI 2.19–4.10), considering hospital survivors only; β 1.54 for corticosteroids (95% CI -0.02–3.11), considering hospital survivors with respiratory failure at baseline only. Another observational study (n=604) reported fewer ventilator-free days at Day 28 (mean 12.5 (SD 10.7) vs 15.7 (10.1) days, $p < 0.001$) and fewer ICU-free days at Day 28 (mean 9.5 (9.9) vs 13.2 (9.4) days, $p < 0.001$) in patients who received corticosteroids, very low-quality evidence.	Corticosteroids may increase the duration of hospitalization in this patient population. Very low confidence.
ICU admission/mechanical ventilation	No data	There is no evidence to inform a conclusion.
Complications: pneumonia	No data	There is no evidence to inform a conclusion.
Complications: cardiac events, including myocardial infarction, stroke, angina, heart failure, sudden cardiac death	No data	There is no evidence to inform a conclusion.
Complications: neuropsychiatric events, including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide	No data	There is no evidence to inform a conclusion.
Complications: serious adverse events (SAEs)	No data	There is no evidence to inform a conclusion.
Emergence of resistance	No data	There is no evidence to inform a conclusion.
Complications: nosocomial infections	1 observational study (n=315) found no difference in hospital-acquired respiratory or bloodstream infections (35.7% with corticosteroids and 31.0% without corticosteroids, $p = 0.50$). Another observational study (n=130) found no difference in nosocomial infection (hospital-acquired pneumonia; hospital-acquired pneumonia with bacteraemia; nosocomial bacteraemia or candidaemia; invasive pulmonary aspergillosis or mucormycosis – all considered separately), p 0.289–1.000, very low-quality evidence.	Corticosteroids may have no effect on the incidence of nosocomial infection in this patient population. Very low confidence.

Note: Subgroup considerations – there was no credible subgroup effect for ward vs ICU patients. Other subgroup effects could not be examined. IQR: interquartile range; SD: standard deviation.

4.2 Passive immune therapy

RECOMMENDATION 6

In persons with suspected or confirmed influenza virus infection with or at risk of severe illness (i.e. including seasonal influenza, pandemic influenza and zoonotic influenza), **we suggest not administering passive immune therapy (vs administering passive immune therapy)** (conditional recommendation, very low-quality evidence).

Rationale

This recommendation is based on **insufficient evidence for benefit rather than evidence for harm.** When moving from evidence to the conditional recommendation against the use of passive immune therapy for the population of interest, the GDG emphasized the very low to low certainty that passive immune therapy has any effect on critical outcomes (see Table 4.2). Given the very low to low certainty evidence for these outcomes, the GDG concluded that the evidence did not prove that passive immune therapy has no benefit; rather, there was no evidence based on currently available data that it improves patient-important outcomes.

Values and preferences/feasibility and accessibility/acceptability

The GDG was confident that there would be limited variability in the values and preferences of patients and their families with regard to the evidence presented. The GDG inferred that most patients would be reluctant to use passive immune therapy given very low to low certainty of any beneficial effect on critical outcomes. The GDG recognizes that passive immune therapy may have very limited availability due to the technical expertise and cost required for blood product fractionation and manufacture.

Implementation considerations

This recommendation may change with additional data from ongoing RCTs.

Summary of the evidence

P – Persons with suspected or confirmed influenza virus infection with or at risk of severe illness, including seasonal influenza, pandemic influenza and zoonotic influenza
I – Passive immune therapy (including convalescent plasma and hyperimmune immunoglobulin)
C – No passive immune therapy
O – Critical outcomes (see Table 4.2)

Table 4.2. Evidence summary for passive immune therapy (no indirect data)

Outcome	Direct	Conclusion
Mortality	4 RCTs (n=562), OR 0.84 (95% CI 0.37–1.90), low-quality evidence; 4 RCTs and 1 observational study (n=655), aOR 0.56 (95% CI 0.24–1.33), very low-quality evidence.	Passive immune therapy may have no effect on the risk of mortality in this patient population. Very low confidence.
Clinical outcomes at Day 7 on an ordinal scale	The six categories on this scale were: 1) death; 2) hospitalization in ICU; 3) non-ICU hospitalization, requiring supplemental oxygen; 4) non-ICU hospitalization, not requiring supplemental oxygen; 5) not hospitalized, but unable to resume normal activities; or 6) not hospitalized with full resumption of normal activities. 3 RCTs (n=528), aOR 1.42 (95% CI 1.05–1.92), low-quality evidence. Note: an aOR of > 1 indicated better outcomes (a higher score) with passive immune therapy.	Passive immune therapy may improve outcomes at Day 7 in this patient population. Low confidence. Note: this outcome is not considered a critical outcome because it is a non-standard ordinal scale of possible clinical outcomes, and was not based on mortality alone.
Hospitalization	1 RCT (n=138) found no difference in length of hospitalization (median [IQR] 5 [3–12] vs 6 [4–12] days, p = 0.30), in patients who received high-titre vs control plasma, low-quality evidence. 1 RCT (n=87) found no difference in length of hospitalization (median [IQR] 6 [4–16] vs 11 [5–25] days, p = 0.13), in patients who received high-titre plasma plus standard of care vs standard of care alone, low-quality evidence. 1 RCT (n=34) found no difference in length of hospitalization (median [IQR] 16 [11.5–13.5] vs 16 [7–29] days, p = NS), in patients who received hyperimmune immunoglobulin vs immunoglobulin, low-quality evidence.	Passive immune therapy may have no effect on the length of hospitalization in this patient population. Low confidence.
ICU admission/mechanical ventilation	1 RCT (n=78) found no difference in proportion of patients progressing to intensive care (3% in high-titre group vs 0% in control, p = 0.55), low-quality evidence. 1 RCT (n=99) found no difference in the proportion of patients progressing to mechanical ventilation (3% in high-titre group vs 4% in control, p = 1.00), low-quality evidence. 1 RCT (n=39) found no difference in length of mechanical ventilation (median [IQR] 9 [4–16] vs 15.5 [7–29] days, p = 0.22), in patients who received high-titre vs control plasma, low-quality evidence. 1 RCT (n=87) found no difference in length of mechanical ventilation (median [IQR] 0 [0–6] vs 3 [0–14] days, p = 0.14), in patients who received high-titre plasma plus standard of care vs standard of care alone, low-quality evidence.	Passive immune therapy may have no effect on progression to intensive care in this patient population. Low confidence. Passive immune therapy may have no effect on the progression to mechanical ventilation in this patient population. Low confidence. Passive immune therapy may have no effect on the length of mechanical ventilation in this patient population. Low confidence.
Complications: infections	2 RCTs (n=406), RR 0.82 (95% CI 0.33–2.07), low-quality evidence.	Passive immune therapy may have no effect on infections in this patient population.
Complications: cardiac events, including myocardial infarction, stroke, angina, heart failure, sudden cardiac death	2 RCTs (n=406) RR 0.62 (95% CI 0.15–2.56), low-quality evidence.	Passive immune therapy may have no effect on cardiac complications in this patient population. Low confidence.
Complications: neuropsychiatric events, including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide	2 RCTs (n=406) RR 1.04 (95% CI 0.11–9.91), low-quality evidence.	Passive immune therapy may have no effect on neuropsychiatric complications in this patient population. Low confidence.

Table 4.2. *continued*

Outcome	Direct	Conclusion
Complications: serious adverse events (SAEs)	3 RCTs (n=544), RR 0.79 (0.46–1.36), moderate quality evidence. 1 RCT (n=34) reported no SAEs in patients receiving hyperimmune immunoglobulin or immunoglobulin, low-quality evidence. 1 observational study reported no SAEs in 20 patients receiving convalescent plasma, very low-quality evidence.	Passive immune therapy may have no effect on the number of SAEs in this patient population. Very low confidence.
Persistent viral shedding	1 RCT (n=270), no difference in change of viral load from baseline to Day 3 ($p = 0.49$) after adjusting for confounders between patients who received anti-influenza hyperimmune intravenous immunoglobulin vs placebo, high-quality evidence. 1 RCT (n=138), OR for virus in oropharyngeal sample at Day 3, 0.47 (95% CI 0.13–1.43), low-quality evidence. 1 RCT (n=34) showed faster respiratory viral load reduction in the hyperimmune immunoglobulin group ($p = 0.04$ and $p = 0.02$ at Day 5 and 7 post treatment; no difference on Days 1–3), low-quality of evidence. 1 observational study (n=44 with data) showed lower respiratory tract viral load at Day 3 ($p < 0.001$), Day 5 ($p = 0.02$), Day 7 ($p = 0.04$), but not Day 9 ($p = 0.90$) in patients who received convalescent plasma vs control, very low-quality evidence.	Passive immune therapy may not reduce viral shedding in this patient population. Very low confidence.
Emergence of resistance	No data	There is no evidence to inform a conclusion.

Note: Subgroup considerations – subgroup effects could not be examined. NS: not significant.

4.3 Macrolide antibiotics

RECOMMENDATION 7

In persons with suspected or confirmed influenza virus infection with or at risk of severe illness (i.e. including seasonal influenza, pandemic influenza and zoonotic influenza), **we suggest not administering a macrolide antibiotic for treatment of influenza (vs administering a macrolide)** (conditional recommendation, very low-quality evidence).

Rationale

This recommendation is based on **insufficient evidence for benefit rather than evidence for harm**. When moving from evidence to the conditional recommendation against the use of macrolide antibiotics for the population of interest, the GDG emphasized the very low to low certainty that macrolides have any effect on critical outcomes (see Table 4.3). Given the very low to low certainty evidence for these outcomes, the GDG concluded that the evidence did not prove that macrolides have no benefit; rather, there was no evidence based on currently available data that they improve patient-important outcomes.

Values and preferences/feasibility and accessibility/acceptability

The GDG was confident that there would be limited variability in the values and preferences of patients and their families with regard to the evidence presented. The GDG inferred that most patients would be reluctant to use macrolides given very low to low certainty of any beneficial effect on critical outcomes. The GGD noted that macrolides may be used to treat bacterial co-infection.

Summary of the evidence

P – Persons with suspected or confirmed influenza virus infection with or at risk of severe illness, including seasonal influenza, pandemic influenza and zoonotic influenza
I – Macrolide
C – No macrolide
O –Critical outcomes (see Table 4.3)

Table 4.3. Evidence summary to macrolides (no direct data)

Outcome	Indirect	Conclusion
Mortality	1 RCT with events (n=217), OR 0.11 (95% CI 0.01–0.85), low-quality evidence. 1 RCT and 1 observational study (n=950), adjusted OR 0.33 (95% CI 0.03–4.08); very low-quality evidence. The RCT had a combined intervention of a macrolide and a non-steroidal anti-inflammatory drug (NSAID).	It is uncertain whether macrolides have an effect on the risk of mortality in this patient population. Very low confidence based on both mortality analyses.
Hospitalization	1 RCT (n=217), median [IQR] acute care hospital days, 2 [1–3] (macrolide + NSAID) vs 3 [2–4] (control), $p < 0.001$, low-quality evidence.	Macrolides may reduce length of hospitalization in this patient population. Low confidence.
ICU admission/mechanical ventilation	1 RCT (n=217), 1.9% on mechanical ventilation during hospitalization (macrolide + NSAID) vs 5.5% (control), p = 0.16, very low-quality evidence. 1 RCT (n=217), 1.9%/15.9% admitted to ICU/high dependency unit (HDU) during hospitalization (macrolide + NSAID) vs 6.4%/30.9% (control), p = 0.10/p = 0.009, very low-quality evidence.	It is uncertain whether macrolides have an effect on the risk of progression to mechanical ventilation in this patient population. Very low confidence. It is uncertain whether macrolides have an effect on the risk of progression to ICU/HDU admission in this patient population. Very low confidence.
Complications: pneumonia	No data	There is no evidence to inform a conclusion.
Complications: cardiac events, including myocardial infarction, stroke, angina, heart failure, sudden cardiac death	No data	There is no evidence to inform a conclusion.
Complications: neuropsychiatric events, including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide	No data	There is no evidence to inform a conclusion.
Complications: serious adverse events (SAEs)	No data	There is no evidence to inform a conclusion.
Persistent viral shedding	No data	There is no evidence to inform a conclusion.
Emergence of resistance	No data	There is no evidence to inform a conclusion.
Complication: nosocomial infection	1 RCT (n=217), 5.6% developed nosocomial infection (macrolide + NSAID) vs 5.5% (control), p = 0.96, very low-quality evidence.	It is uncertain whether macrolides have an effect on the nosocomial infection in this patient population. Very low confidence.

Note: Subgroup considerations – subgroup effects could not be examined. NS: not significant.

5. Diagnostic tests for clinical decision-making: treat or not treat

5. DIAGNOSTIC TESTS FOR CLINICAL DECISION-MAKING: TREAT OR NOT TREAT

5.1 Recommendations 8 and 9

When influenza viruses are suspected or known to be circulating in the community, in patients presenting to the emergency department (or equivalent area for assessment of acutely ill patients) with signs and symptoms suggestive of influenza (suspected influenza), with or at risk for severe illness, the recommended testing strategy depends on the diagnostic test characteristic and expected timing of results.

RECOMMENDATION 8

In settings where batch RT-PCR or other rapid molecular influenza assays (with similar high sensitivity and high specificity) are available and results expected within 24 hours, we suggest a strategy of testing for influenza, treating with oseltamivir as soon as possible, and re-evaluating treatment when the test result is available (conditional recommendation, low-quality evidence).

RECOMMENDATION 9

In settings where batch RT-PCR or other rapid molecular influenza assays (with similar high sensitivity and high specificity) are not available to provide results within 24 hours, we suggest a strategy of not testing for influenza and treating with oseltamivir as soon as possible (conditional recommendation, low-quality evidence).

5.2 Rationale

These recommendations are conditional because they are not derived from randomized trials of testing strategies. Instead, they are derived from a decision analysis model with input parameters for diagnostic test characteristics (including the performance of clinical judgment), illness epidemiology, treatment effects, and utilities, many of which are based on low-quality evidence. The decision analysis used data from high-income countries, and did not formally incorporate costs.

The "treat everyone" and "batch RT-PCR – treat" strategies were ranked first and second for impact on quality-adjusted life years (QALY), respectively. The other strategies involving point-of-care diagnostic tests: (A) rapid influenza diagnostic test (RIDT); (B) digital immunoassay (DIA); and (C) nucleic acid amplification test (NAAT); were ranked lower (see Table 5.1) because sensitivity was inferior to batch RT-PCR, as reported in a systematic review *(15)*. Commercially available molecular influenza assays *(16)* were not included in the decision-making model and thus not ranked.

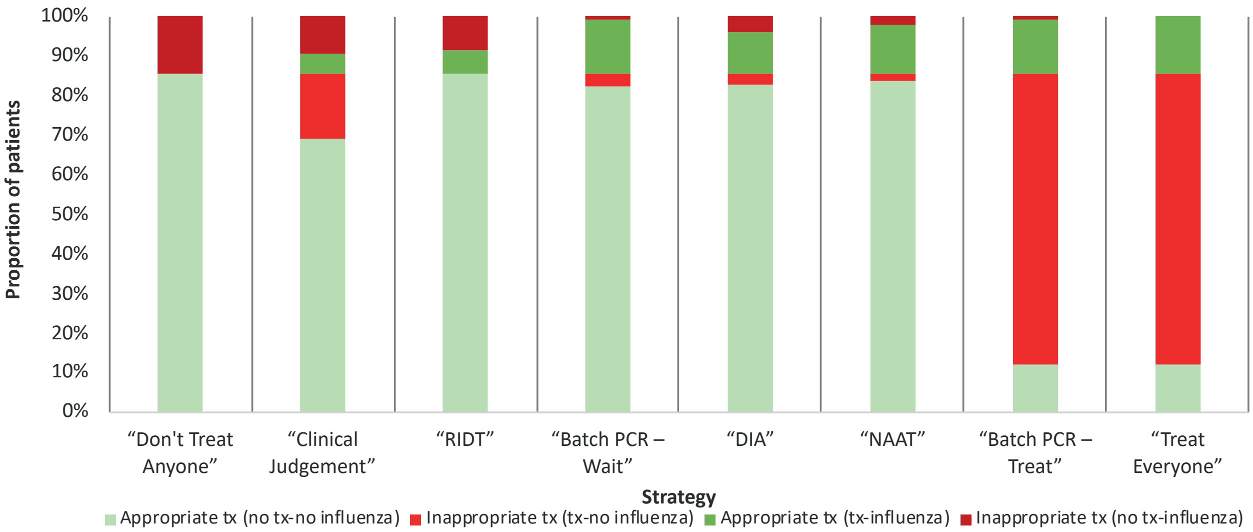
5.3 Values and preferences/feasibility and accessibility/ acceptability

The GDG placed high value on knowledge of results of diagnostic testing, which would be expected to inform other diagnostic investigations and treatments, and on limiting NAI treatment of patients shown not to have influenza. For settings where batch RT-PCR or an equally performing rapid molecular assay are available and results expected within 24 hours, **the recommendation is for the second ranked strategy** of "batch RT-PCR – treat", because of additional considerations of these values and preferences. With the "treat everyone" strategy, all patients with suspected influenza who in fact do not have influenza are treated, thereby increasing wasted NAI utilization and costs.

Other settings may have no access to batch RT-PCR (or an equally performing rapid molecular assay), or the turnaround time for testing may be very long (e.g. > 48 hours). These situations may be due to financial and logistical barriers to batch RT-PCR acquisition, training of laboratory personnel, or establishment of a laboratory network that can serve all emergency departments (or equivalent areas for assessment of acutely ill patients). In these circumstances, "treat everyone" may be the only feasible approach and will yield maximum QALYs of the strategies tested. However, the GDG acknowledges that approach has several risks: treating non-influenza illnesses with NAIs: depleting financial resources and NAI supply; and diagnostic closure, whereby other diagnoses may not be pursued.

See Fig. 5.1 for treatment appropriateness (proportion of patients with influenza who are appropriately treated and proportion of patients without influenza who are inappropriately treated) under the scenarios examined.

Fig. 5.1. Treatment appropriateness



Notes:

1. "Inappropriate tx (tx – no influenza)" – (number of patients treated, but did not have influenza)/(total number of patients treated)
2. "Inappropriate tx (no tx – influenza)" – (number of patients with influenza, and not treated)/(total number of patients with influenza)
3. "Appropriate tx (tx – influenza)" – (number of patients with influenza, and treated)/(total number of patients with influenza)

"Inappropriate tx (no tx – influenza)" and "Appropriate tx (tx – influenza)" are complementary proportions and sum up to 1.
"Inappropriate tx (tx – no influenza)" and "Appropriate tx (no tx – no influenza)" are complementary proportions and sum up to 1.
DIA: digital immunoassay, NAAT: nucleic acid amplification test, RT-PCR: reverse transcription polymerase chain reaction, QALY: quality-adjusted life year, RIDT: rapid influenza diagnostic test, tx: treatment.

5.4 Implementation considerations

Adaptation of this recommendation to low- and middle-income countries would require a decision analysis accounting for differences in diagnostic test parameters, treatment benefits and seasonal prevalence of influenza compared with high-income settings; costs of treatment and diagnostic tests had little impact on cost-effectiveness in the decision analysis.

In some settings, other commercial rapid molecular influenza assay tests *(16)* may be available but these were not included in this review. Also, point-of-care rapid tests may be used differently from the circumstances of included studies, for example, earlier in the course of illness. If such tests are shown to have similar high sensitivity as batch RT-PCR, then they would be expected to achieve a higher ranking in the decision analysis *(15, 16)*. Such tests would then be preferred because of minimization of adverse events (very few patients without influenza treated inappropriately) and maximization of patients with influenza identified and treated.

In some settings, where "treat everyone" is the only feasible approach, then efforts should be made to establish influenza sentinel surveillance (to better inform the prior probability that a patient with suspected influenza has influenza) and diagnostic testing (batch RT-PCR or equally performing molecular influenza assays).

Detailed information about optimal specimen collection and test interpretation, can be found in other published influenza clinical practice guidelines *(17)*.

5.5 Summary of the evidence

Population: patients presenting to the emergency department (or equivalent area for assessment of acutely ill patients) with signs and symptoms suggestive of influenza (suspected influenza), who are either severely ill or who have risk factors for severe illness.

Interventions: diagnostic strategies:
1. No test, and do not treat anyone with ILI with a NAI ("don't treat anyone").
2. No test and treat everyone with ILI with a NAI ("treat everyone").
3. Test all patients with a rapid point-of-care test and treat positives with a NAI.
4. Test all patients with batch RT-PCR assay, and treat with a NAI until results become available at 24 hours ("batch RT-PCR – treat").
5. Test all patients with batch RT-PCR, but do not treat with a NAI until results are available at 24 hours ("batch RT-PCR – wait").

For strategy 3, three diagnostic tests were evaluated, each of which gives a test result within 30 minutes or less: a) rapid influenza diagnostic test (RIDT); b) digital immunoassay (DIA); and c) nucleic acid amplification test (NAAT). In addition, "clinical judgment" was evaluated.

Outcomes: modelled QALYs; hospitalization; mortality; adverse events; proportions of patients with and without influenza treated appropriately.

The strategy of "treat everyone" was associated with the highest number of QALYs, and "batch RT-PCR – treat" was associated with the second highest number of QALYs in the base case. In the base model, there is a low probability of adverse events from NAIs, a low disutility (utility decrement) associated with adverse events (e.g. nausea and vomiting), NAI treatment is available, and there is no harm (disutility), other than possible adverse events associated with treatment, for inappropriately treating suspected influenza patients who do not have influenza with NAIs.

"Batch RT-PCR – treat" was the top-ranked strategy if adverse events of NAIs became more common (≥ 40% of those treated), if the disutility of adverse events increased, or if batch RT-PCR had near perfect sensitivity (> 0.995). See Table 5.1 for base-case results.

Table 5.1. Base-case results (health outcomes and QALYs)

	Health outcomes (per 100 000)			
Strategy	**Adverse events**	**Hospitalization**	**Mortality**	**QALYs**
"Treat everyone"	7599	1281	1499	15.0477
"Batch PCR – treat"	2297	1304	1542	15.0457
"NAAT"	1084	1326	1556	15.0411
"DIA"	1064	1370	1601	15.0343
"Batch PCR – wait"	1341	1296	1674	15.0252
"RIDT"	695	1479	1708	15.0178
"Clinical judgment"	2060	1500	1722	15.0148
"Don't treat anyone"	378	1637	1805	14.9961

As stated above, this decision analysis does not take into account the risk of treating non-influenza illnesses with NAIs if diagnostic testing is not pursued, which may deplete financial resources and NAI supply and lead to diagnostic closure for individual patients, whereby other diagnoses may not be pursued. The risk of inappropriate treatment of patients without influenza with the "batch PCR – treat" approach (vs the "batch PCR – wait") approach was not felt to be of crucial importance because the duration of such inappropriate treatment would be short-lived (1 or 2 days).

6. Knowledge gaps/research priorities

6. KNOWLEDGE GAPS/RESEARCH PRIORITIES

The GDG acknowledged research gaps regarding the effectiveness of anti-influenza therapies that should be addressed given the large number of patients affected yearly, predictability of yearly outbreaks, and global health burden. Priority areas for future study include:

- Randomized clinical trials, including adaptive trials in patients with suspected or confirmed influenza and severe illness:
  - oseltamivir vs no oseltamivir
  - other neuraminidase inhibitor (peramivir, zanamivir or lanamivir) vs not
  - oseltamivir vs oseltamivir and adjunctive therapy
  - combination antivirals vs single antiviral
  - combination antivirals and immunomodulators vs single antiviral
  - optimal therapy in oseltamivir resistance.

- Development of a set of core outcomes, including other endpoints that would serve as a reliable surrogate for mortality.

- Treatment strategies in additional subgroups:
  - immunocompromised patients with influenza, focused on resource-limited settings with high prevalence of severe malnutrition and tuberculosis
  - influenza B.

- Linked diagnostic and treatment strategies for patients with suspected influenza:
  - treat all suspected cases early vs delayed treatment until diagnostic confirmation.

- Other interventions:
  - concurrent antibiotics in critically ill patients with influenza virus infection
  - optimizing supportive care and advanced organ support for critically ill patients with influenza virus infection.

Note on baloxavir: GDG acknowledges that baloxavir is now approved in several countries for early treatment of uncomplicated influenza, *(20)* but it was not included in this guidance because there were no published data on baloxavir treatment of patients with influenza virus infection with or at risk for severe illness when the systematic reviews were commissioned. Clinical trials are currently ongoing on this population and once results are available, this guidance will be updated.

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Annexes

ANNEX 1. TABLE OF OUTCOMES

Outcomes were prioritized by GDG members using a 10-point scale of importance. Critical outcomes had a median score of 7 or higher, whereas important but non-critical outcomes had a median score of 4 to 6. The outcomes of ICU admission and mechanical ventilation are generally not reported separately and therefore the GDG grouped these into a single outcome.

Importance	Outcome	Median (IQR) score (out of 10)
Critical	Hospital mortality	8 (8–8.5)
	ICU mortality	8 (7–8)
	Progression of disease severity to hospitalization	8 (7–8)
	Progression of disease severity to ICU admission	8 (6.75–8.5)
	28-day mortality	7 (6.75–8)
	Progression to mechanical ventilation	7 (6–8)
Important	90-day mortality	6 (5–8.5)
	Emergence of resistance	6 (5–6.5)
	Development of complications	6 (4–7)
	Duration of viral shedding	5 (4–7)
	Adverse events relating to interventions	5 (4–7)
	Length of mechanical ventilation	5 (4–6.5)
	Length of hospitalization	5 (4–5)
	Duration of symptoms	4 (3–5.5)

Note: IQR: interquartile range.

ANNEX 2. GUIDELINE DEVELOPMENT GROUP MEMBERSHIP

WHO Steering Committee 2017–2019

Isabel Bergeri	IHM/WHE	Headquarters
Sylvie Briand	IHM/WHO	Headquarters
Natalie Broutet	WHO	Headquarters
Shoshanna Goldin	IHM/WHE	Headquarters
Masaya Kato	Influenza	Western Pacific Region
Nicola Malgrini	EML/WHO	Headquarters
Ann Moen	IHM/WHE	Headquarters
Dina Pfeifer	IHM/WHE	European Region
Angel Rodriguez	Influenza	Region of the Americas
Gina Samaan	IHM/WHE	Headquarters
Katelijn Vandemaele	IHM/WHE	Headquarters
Adriana Velazquez Berumen	EDL/WHO	Headquarters
Wilson Were	IMCI/WHO	Headquarters
Wenqing Zhang	IHM/WHE	Headquarters

Notes: EDL: Essential In Vitro Diagnostics List; EML: Essential Medicines List; IHM: Infectious Hazard Management; IMCI: Integrated Management of Childhood Illness; WHE: WHO Health Emergencies Programme.

GDG membership

Name	Affiliation	Region	2017	2019
Neill Adhikari, methodologist, co-chair, non-voting	Sunnybrook Health Sciences Centre and University of Toronto, Canada	Region of the Americas	●	●
François Lamontagne, methodologist, co-chair, non-voting	Université de Sherbrooke, Sherbrooke, Quebec, Canada	Region of the Americas		●
Gordon Guyatt, methodologist and co-chair, non-voting	Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University, Canada	Region of the Americas	●	
Yaseen Arabi	King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia	Eastern Mediterranean Region	●	
Lucille Blumberg	National Institute for Communicable Diseases, Johannesburg, South Africa	African Region	●	
Abdullah Brooks	International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh	South-East Asia Region	●	
Tawee Chotpitayasunondh	Queen Sirikit National Health Institute of Child Health Bangkok, Thailand	South-East Asia Region	●	●
Vu Quoc Dat	Hanoi Medical University, Viet Nam	South-East Asia Region		●

Name	Affiliation	Region	2017	2019
Robert Fowler	Sunnybrook Health Sciences Centre and University of Toronto, Canada	Region of the Americas	●	
Menno de Jong	VU University Medical Centre, Amsterdam, Netherlands	European Region		●
Zhancheng Gao	Peking University People's Hospital, Beijing, China	Western Pacific Region	●	●
Andy Gray	Division of Pharmacology, Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal, South Africa	African Region	●	●
Rashan Haniffa	University College London, London, United Kingdom/Network For Improving Critical-Care Systems And Training, Colombo, Sri Lanka	South-East Asia Region		●
Madiha Hashmi	Pakistan Society of Critical Care Medicine, Karachi, Pakistan	Eastern Mediterranean Region		●
David Hui	Stanley Ho Center for Emerging Infectious Diseases, Chinese University of Hong Kong, China	Western Pacific Region	●	●
Niranjan Kissoon	Global Child Health, UBC and BC Children's Hospital and Sunny Hill Health Centre, Vancouver, Canada	Region of the Americas	●	●
Arthur Kwizera	Makerere University College of Health Sciences, Mulago National Referral Hospital, Kampala, Uganda	African Region		●
Thiago Lisboa	Department of Critical Care and Emergency Medicine, Hospital de Clinicas de Port Alegre, Porto Alegre, Brazil	Region of the Americas		●
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Natalia Pshenichanya	International Department for Organization of Medical Care, National Medical Research Center of Phthisiopulmonology and Infectious Diseases, Moscow, Russian Federation	European Region		●
Norio Sugaya	Keiyu Hospital, Yokohama, Japan	Western Pacific Region	●	●
Sebastian Ugarte	University Andres Bello, Santiago, Chile	Region of the Americas		●
Tim Uyeki	US Centers for Disease Control and Prevention (CDC), Atlanta, USA	Region of the Americas	●	●
Sibongile Walaza	National Institute for Communicable Disease, Johannesburg, South Africa	African Region		●
Hui-Ling Yen	School of Public Health, University of Hong Kong, China	Western Pacific Region	●	●

GDG temporary advisors, presenters, 2019

	Affiliation	Region
Temporary advisor		
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Mike Ison, non-voting	Department of Surgery, Division Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, USA	Region of the Americas
Presenter		
Beate Sander, non-voting	Institute for Clinical Evaluative Sciences and University Health Network, Toronto General Hospital, Toronto, Canada	Region of the Americas
Nancy Santesso, non-voting	McMaster University, Hamilton, Canada	Region of the Americas
Barnaby Young, non-voting	National Centre for Infectious Diseases, Tan Tock Seng Hospital, Singapore	South-East Asia Region

GDG temporary advisors, rapporteur, presenter, 2017

	Affiliation	Region
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External peer reviewers, December 2019

Name	Affiliation	Region
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Yee-Sin Leo	National Centre for Infectious Diseases, Singapore	Western Pacific Region
Wei Shen Lim	Nottingham University NHS Trust, United Kingdom	European Region

ANNEX 3. EVIDENCE PROFILES FOR ANTIVIRALS

Evidence profiles are based on a 2019 report submitted by Schünemann H, et al. (McMaster University) to WHO entitled, *Antivirals for high-risk patients with confirmed or suspected influenza: systematic reviews and meta-analyses of the evidence from non-randomized studies and randomized controlled trials*. Search dates are up to July 2017 for non-randomized studies and December 2018 for randomized studies.

Oseltamivir compared with no treatment or placebo for high-risk patients with confirmed or suspected influenza

Certainty assessment							**Summary of findings**				
No. of participants (studies) **Follow-up**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no treatment or placebo	With oseltamivir		Risk with no treatment	Risk difference with oseltamivir
Mortality, all high risk, all laboratory confirmed, adjusted OR											
4725 (8 observational studies)[1,2,3,4,5,6,7,8]	very serious[a]	not serious[b]	not serious	not serious	none	●●○○ LOW	906	3819	**OR 0.38** (0.19–0.75)	**Moderate**	
										200 per 1000	**113 fewer per 1000** (from 155 fewer to 42 fewer)
Hospitalization, high risk, adjusted OR											
14 445 (2 observational studies)[9,10]	very serious[a]	not serious[c]	not serious	not serious[d]	none	●●○○ LOW	9892	4553	**OR 0.65** (0.48–0.87)	**High**	
										100 per 1000	**33 fewer per 1000** (from 49 fewer to 12 fewer)
Hospitalization, lower risk											
7765 (12 RCTs)[11,12,13,14,15,16,17,18,19, 20,21,22]	serious[e]	not serious[f,g]	serious[h]	not serious	none	●●○○ LOW	39/3314 (1.2%)	32/4451 (0.7%)	**RR 1.07** (0.69–1.64)	**High**	
										100 per 1000	**7 more per 1000** (from 31 fewer to 64 more)
ICU admission/mechanical ventilation, all high risk, adjusted OR											
4074 (4 observational studies)[23,24,25,26]	very serious[a]	not serious[i]	not serious	not serious	none	●●○○ LOW	3416	658	**OR 1.07** (0.54–2.13)	**High**	
										100 per 1000	**6 more per 1000** (from 43 fewer to 91 more)

Certainty assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no treatment or placebo	With oseltamivir		Risk with no treatment	Risk difference with oseltamivir
Complications: pneumonia, high risk, adjusted OR											
14 445 (2 observational studies)[9,10]	very serious[a]	not serious[j]	not serious	not serious	none	●●○○ LOW	9892	4553	**OR 0.80** (0.62–1.04)	**High** 20 per 1000	 **4 fewer per 1000** (from 8 fewer to 1 more)
Complications: pneumonia, lower risk											
6494 (12 RCTs)[11,12,13,14,15,16,17,19,20,21,27,28]	serious[e]	not serious[k]	serious[h]	not serious[d]	none	●●○○ LOW	67/2782 (2.4%)	57/3712 (1.5%)	**RR 0.76** (0.53–1.09)	**Low** 20 per 1000	 **5 fewer per 1000** (from 9 fewer to 2 more)
Complications: cardiovascular, high risk, adjusted OR											
37 482 (1 observational study)[29]	very serious[a]	not serious[f]	not serious	not serious	none	●●○○ LOW	30 711	6771	**OR 0.41** (0.34–0.49)	**High** 10 per 1000	 **6 fewer per 1000** (from 7 fewer to 5 fewer)
Complications: cardiac events, lower risk											
3943 (6 RCTs)[11,12,13,14,15,16]	serious[e]	not serious[f]	serious[h]	not serious	none	●●○○ LOW	20/1505 (1.3%)	15/2438 (0.6%)	**RR 0.49** (0.25–0.97)	**High** 10 per 1000	 **5 fewer per 1000** (from 8 fewer to 0 fewer)
Complications: psychiatric adverse events, lower risk											
5616 (8 RCTs)[11,12,13,15,16,17,18,28]	serious[e]	not serious	serious[h]	not serious[d]	none	●●○○ LOW	13/2341 (0.6%)	18/3275 (0.5%)	**RR 0.93** (0.43–2.03)	**High** 10 per 1000	 **1 fewer per 1000** (from 6 fewer to 10 more)
Complications: neuropsychiatric adverse events, lower risk adjusted OR											
359 228 (3 observational studies)	very serious[a]	not serious[f]	serious[h]	not serious[d]	none	●○○○ VERY LOW	241 090	118 138	**OR 0.86** (0.79–0.93)	**Low** 10 per 1000	 **1 fewer per 1000** (from 2 fewer to 1 fewer)

Certainty assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no treatment or placebo	With oseltamivir		Risk with no treatment	Risk difference with oseltamivir
Serious adverse events, lower risk											
7324 (13 RCTs)[11,12,13,14,15,16,17,20,21,22,27,30,31]	serious[e]	not serious[l]	serious[h]	not serious[d]	none	●●○○ LOW	39/3064 (1.3%)	43/4260 (1.0%)	**RR 0.91** (0.56–1.46)	**High**	
										10 per 1000	**1 fewer per 1000** (from 4 fewer to 5 more)
Viral shedding (persistent virus isolation), all risk groups, unadjusted											
449 (4 observational studies)[32,33,34,35]	extremely serious[a]	not serious	not serious	serious[m]	none	●○○○ VERY LOW	56/243 (23.0%)	56/206 (27.2%)	**OR 0.51** (0.21–1.23)	230 per 1000	**98 fewer per 1000** (from 171 fewer to 39 more)
Resistance, all risk groups, unadjusted											
3549 (6 observational studies)[32,34,36,37,38,39]	extremely serious[a]	not serious	not serious	not serious[d]	none	●○○○ VERY LOW	15/1842 (0.8%)	32/1707 (1.9%)	**OR 1.77** (0.84–3.74)	8 per 1000	**6 more per 1000** (from 1 fewer to 22 more)
Duration of hospitalization, high risk, adjusted MD (assessed with: days)											
588 (1 observational study)[40]	very serious[a]	not serious	not serious	not serious	none	●●○○ LOW	159	429	—	The mean was 8.5 days	MD **1.9 days lower** (2.88 lower to 0.92 lower)
Time to alleviation of symptoms, lower risk											
5840 (8 RCTs)[11,12,13,14,15,16,17,28]	serious[n]	not serious	serious[c,h]	not serious	none	●●○○ LOW	497	5343	—	The mean was 200 hours	MD **17 hours lower** (25.1 lower to 8.42 lower)
Time to alleviation of symptoms, high risk, unadjusted MD											
763 (3 observational studies)[41,42,43]	very serious[a]	not serious	not serious	serious[o]	none	●○○○ VERY LOW	318	445	—	The mean was 200 hours	MD **9 hours lower** (25.2 lower to 6.66 higher)

Notes: CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio.

Explanations

[a] Risk of bias using ROBINS-I tool, residual confounding a very serious concern. GDG did not rate down for possible concern with time dependent bias.
[b] Muthuri et al. (2014): NRS IPD included 27 740 patients (confirmed and suspected). Adjusted OR for mortality in patients treated with a neuraminidase inhibitor was 0.81 (95% CI 0.70–0.93), compared with no treatment, and did not change substantially when only laboratory confirmed cases were included: 0.82 (95% CI 0.70–0.95).
[c] Results from studies with clinically suspected influenza.
[d] Although few events, confidence intervals around absolute effects are narrow.
[e] Half of the studies had risk of bias for randomization procedures and some studies for blinding, events not defined or not measured by protocol.
[f] Results from primarily suspected influenza.
[g] Dobson et al. (2015): RCT review found greater reduction in infected patients at low risk 0·37 (0·17–0·81) and uninfected patients at low risk 0·61 (0·36–1·03).
[h] Studies included in review were in low-risk patients primarily.
[i] Analysis separating out laboratory confirmed resulted in similar OR 1.17. No subgroup interaction for comparison by confirmation.
[j] Additional analysis available in patients at low risk showed similar results. All patients with suspected influenza. Comparison with data from Muthuri et al. (2014) IPD of hospitalized patients in NRS found aOR 0.83 (95% CI 0.64–1.06) and no difference with confirmed or suspected.
[k] Similar results from Dobson et al. (2015) review of RCTs. However, analysis in updated Jefferson et al. (2014) review in children found RR 1.09 [0.65, 1.82].
[l] Patients primarily low risk but confirmed influenza. Similar results in Dobson et al. (2015) review in confirmed and suspected influenza.
[m] Few events/participants.
[n] Risk of bias due to lack of random sequence generation, no allocation concealment, and/or no blinding in studies.
[o] Results include potential for large reduction and small increase in time.

References (see end of annex for full list; search by author and year)

[1] Liem, 2009
[2] Lee, 2010
[3] Taylor, 2014
[4] Choi, 2011
[5] Oner, 2012
[6] McGeer, 2009
[7] McGeer, 2007
[8] Hanshaoworakul, 2009
[9] Orzeck, 2007
[10] Piedra, 2009
[11] M76001
[12] WV15670
[13] WV15671
[14] WV15707
[15] WV15812/WV15872
[16] WV15819/WV15876/WV15978
[17] WV16277
[18] Fry, 2014
[19] NV16871
[20] WV15758
[21] WV15759/WV15871
[22] Hayden (NCT02954354), 2018
[23] Coffin, 2011
[24] Oboho, 2016
[25] Loubet, 2016
[26] Hagerman, 2015
[27] Dawood, 2016
[28] WV15730
[29] Casscells, 2009
[30] He, 2017
[31] McLean (NCT00555893), 2015
[32] Hien, 2010
[33] Fairchock, 2015
[34] Meschi, 2011
[35] Lee, 2007
[36] Kim, 2013
[37] Redlberger-Fritz, 2014
[38] Lackenby, 2013
[39] Da Dalt, 2011
[40] Delgado-Rodriguez, 2012
[41] Wang, 2012
[42] Imamura, 2003
[43] Bueno 2013

Inhaled zanamivir compared with no antivirals/placebo for high-risk patients with confirmed or suspected influenza

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no antivirals/ placebo	With zanamivir		Risk with no antivirals/ placebo	Risk difference with zanamivir
Mortality											
0 (16 RCTs)[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16]						—	All-cause mortality: 8 deaths. Influenza-related mortality: 2 deaths due to influenza A pneumonia. One participant was on zanamivir and the other on inhaled rimantadine plus placebo. 6 deaths caused by neoplasias or cardiovascular events in elderly patients with multiple pathologies.				
Mortality, high risk population											
87 (1 observational study)[17]	very serious[a]	not serious	not serious[b]	very serious[c]	none	●○○○ VERY LOW	5/74 (6.8%)	0/13 (0.0%)	**OR 0.47** (0.02–8.97)	**High** 200 per 1000	**95 fewer per 1000** (from 195 fewer to 492 more)
Hospitalization, lower risk											
4674 (1 observational study)[18]	very serious[d]	not serious	serious[e]	not serious	none	●○○○ VERY LOW	24/2337 (1.0%)	14/2337 (0.6%)	**OR 0.58** (0.30–1.13)	**High** 100 per 1000	**39 more per 1000** (from 68 fewer to 12 more)
ICU admission, high-risk population											
87 (1 observational study)[17]	very serious[a]	not serious	not serious[b]	very serious[c]	none	●○○○ VERY LOW	15/74 (20.3%)	3/13 (23.1%)	**OR 1.18** (0.29–4.83)	**High** 100 per 1000	**16 more per 1000** (from 69 fewer to 249 more)
Complications: pneumonia, lower risk population											
6613 (13 RCTs)[4,5,6,7,8,9,10,12,13,14,15,16,19]	serious[f]	not serious	serious[g]	not serious[h]	none	●●○○ LOW	45/2918 (1.5%)	44/3695 (1.2%)	**RR 0.87** (0.57–1.32)	**Moderate** 20 per 1000	**3 fewer per 1000** (from 9 fewer to 6 more)

Certainty assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)** With no antivirals/ placebo	With zanamivir	**Relative effect (95% CI)**	**Anticipated absolute effects** Risk with no antivirals/ placebo	Risk difference with zanamivir
Complications: bronchospasm											
0 (studies)						—			not estimable	0 per 1000	
Complications: respiratory disease, lower risk population											
4674 (1 observational study)[18]	very serious[d]	not serious	serious[e]	not serious	none	●○○○ VERY LOW	263/2337 (11.3%)	301/2337 (12.9%)	**OR 1.17** (0.98–1.39)	0 per 1000	**17 more per 1000** (from 2 fewer to 37 more)
Complications: cardiovascular body system, lower risk population											
5204 (11 RCTs)[2,4,5,6,8,9,10,11,12,13,14]	serious[f]	not serious	serious[g]	not serious[h]	none	●●○○ LOW	18/2202 (0.8%)	27/3002 (0.9%)	**RR 0.98** (0.50–1.91)	**Moderate** 10 per 1000	**0 fewer per 1000** (from 5 fewer to 9 more)
Complications: psychiatric, lower risk population											
4732 (10 RCTs)[1,2,4,5,8,9,10,12,13,19]	serious[f]	not serious	serious[g]	not serious[h]	none	●●○○ LOW	11/1991 (0.6%)	22/2741 (0.8%)	**RR 1.16** (0.57–2.38)	**Moderate** 10 per 1000	**2 more per 1000** (from 4 fewer to 14 more)
Serious adverse events, lower risk population											
4388 (10 RCTs)[3,4,5,6,7,9,10,13,14,19]	serious[f]	not serious	serious[g]	not serious[h]	none	●●○○ LOW	25/2087 (1.2%)	27/2301 (1.2%)	**RR 0.86** (0.49–1.50)	**Moderate** 10 per 1000	**1 fewer per 1000** (from 5 fewer to 5 more)
Viral shedding, lower risk population											
236 (2 observational studies)[20,21]	extremely serious[a]	not serious	serious[g]	very serious[i]	none	●○○○ VERY LOW	0/0	40/236 (16.9%)	**Proportion 0.19** (0.14–0.24)	—	**190 more per 1000** (from 140 more to 240 more)
Resistance, lower risk population											
508 (2 RCTs)[22,23]	not serious	not serious	serious[g]	very serious[c]	none	●○○○ VERY LOW	0/257 (0.0%)	0/251 (0.0%)	not estimable	—	—

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no antivirals/ placebo	With zanamivir		Risk with no antivirals/ placebo	Risk difference with zanamivir
Time to alleviation of symptoms, lower risk population											
6134 (15 RCTs)[1,2,3,4,6,7,8,9,10,11,13,14,15,16,19]	serious[f]	not serious	serious[g]	not serious	none	●●○○ LOW	2707	3427	—	The mean time to alleviation of symptoms ranged from **4 to 11** days	MD **0.66 days lower** (0.87 lower to 0.44 lower)
Time to alleviation of symptoms, lower risk population											
770 (3 observational studies)[20,21,24]	extremely serious[a]	not serious	serious[g]	not serious	none	●○○○ VERY LOW	210	560	—	The mean time to alleviation of symptoms ranged from **25 to 50** hours	MD **23 hours lower** (28.69 lower to 17.98 lower)

Notes: CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio.

Explanations

- [a] Due to failure to adjust for confounding variables.
- [b] Includes 1 study in pregnant women only. Includes suspected and confirmed influenza.
- [c] Due to few participants and few events.
- [d] Risk of bias using ROBINS-I tool, residual confounding a very serious concern.
- [e] Lower risk population; unclear if confirmed or suspected influenza.
- [f] Serious risk of bias due to lack of random sequence generation and no blinding in most studies.
- [g] Lower risk population with confirmed influenza.
- [h] Few events however, absolute effects are precise.
- [i] Proportion calculated in people receiving zanamivir.

References (see end of annex for full list; search by author and year)

1 JNAI-01
2 JNAI-04
3 JNAI-07
4 NAI30008
5 NAI30011
6 NAI30012
7 NAI30015
8 NAIA/B2008
9 NAIA2005
10 NAIA3002
11 NAIB2005
12 NAIB2007
13 NAIB3001
14 NAIB3002
15 NAI30009
16 NAI30028
17 Siston, 2010
18 Cole, 2002
19 NAI30010
20 Kawai, 2008
21 Sugaya, 2008
22 Boivin, 2000
23 Hedrick, 2000
24 Saito, 2010

Laninamivir compared with no antivirals for high-risk patients with confirmed or suspected influenza

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no antivirals	With laninamivir		Risk with no antivirals	Risk difference with laninamivir
Mortality, lower risk population with suspected influenza											
639 (1 RCT)[1]						—	There were no deaths reported with laninamivir or placebo.				
Complications: pneumonia, lower risk population with suspected influenza											
434 (1 RCT)[1]	not serious	not serious	serious[a]	very serious[b]	none	●○○○ VERY LOW	1/211 (0.5%)	0/223 (0.0%)	**RD 0.00** (-0.02–0.01)	**High** 10 per 1000	**10 fewer per 1000** (from10 fewer to 10 fewer)
Complications: respiratory events, lower risk population with confirmed influenza, adjusted OR											
69 697 (1 observational study)[2]	very serious[c]	not serious	serious[a]	not serious	none	●○○○ VERY LOW	34 848	34 849	**OR 0.27** (0.12–0.63)	**High** 20 per 1000	**15 fewer per 1000** (from 18 fewer to 7 fewer)
Complications: serious neuropsychiatric events, lower risk population with confirmed influenza											
69 697 (1 observational study)[2]	extremely serious[d]	not serious	serious[a]	not serious	none	●○○○ VERY LOW	Authors reported that incidence in the laninamivir group and placebo group was 0.02%.				
Complications: severe adverse events, lower risk population with suspected influenza											
434 (1 RCT)[1]	not serious	not serious	serious[a]	very serious[b]	none	●○○○ VERY LOW	1/211 (0.5%)	1/223 (0.4%)	**RD 0.00** (-0.01–0.01)	**Moderate** 10 per 1000	**10 fewer per 1000** (from 10 fewer to 10 fewer)
Complications: serious adverse events, lower risk population with confirmed influenza, adjusted OR											
69 697 (1 observational study)[2]	very serious[c]	not serious	serious[a]	not serious	none	●○○○ VERY LOW	2/34 849 (0.0%)	0/34 848 (0.0%)	**OR 0.28** (0.15–0.51)	**Moderate** 10 per 1000	**7 fewer per 1000** (from 8 fewer to 5 fewer)

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no antivirals	With laninamivir		Risk with no antivirals	Risk difference with laninamivir
Resistance, lower risk children with suspected influenza											
28 (1 observational study)[3]	extremely serious[e]	not serious	serious[a]	serious[f]	none	●○○○ VERY LOW		0/28 (0.0%)	not pooled		
Time to resolution of symptoms, lower risk population with confirmed or suspected influenza											
372 (2 RCTs)[1,4]	serious[g]	not serious	serious[a]	serious[h]	none	●○○○ VERY LOW	One study found a median difference of -22 hours (95% CI -44.7–5.6) for 10 mg laninamivir and -34.1 hours (95% CI -43.8–4.4) for 20 mg compared with placebo. Another study found a difference of 1 to 2 hours with doses of 40 mg and 80 mg versus placebo.				

Notes: CI: confidence interval; OR: odds ratio; RCT: randomized clinical trial; RD: risk difference.

Explanations

[a] Lower risk population.
[b] No or very few events.
[c] Although analysis was adjusted, there is still risk of residual confounding.
[d] Analysis was not adjusted, therefore, critical risk of bias due to confounding.
[e] No independent comparison group.
[f] Proportion only in group receiving laninamivir.
[g] Potential risk of bias due to uncertainty regarding random sequence generation and blinding of outcome assessment in one study.
[h] Due to small number of participants and inconsistent results.

References (see end of annex for full list; search by author and year)

1 NCT01793883
2 Niwa, 2015
3 Kondo, 2016
4 JapicCTI-90813

Peramivir compared with placebo for high-risk patients with confirmed or suspected influenza

Certainty assessment							Certainty assessment				
No. of participants (studies) Follow-up	No. of participants (studies) Follow-up	No. of participants (studies) Follow-up	No. of participants (studies) Follow-up	No. of participants (studies) Follow-up	No. of participants (studies) Follow-up	No. of participants (studies) Follow-up	No. of participants (studies) Follow-up		No. of participants (studies) Follow-up	No. of participants (studies) Follow-up	
							With placebo	With peramivir		Risk with placebo	Risk difference with peramivir
Mortality											
121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]
Complications: pneumonia											
121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	121 (1 RCT)[1]	
										20 per 1000	**2 more per 1000** (from13 fewer to 49 more)
Serious adverse events, lower risk population											
1042 (3 RCTs)[2,3,4]	1042 (3 RCTs)[2,3,4]	1042 (3 RCTs)[2,3,4]	1042 (3 RCTs)[2,3,4]	1042 (3 RCTs)[2,3,4]	1042 (3 RCTs)[2,3,4]	1042 (3 RCTs)[2,3,4]	1042 (3 RCTs)[2,3,4]	1042 (3 RCTs)[2,3,4]	1042 (3 RCTs)[2,3,4]	1042 (3 RCTs)[2,3,4]	
										10 per 1000	**5 fewer per 1000** (from 8 fewer to 4 more)
Viral shedding: persistent virus, lower risk population											
281 (1 RCT)[3]	281 (1 RCT)[3]	281 (1 RCT)[3]	281 (1 RCT)[3]	281 (1 RCT)[3]	281 (1 RCT)[3]	281 (1 RCT)[3]	281 (1 RCT)[3]	281 (1 RCT)[3]	281 (1 RCT)[3]	281 (1 RCT)[3]	281 (1 RCT)[3]
Resistance, lower risk population											
144 (1 RCT)[5]	serious[a]	not serious	serious[d]	very serious[b]	none	⨁◯◯◯ VERY LOW	0/37 (0.0%)	0/107 (0.0%)	not estimable	0 per 1000	**0 fewer per 1000** (from 0 fewer to 0 fewer)

Certainty assessment							**Certainty assessment**				
No. of participants (studies) **Follow-up**	**No. of participants (studies)** **Follow-up**	**No. of participants (studies)** **Follow-up**	**No. of participants (studies)** **Follow-up**	**No. of participants (studies)** **Follow-up**	**No. of participants (studies)** **Follow-up**	**No. of participants (studies)** **Follow-up**	**No. of participants (studies)** **Follow-up**		**No. of participants (studies)** **Follow-up**	**No. of participants (studies)** **Follow-up**	
							With placebo	With peramivir		Risk with placebo	Risk difference with peramivir
Time to resolution of symptoms											
121 (1 RCT)[1]	serious[a]	not serious	not serious[c]	serious[b]	none	●○○○ VERY LOW	One study in hospitalized patients found time to reduction in symptoms was reduced by a median of 1.2 hours. Three other studies in low-risk patients found a reduction by a median of 20 hours with peramivir.				

Notes: CI: confidence interval; RR: risk ratio.

Explanations

[a] Some concern with risk of bias due to unclear allocation concealment.
[b] Few or very few events/participants.
[c] All with confirmed influenza.
[d] Population was low risk population.

References (see end of annex for full list; search by author and year)

1 de Jong, 2014
2 NCT000705406
3 Kohno, 2010
4 NCT000419263
5 Barrosso, 2005

Early oseltamivir compared with late oseltamivir for high-risk patients with confirmed or suspected influenza (non-randomized studies only)

Certainty assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With late oseltamivir	With early oseltamivir		Risk with late oseltamivir	Risk difference with early oseltamivir
Mortality, adjusted, high-risk population											
1482 (4 observational studies)[1,2,3,4]	very serious[a]	not serious	not serious[b]	not serious	none	●●○○ LOW	1137	345	**OR 0.48** (0.32 to 0.71)	**High** 200 per 1000	**93 fewer per 1000** (from 126 fewer to 49 fewer)
Hospitalisation, unadjusted, high-risk population											
971 (2 observational studies)[5,6]	extremely serious[c]	not serious	not serious[d]	not serious	none	●○○○ VERY LOW	199	772	**OR 0.42** (0.26 to 0.69)[e]	**High** 450 per 1000	**194 fewer per 1000** (from 275 fewer to 89 fewer)
ICU admission/ventilatory support/respiratory failure, adjusted, high-risk population											
560 (1 observational study)[7]	very serious[a]	not serious	not serious[b,f]	not serious[g]	none	●●○○ LOW	42/351 (12.0%)	15/209 (7.2%)	**OR 0.42** (0.20 to 0.88)	120 per 1000	**66 fewer per 1000** (from 93 fewer to 13 fewer)
Complications: pneumonia and other respiratory, adjusted, high-risk population											
1144 (3 observational studies)	very serious[a]	not serious[h]	not serious[b]	not serious[i]	none	●●○○ LOW	696	448	**OR 0.24** (0.10 to 0.58)	**High** 250 per 1000[j]	**176 fewer per 1000** (from 218 fewer to 88 fewer)
Adverse events, unadjusted, high-risk population											
43 (1 observational study)[8]	extremely serious[c]	not serious	not serious	very serious[k]	none	●○○○ VERY LOW	0/30 (0.0%)	0/13 (0.0%)	not estimable		
Viral shedding, unadjusted, high-risk population (assessed with: approximately 7 days after symptom onset)											
199 (3 observational studies)[9,10,11]	extremely serious[c]	not serious	not serious	very serious[k]	none	●○○○ VERY LOW	47/98 (48.0%)	25/101 (24.8%)	**OR 0.29** (0.15 to 0.56)	480 per 1000	**269 fewer per 1000** (from 358 fewer to 139 fewer)

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With late oseltamivir	With early oseltamivir		Risk with late oseltamivir	Risk difference with early oseltamivir
Duration of viral shedding, unadjusted, high-risk population											
296 (2 observational studies)[9,12]	extremely serious[c]	serious[l]	not serious	serious	none	●○○○ VERY LOW	191	105	—		MD **2.72 days lower** (8.96 lower to 3.53 higher)
Duration of viral shedding, adjusted, lower and higher risk population											
983 (1 observational study)[13]	extremely serious[c]	not serious[l]	not serious	not serious	none	●○○○ VERY LOW	Yu (2010) reported that the duration of viral shedding was 1.3 times shorter in patients provided early oseltamivir treatment compared with patients provided late treatment (adjusted Beta: 0.13, 95% CI: 0.10 to 0.16). Pooled data from two studies (Na 2011 – high risk, Ryoo 2013 – unclear risk) found that late oseltamivir treatment increases the odds of prolonged viral shedding compared with early treatment (aOR: 5.25, 95% CI: 1.07 to 25.67).[14,15]				
Duration of hospitalization (assessed with: mean days, adjusted, high-risk population)											
495 (1 observational study)[16]	very serious[a]	not serious	not serious[b]	not serious	none	●●○○ LOW	66	429	—	The mean duration of hospitalization was **8.8** days[n]	MD **4.1 days lower** (5.39 lower to 2.81 lower)[m]
Time to alleviation of symptoms, unadjusted, high-risk population											
384 (2 observational studies)[17,18,19,20,21,22]	extremely serious[c]	not serious	not serious	not serious	none	●○○○ VERY LOW	Pooled data from Lim (2015) and Wang (2012) in high-risk populations found little to no difference in duration of fever when comparing early oseltamivir treatment with late treatment (MD: -0.14, 95% CI: -1.34 to 1.06). Four studies that could not be pooled (Giannattasio 2010, Kittikraisak 2016, Redlberger-Fritz 2014 and Viasus 2011a with approximately 1000 patients) suggest duration of symptom reductions of varying magnitudes (see footnote to forest plot for details).				

Notes: CI: confidence interval; MD: mean difference; OR: odds ratio.

Explanations

[a] Although adjusted analysis, residual confounding results in risk of bias.
[b] All studies included confirmed influenza.
[c] Analysis not adjusted for known confounders and also risk of bias for unknown confounders.
[d] Population with suspected or confirmed influenza.
[e] Adjusted analysis in low-risk populations (n=575 520) found aOR 0.10 (0.09–0.11).
[f] includes organ transplant and haematopoietic stem cell transplant recipients (Kumar et al., 2018).
[g] Although few events, unadjusted analyses in over 12 studies in high-risk population found OR 0.32 (0.16–0.65), so not rated down for imprecision.
[h] Although I2=84%, point estimates ranged from 0.04 to 0.51 (an important reduction), therefore not rated down for inconsistency.
[i] Although few events, unadjusted analyses in a study of over 550 000 low-risk outpatients found OR 0.17 (0.16–0.18), so not rated down for imprecision.
[j] Based on the baseline risk reported in Kumar et al. (2018), Viasus et al. (2011b) reported ~45%, and Choi et al. (2011) did not report. Typically, we estimate baseline risk for pneumonia in moderate risk groups without influenza treatment at 20 per 1000. A baseline risk of 250 per 1000 may be high.
[k] No or very few events and very few participants.
[l] Due to unexplained heterogeneity (I2=85%).
[m] Baseline risk calculated from mean duration of hospitalization in one study (Delgado-Rodriguez et al, 2012).
[n] Data could not be pooled from one study. Specifically, Oboho et al. (2016) reported that amongst pregnant women with severe influenza, oseltamivir treatment within 48 hours of symptom onset was associated with a shorter duration of hospitalization (median: 2.2 days, IQR: 0.9–5.8, n=8) compared with treatment beyond 48 hours (median: 7.8 days, IQR: 3.0–20.6, n=7) after adjusting for comorbidities, influenza vaccination status and pregnancy trimester.

References (see end of annex for full list; search by author and year)

[1] Rodriguez, 2011
[2] Canadell, 2015
[3] Chan, 2012
[4] Choi, 2011
[5] Siston, 2010
[6] Hansen, 2012
[7] Kumar, 2010
[8] Lopez-Aldeguer, 2012
[9] Meschi, 2011
[10] Ling, 2010
[11] Lee, 2009
[12] Hien, 2010
[13] Yu, 2010
[14] Na, 2011
[15] Ryoo, 2013
[16] Delgado-Rodriguez, 2012
[17] Lim, 2015
[18] Wang, 2012
[19] Giannattasio, 2010
[20] Kittikraisak, 2016
[21] Redlberger-Fritz, 2014
[22] Viasus, 2011a

Oseltamivir compared with inhaled zanamivir for high-risk patients with confirmed or suspected influenza

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With zanamivir	With oseltamivir		Risk with zanamivir	Risk difference with oseltamivir
Mortality, high-risk population, unadjusted											
1660 (4 observational studies)[1,2,3,4]	extremely serious[a]	not serious	not serious[b]	serious[c]	none	●○○○ VERY LOW	14/65 (21.5%)	325/1595 (20.4%)	**OR 1.05** (0.48–2.29)	**Moderate** 100 per 1000	 **4 more per 1000** (from 49 fewer to 103 more)
Mortality (all-cause, 28 days), high-risk population											
488 (1 RCT)[5]	not serious	not serious	not serious[d]	very serious[e]	none	●●○○ LOW	22/325 (6.8%)	10/163 (6.1%)	**RR 0.91** (0.44–1.83)	**Moderate** 100 per 1000	 **9 fewer per 1000** (from 56 fewer to 83 more)
Hospitalization, high-risk population, unadjusted											
489 (1 observational study)[6]	extremely serious[a]	not serious	not serious[f]	serious[c]	none	●○○○ VERY LOW	8/13 (61.5%)	329/476 (69.1%)	**OR 1.40** (0.45–4.35)	615 per 1000	**76 more per 1000** (from 197 fewer to 259 more)
ICU admission, high-risk population, unadjusted											
489 (1 observational study)[6]	extremely serious[a]	not serious	not serious[f]	serious[c]	none	●○○○ VERY LOW	3/13 (23.1%)	71/476 (14.9%)	**OR 0.58** (0.16–2.18)	231 per 1000	**83 fewer per 1000** (from 185 fewer to 165 more)
Mechanical ventilation, high-risk population											
488 (1 RCT)[5]	not serious	not serious	not serious[d]	serious[e]	none	●●●○ MODERATE	83/325 (25.5%)	50/163 (30.7%)	**RR 1.20** (0.89–1.62)	255 per 1000	**51 more per 1000** (from 28 fewer to 158 more)
Complications: pneumonia, high-risk population											
615 (1 RCT)[5]	not serious	not serious	not serious[d]	very serious[e]	none	●●○○ LOW	23/410 (5.6%)	11/205 (5.4%)	**RD -0.00** (-0.04, 0.04)	56 per 1000	**0 fewer per 1000** (from 40 fewer to 40 more)

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With zanamivir	With oseltamivir		Risk with zanamivir	Risk difference with oseltamivir
Severe adverse events: overall, high-risk population											
615 (1 RCT)[5]	not serious	not serious	not serious[d]	serious[e]	none	●●●○ MODERATE	23/410 (5.6%)	83/205 (40.5%)	**RD 0.35** (0.28, 0.42)	56 per 1000	**350 fewer per 1000** (from 420 fewer to 280 fewer)
Severe adverse events: cardiac events, high-risk population											
615 (1 RCT)[5]	not serious	not serious	not serious[d]	very serious[e]	none	●●○○ LOW	14/410 (3.4%)	6/205 (2.9%)	**RD -0.00** (-0.03, 0.02)	34 per 1000	**0 fewer per 1000** (from 20 fewer to 30 more)
Severe adverse events: psychiatric events, high-risk population											
615 (1 RCT)[5]	not serious	not serious	not serious[d]	very serious[e]	none	●●○○ LOW	3/410 (0.7%)	1/205 (0.5%)	**RD -0.00** (-0.02, 0.01)	7 per 1000	**0 fewer per 1000** (from 10 fewer to 20 more)
Duration of viral shedding (days), lower risk population, unadjusted											
86 (1 observational study)[7]	extremely serious[a]	not serious	serious[g]	serious[e]	none	●○○○ VERY LOW	39	47	—	The mean was **4.33** days	MD **0.42 days higher** (0.18 lower to 1.02 higher)
Viral shedding (persistent virus) (days), lower risk population, unadjusted											
46 (1 observational study)[8]	extremely serious[a]	not serious	serious[g]	serious[e]	none	●○○○ VERY LOW	4/23 (17.4%)	9/23 (39.1%)	**OR 3.05** (0.78–11.96)	174 per 1000	**217 more per 1000** (from 33 fewer to 542 more)
Duration of hospitalization (days), high risk population											
488 (1 RCT)[5]	not serious	serious[c]	not serious[d]	not serious	none	●●●○ MODERATE	163	325	—	The mean was **19.25** days	MD **7.07 days higher** (4.44 lower to 18.58 higher)
Time to alleviation of symptoms (hours), lower risk population, unadjusted											
3121 (10 observational studies)[7,8,9,10,11,12,13,14,15,16]	extremely serious[a]	serious[h]	serious[b,g]	not serious	none	●○○○ VERY LOW	1409	1712	—	**The mean ranged from 43.2–45.6 hours**	MD **11 hours higher** (1.78 higher to 20.69 higher)

Notes: CI: confidence interval; MD: mean difference; OR: odds ratio.

Explanations

[a] Studies not adjusted for potential confounding factors.
[b] In patients with confirmed and suspected influenza.
[c] Wide confidence interval, including potential for no difference and important difference between oseltamivir and zanamivir.
[d] 78% patients with laboratory-confirmed influenza.
[e] Very few events or participants.
[f] Results calculated from pregnant women only; therefore, may not be applicable to typical patients and quality downgraded.
[g] In people at low risk of complications.
[h] High heterogeneity among studies considered with width of confidence intervals which include potential for small difference to large difference between oseltamivir and zanamivir.

References (see end of annex for full list; search by author and year)

[1] Canadell, 2015
[2] Hong, 2013
[3] Siston, 2010
[4] Torres, 2010
[5] Marty, 2017
[6] Siston, 2010
[7] Takemoto, 2013
[8] Sugaya, 2008
[9] Kawai, 2013
[10] Kawai, 2008
[11] Kawai, 2009
[12] Komiya, 2009
[13] Miyachi, 2011
[14] Saito, 2010
[15] Shobugawa, 2012
[16] Tuna, 2012

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ANNEX 4. EVIDENCE PROFILES FOR ADJUNCTIVE THERAPIES

Adjunctive corticosteroid therapy compared with no corticosteroids/placebo for influenza infection

Certainty assessment							Summary of findings				
No. of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Without corticosteroids	With corticosteroids		Risk with no corticosteroids	Risk difference with corticosteroids
Crude mortality, OR											
8409 (11 non-randomized studies)[1,2,3,4,5,6,7,8,9,10,11]	very serious[a]	serious[b]	not serious	not serious	none	●○○○ VERY LOW	546/5260 (10.4%)	767/3149 (24.4%)	**OR 2.84** (2.12–3.80)	104 per 1000	**144 more per 1000** (from 93 more to 202 more)
Adjusted mortality, adjusted OR											
1277 (6 non-randomized studies)[1,2,3,4,7,10]	serious[c]	not serious	not serious	not serious	none	●●○○ LOW	110/674 (16.3%)	200/603 (33.2%)	**OR 2.46** (1.49–4.06)	104 per 1000	**118 more per 1000** (from 43 more to 216 more)
Adjusted mortality, adjusted hazard ratio											
7132 (5 non-randomized studies)[5,6,8,9,11]	serious[d]	not serious	not serious	not serious	none	●●○○ LOW	436/4586 (9.5%)	567/2546 (22.3%)	**HR 1.32** (0.95–1.85)	104 per 1000	**31 more per 1000** (from 5 fewer to 80 more)

Notes: CI: confidence interval; R: hazard ratio; OR: odds ratio.

Explanations

a Estimate not adjusted for confounding.
b Variability in effect estimates between studies.
c Significant residual risk of bias from unadjusted confounders.
d Significant residual risk of bias from unadjusted confounders.

References (see end of annex for full list; search by author and year)

1 Liem, 2009
2 Xi, 2010
3 Linko, 2011
4 Kim, 2011
5 Brun-Buisson, 2011
6 Lee, 2015
7 Delaney, 2016
8 Cao, 2016
9 Li, 2017
10 Yeh, 2017
11 Moreno, 2018

Adjunctive passive immune therapy compared with no passive immune therapy/placebo for influenza treatment

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no passive immune therapy	With passive immune therapy		Risk with no passive immune therapy	Risk difference with passive immune therapy
Mortality (randomized clinical trials only), OR											
562 (4 RCTs)[1,2,3,4]	not serious	not serious	serious[a]	serious[b]	not assessable	⨁⨁◯◯ LOW	15/259 (5.8%)	15/303 (5.0%)	**OR 0.84** (0.37–1.90)	58 per 1000	**9 fewer per 1000** (from 36 fewer to 47 more)
Mortality, adjusted OR											
655 (4 RCTs, 1 non-randomized)[1,2,3,4,5]	not serious	serious[c]	not serious	serious[d]	not assessable	⨁◯◯◯ VERY LOW	19/323 (5.9%)	55/332 (16.6%)	**OR 0.56** (0.24–1.33)	58 per 1000	**25 fewer per 1000** (from 43 fewer to 18 more)
Clinical outcome at Day 7, ordinal score, adjusted OR											
512 (3 RCTs)[2,3,4]	not serious	serious[e]	not serious	serious[f]	not assessable	⨁⨁◯◯ LOW	—	—	**OR 1.42** (1.05–1.92)	Not meaningful	
Progression to mechanical ventilation, RR											
99 (1 RCT)[3]	not serious	not serious	not serious	very serious[g]	not assessable	⨁◯◯◯ VERY LOW	2/33 (6.1%)	3/66 (4.5%)	**RR 0.75** (0.13–4.27)	61 per 1000	**15 fewer per 1000** (from 53 fewer to 198 more)
Progression to intensive care, RR											
78 (1 RCT)[3]	not serious	not serious	not serious	very serious[h]	not assessable	⨁◯◯◯ VERY LOW	0/27 (0%)	3/51 (5.9%)	**RR 3.77** (0.20–70.40)	Not meaningful	
Serious adverse events, RR											
544 (3 RCTs)[2,3,4]	not serious	serious[i]	not serious	not serious	not assessable	⨁⨁⨁◯ MODERATE	61/251 (24.3%)	65/293 (22.2%)	**RR 0.84** (0.57–1.26)	243 per 1000	**39 fewer per 1000** (from 105 fewer to 63 more)
Infectious complications, RR											
406 (2 RCTs)[2,4]	not serious	not serious	not serious	very serious[j]	not assessable	⨁◯◯◯ VERY LOW	10/204 (4.9%)	8/202 (4.0%)	**RR 0.82** (0.33–2.07)	49 per 1000	**9 fewer per 1000** (from 33 fewer to 52 more)

Certainty assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no passive immune therapy	With passive immune therapy		Risk with no passive immune therapy	Risk difference with passive immune therapy
Cardiac complications, RR											
406 (2 RCTs)[2,4]	not serious	not serious	not serious	very serious[j]	not assessable	⨁◯◯◯ VERY LOW	5/204 (2.5%)	3/202 (1.5%)	**RR 0.62** (0.15–2.56)	25 per 1000	**9 fewer per 1000** (from 21 fewer to 38 more)
Neuropsychiatric complications, RR											
406 (2 RCTs)[2,4]	not serious	not serious	not serious	very serious[j]	not assessable	⨁◯◯◯ VERY LOW	1/204 (0.5%)	1/202 (0.5%)	**RR 1.04** ((0.11–9.91)	5 per 1000	**0 per 1000** (from 4 fewer to 44 more)

Notes: CI: confidence interval; OR: odds ratio; RCT: randomized clinical trial; RR: risk ratio.

Explanations

- [a] Variability between study populations.
- [b] Few events observed in the included studies.
- [c] Variability in effect estimate between studies.
- [d] Wide confidence intervals for the effect estimate.
- [e] Variability in effect estimate between studies.
- [f] Confidence intervals for the effect estimate close to 1.
- [g] Single study with small number of events.
- [h] Single study with a small number of events.
- [i] Some heterogeneity in outcomes, and overlap in participants between Beigel et al. (2017) and Beigel et al. (2019).
- [j] Small number of events.

References (see end of annex for full list; search by author and year)

1 Hung, 2013
2 Beigel, 2017
3 Beigel, 2019
4 Davey, 2019
5 Hung, 2011

Adjunctive macrolides compared with no macrolides/placebo for influenza treatment

Certainty assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no macrolides	With macrolides		Risk with no macrolides	Risk difference with macrolides
Mortality (randomized clinical trials only), OR											
217 (1 RCT)[1]	not serious	not serious	not serious	serious[a]	not assessable	⬤⬤◯◯ LOW	9/110 (8.2%)	1/107 (0.9%)	**OR 0.11** (0.01–0.85)	82 per 1000	**72 fewer per 1000** (from 81 fewer to 11 fewer)
Mortality, adjusted OR											
950 (1 RCT, 1 non-randomized)[2]	not serious	serious[b]	not serious	serious[c]	not assessable	⬤◯◯◯ VERY LOW	162/653 (24.8%)	37/297 (12.5%)	**OR 0.33** (0.03–4.08)	82 per 1000	**53 fewer per 1000** (from 79 fewer to 185 more)

Notes: CI: confidence interval; OR: odds ratio; RCT: randomized clinical trial.

Explanations

[a] Only one study with wide confidence intervals for effect of intervention.
[b] Results different between the two included studies.
[c] Wide confidence intervals for estimate.

References (see end of annex for full list; search by author and year)

1 Hung, 2017
2 Martin-Loeches, 2017

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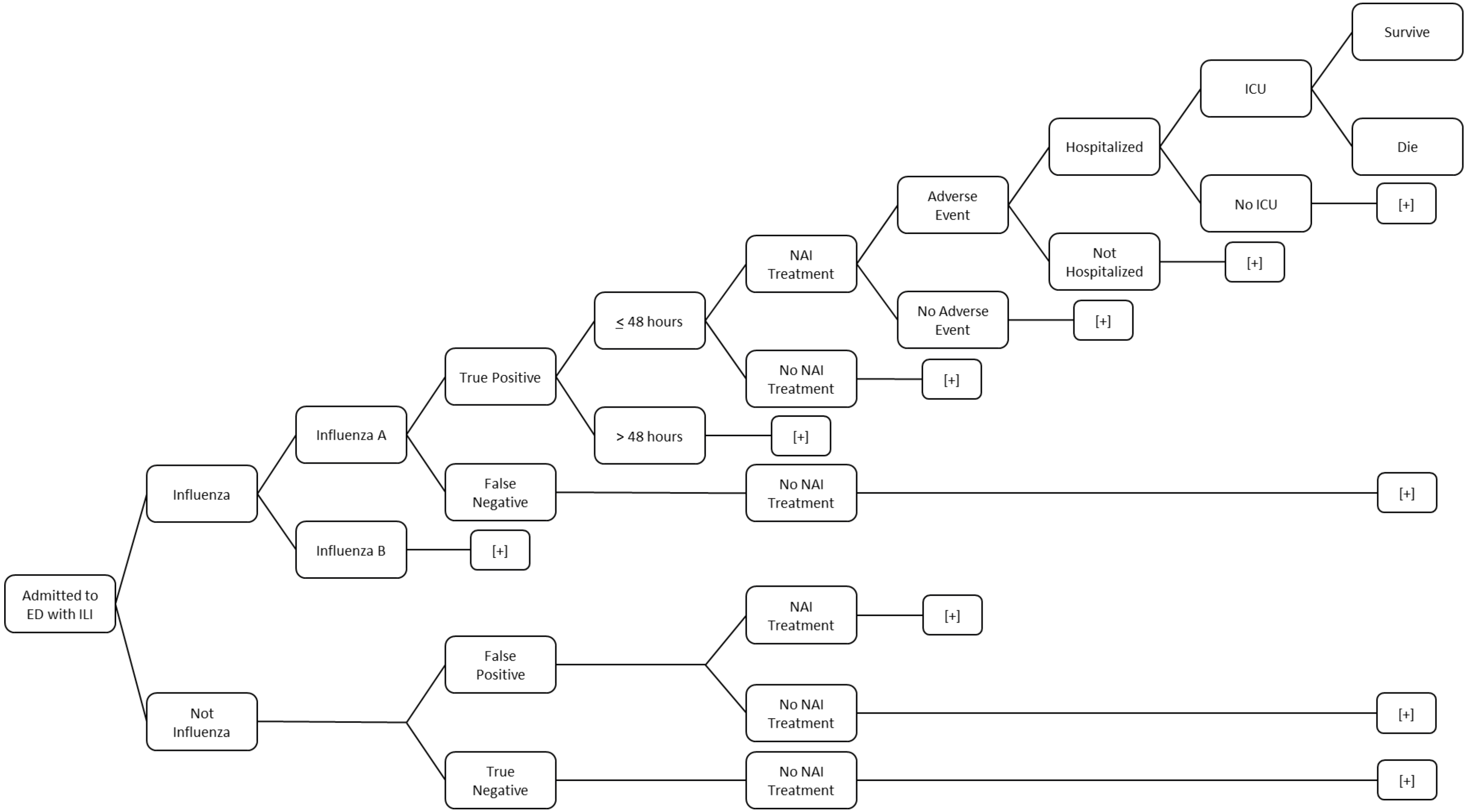
ANNEX 5. DIAGNOSTIC DECISION-MAKING ANALYSIS METHODS

Fig. A5.1. Model schematic



Notes: ED: emergency department; ICU: intensive care unit; ILI: influenza-like illness; NAI: neuraminidase inhibitor; [+]: sub-tree clone.

Table A5.1. Key parameters for adults

Variable	Base-case value	Range	Range type[a]	Source
Diagnostic tests				
RIDT, sensitivity, influenza A	0.426	0.348–0.509	Full	*(1)*
RIDT, sensitivity, influenza B	0.332	0.199–0.507	Full	*(1)*
RIDT, specificity, influenza A	0.995	0.986–0.998	Full	*(1)*
RIDT, specificity, influenza B	0.999	0.994–1	Full	*(1)*
DIA, sensitivity, influenza A	0.754	0.666–0.826	Full	*(1)*
DIA, sensitivity, influenza B	0.57	0.395–0.716	Full	*(1)*
DIA, specificity, influenza A	0.967	0.947–0.98	Full	*(1)*
DIA, specificity, influenza B	0.988	0.975–0.995	Full	*(1)*
NAAT, sensitivity, influenza A	0.874	0.711–0.956	Full	*(1)*
NAAT, sensitivity, influenza B	0.757	0.518–0.907	Full	*(1)*
NAAT, specificity, influenza A	0.98	0.932–0.995	Full	*(1)*
NAAT, specificity, influenza B	0.993	0.978–0.998	Full	*(1)*
Clinical judgment, sensitivity	0.36	0.22–0.52	Full	*(2)*
Clinical judgment, specificity	0.78	0.72–0.83	Full	*(2)*
Batch PCR, sensitivity and specificity	0.95	0.75–1	Plausible	Assumption, based on *(1)*
ILI and influenza-related probabilities				
Pre-test probability of influenza	0.144	0.11–0.18	Plausible	Seasonal assumptions (3)
Influenza A (influenza B is the complement)	0.873	0–1	Full	Seasonal assumptions (3)
Hospitalization	0.116	0.09–0.15	Plausible	*(4)*
ICU hospitalization, < 20 y	0.05882	0.04–0.07	Plausible	*(5)*
ICU hospitalization, ≥ 65 y	0.134	0.1–0.17	Plausible	*(5)*
Treatment within 48 hrs of symptom onset	0.4811	0.36–0.6	Plausible	*(6)*
Adverse events, Tx	0.075	0.056–0.094	Plausible	Schünemann, 2019 (WHO Review, Annex 3)
Adverse events, no Tx	0.027	0.02–0.034	Plausible	Schünemann, 2019 (WHO Review, Annex 3)
Mortality (ICU admitted, early Tx)	0.276	0.21–0.35	Plausible	*(6)*
Mortality (ICU-admitted, late Tx)	0.3198	0.24–0.4	Plausible	*(6)*
Mortality (ICU-admitted, no Tx)	0.5344	0.4–0.67	Plausible	*(6)*
Mortality (non-ICU hospitalized, early Tx)	0.0809	0.06–0.1	Plausible	*(6)*
Mortality (non-ICU hospitalized, late Tx)	0.1218	0.09–0.15	Plausible	*(6)*
Mortality (non-ICU hospitalized, no Tx)	0.1218	0.09–0.15	Plausible	*(6)*

Variable	Base-case value	Range	Range type[a]	Source
Utilities				
Average population utilities, age dependent	0.88 to 0.94	0.8722–0.9426	Full	*(7)*
QALYs lost for ILI (disutility), 0–19 y	0.0146	0.0065–0.0146	Full	*(8)*
QALYs lost for ILI (disutility), 20–64 y	0.0174	0.0097–0.0245	Full	*(8)*
QALYs lost for ILI (disutility), ≥ 65 y	0.0293	0.0233–0.0349	Full	*(8)*
QALYs for symptom alleviation from treatment, 0–18 y	0.00096	0.0007–0.0012	Plausible	Assumption, based on *(9)*
QALYs for symptom alleviation from treatment, > 18 y	0.00166	0.0012–0.0021	Plausible	Assumption, based on *(9)*
Adverse event (disutility)	0.0113	0.008–0.014	Plausible	*(10)*

Notes:

DIA: digital immunoassay; ICU: intensive care unit; ILI: influenza-like illness; NAAT: nucleic acid amplification test; PCR: polymerase chain reaction; QALY: quality-adjusted life year; RIDT: rapid influenza diagnostic test; Tx: treatment; y: year.

[a] Plausible ranges are defined as full where lower and upper limits were directly reported from the data source, and "plausible" where uncertainty of key parameter was not reported in the literature and so + 25% was used to create a plausible range for sensitivity analysis.

Key assumptions

Tests

1. Batch PCR sensitivity and specificity were slightly less than perfect (1.00) at 0.95.
2. For the "batch PCR – wait" strategy, we assumed that the base-case probability of patients being treated within 48 hours of symptom onset (48%, *(6)*) was reduced by half (24%) to account for the delayed results and potential start of treatment.

Clinical pathway and treatment

3. Patients testing positive (true or false positive) were assumed to all receive a regimen of NAI treatment, while patients testing negative did not.
4. It was assumed that patients with a false negative result did not receive NAI therapy at any point during their hospitalization.
5. We used hospitalization rates resulting from influenza only, and assumed that ILI did not contribute to hospitalization.
6. We assumed that all patients received oseltamivir as NAI treatment for the purposes of the analysis.
7. In the "batch PCR – treat", we assumed that one day of NAI treatment regimen prior to test results becoming available does not provide QALY benefit to the patients testing negative.

Quality-adjusted life years

8. All patients with ILI or influenza received the same QALY decrement of 0.0146 to 0.0293 depending on their age (0.0293 for the base-case patient 65 years of age).
9. We assumed this QALY decrement was constant over the episode of influenza, and that differential severity or length of stay would not significantly change the decrement.
10. Adverse events did not extend length of stay or increase health care utilization.

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