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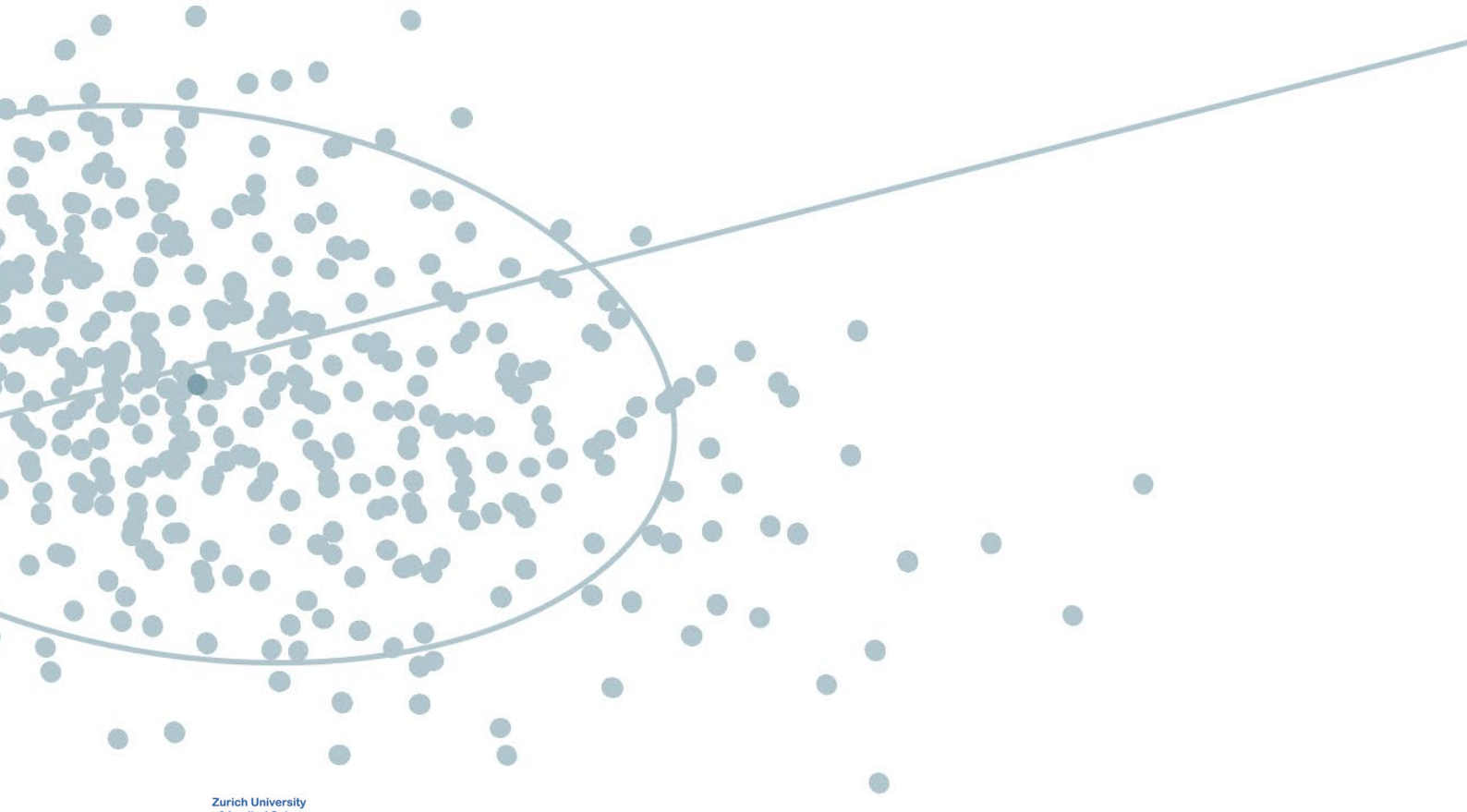
Clinical Evidence Synthesis Report

Oseltamivir and baloxavir marboxil to treat or prevent influenza A and B

Version 03-03-2025



Zurich University of Applied Sciences

School of Management and Law

Winterthur Institute of Health Economics

Title	Oseltamivir and baloxavir marboxil to treat or prevent influenza A and B
Authors/Affiliations	Christina Vetsch-Tzogiou, Cécile Grobet, Linda Vinci, Flurina Meier, Feride Cengelli, Yaroslava Zemlyanska, Irene Kobler, Matthias Maurer, Simon Wieser Winterthur Institute of Health Economics, Zurich University of Applied Sciences
Technology	Oseltamivir (Tamiflu®) Baloxavir marboxil (Xofluza®)
Type of Technology	Pharmaceuticals
Date	03-03-2025

Conflict of Interest:

The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

Federal Office of Public Health FOPH
Health Technology Assessment
Schwarzenburgstrasse 157
CH-3003 Bern
Switzerland
Tel.: +41 58 462 92 30
E-mail: hta@bag.admin.ch

Cover image: Simplified representation of a fictional probabilistic sensitivity analysis on a cost-effectiveness plane with the diagonal willingness-to-pay line.

Executive Summary

Background: In Switzerland, the antivirals oseltamivir (Tamiflu®) and baloxavir marboxil (baloxavir, Xofluza®) are approved for treatment and prevention of influenza A and B. Since the demand for antiviral drugs can quickly and massively increase during influenza pandemics, Switzerland established a stockpile of oseltamivir in 2012. It has been questioned whether oseltamivir should remain in the stockpile or whether it should be replaced or supplemented with baloxavir. To inform these strategic stockpiling decisions, a clinical evidence synthesis regarding the efficacy and safety of oseltamivir and baloxavir is of interest.

Objective: This report presents the clinical evidence on the efficacy and safety of oseltamivir and baloxavir to treat or prevent influenza A and B.

Research questions: 1) Are oseltamivir and baloxavir efficacious and safe compared to each other, placebo or any non-antiviral treatment in patients with influenza A or B? 2) Are oseltamivir and baloxavir efficacious and safe compared to each other, placebo or any non-antiviral treatment in persons receiving prophylactic treatment against influenza?

Methods: A systematic literature search in Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Medline and Web of Science databases was conducted. Eligible studies were randomised controlled trials (RCTs) that compared oseltamivir and baloxavir to each other, placebo or any non-antiviral treatment and assessed relevant outcomes such as mortality, influenza-associated symptoms or complications and first hospitalisation. In addition, RCTs registered with clinicaltrials.gov and the WHO International Clinical Trials Registry Platform were searched, and their completion status was checked. Where possible, meta-analyses were performed to estimate pooled effect estimates. Heterogeneity among pooled effect estimates was explored by subgroup and sensitivity analyses. Outcomes which could not be pooled with meta-analyses were summarised narratively by using the Synthesis Without Meta-analysis (SWiM) guideline. Results were analysed separately for “patients with influenza-like symptoms” and “patients with confirmed influenza”.

The methodological quality of included RCTs were critically appraised according to the Cochrane Risk of Bias tool 2 for randomised trials (RoB 2). The certainty of evidence was assessed for selected outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for pairwise meta-analyses.

Results: The results summarised here are based on meta-analyses; more results were retrieved, summarised narratively, and shown in the report.

For the **treatment of influenza A or B**, the following results were found regarding the primary outcomes. **Mortality** was rarely reported in the included studies, with no statistically significant differences observed between oseltamivir and placebo in patients with influenza-like symptoms (RR 3.00, 95% CI 0.31 to 28.82, low certainty, 2 RCT). No meta-analyses could be conducted

for oseltamivir versus baloxavir, oseltamivir versus any non-antiviral treatment, or baloxavir versus placebo.

Oseltamivir statistically significantly reduced **influenza-associated complications**, such as pneumonia, bronchitis or otitis media, compared to placebo in patients with confirmed influenza (RR 0.60, 95% CI 0.47 to 0.78, moderate certainty, 5 RCT). No meta-analyses could be conducted for oseltamivir versus baloxavir, oseltamivir versus any non-antiviral treatment, and baloxavir versus placebo.

First hospitalisations were infrequent, with no statistically significant difference detected between oseltamivir and placebo in patients with confirmed influenza (RR 0.89, 95% CI 0.36 to 2.20, moderate certainty, 4 RCT). No meta- analyses could be conducted for oseltamivir versus baloxavir, oseltamivir versus any non-antiviral treatment and baloxavir versus placebo.

For the treatment of influenza A or B, the following results were found regarding secondary outcomes.

Time to alleviation of influenza symptoms (TTAS) was statistically significantly shorter with oseltamivir compared to placebo in patients with confirmed influenza (mean difference: -23.74 hours, 95% CI -34.14 to -13.35, low certainty, 9 RCT) and in patients with influenza-like symptoms (mean difference: -19.89 hours, 95% CI -31.21 to -8.58, moderate certainty). TTAS was not statistically significantly different with oseltamivir compared to baloxavir in patients with confirmed influenza (mean difference: 3.08 hours, 95% CI -3.93 to 10.08, low certainty, 3 RCT). No study was identified analysing TTAS for oseltamivir compared to any non-antiviral treatment. TTAS was statistically significantly shorter with baloxavir compared to placebo in patients with confirmed influenza (mean difference: -26.39 hours, 95% CI -32.10 to -20.68, moderate certainty, 3 RCT).

Antibiotic use was statistically significantly lower with oseltamivir compared to placebo in patients with confirmed influenza (RR 0.67, 95% CI 0.54 to 0.84, moderate certainty, 3 RCT). Antibiotic use was not statistically significantly different with oseltamivir compared to baloxavir in patients with confirmed influenza (RR 1.11, 95% CI 0.57 to 2.17, very low certainty, 2 RCT). Antibiotic use was statistically significantly lower with oseltamivir compared to any non-antiviral treatment in patients with influenza-like symptoms (RR 0.70, 95% CI 0.58 to 0.86, low certainty, 2 RCT). No meta-analyses could be conducted for baloxavir versus placebo.

No meta-analyses could be conducted for **length of hospitalisation** and no studies were identified for oseltamivir versus placebo, oseltamivir versus baloxavir and baloxavir versus placebo.

The **number of re-consultations with a doctor** was not statistically significantly different with oseltamivir compared to any non-antiviral treatment in patients with influenza-like symptoms (RR 1.03, 95% CI 0.81 to 1.30). No studies were identified for oseltamivir versus placebo, oseltamivir versus baloxavir and baloxavir versus placebo.

No meta-analyses could be conducted for the number of **onward transmissions to household contacts** and no studies were identified for oseltamivir versus baloxavir and baloxavir versus placebo.

Adverse events were not statistically significantly different between oseltamivir and placebo in patients with influenza-like symptoms (RR 1.12, 95% CI 0.84 to 1.49, very low certainty, 4 RCT). Adverse events were statistically significantly higher with oseltamivir compared to baloxavir in patients with influenza-like symptoms (RR 2.00, 95% CI 1.29 to 3.12, low certainty, 2 RCT). Adverse events were not statistically significantly different with oseltamivir compared to any non-antiviral treatment in patients with influenza-like symptom (RR 1.51, 95% CI 0.48 to 4.74, very low certainty, 2 RCT). No meta-analysis could be conducted for baloxavir versus placebo.

Severe adverse events were rare, with no statistically significant difference between oseltamivir and placebo in patients with influenza-like symptoms (RR 0.96, 95% CI 0.46 to 2.02, low certainty, 4 RCT). No meta-analysis could be conducted for oseltamivir versus baloxavir, oseltamivir versus any non-antiviral treatment and baloxavir versus placebo.

Toxicities were not reported in any of the included studies.

For the treatment of influenza A or B, subgroup analyses were only possible for oseltamivir compared to placebo in patients with confirmed influenza for the secondary outcomes TTAS and time to resolution of fever. For TTAS the difference in effect sizes was statistically significant among the age groups; no statistically significant differences were found across time of drug administration or risk groups. For resolution of fever no statistically significant differences were found among age and risk groups.

For the **prevention of influenza A or B,** the following results were found regarding the primary outcomes.

Mortality was not statistically significantly different with oseltamivir compared to placebo (RR 1.13, 95% CI 0.19 to 6.79, low certainty, 3 RCT). No meta-analyses could be conducted for baloxavir versus placebo and no studies were identified for oseltamivir versus baloxavir and oseltamivir versus any non-antiviral treatment.

Oseltamivir statistically significantly reduced **laboratory-confirmed influenza** compared to placebo (RR 0.66, 95% CI 0.45 to 0.97, low certainty, 5 RCT). No meta-analyses could be conducted for baloxavir versus placebo and no studies were identified for oseltamivir versus baloxavir and oseltamivir versus any non-antiviral treatment.

Influenza confirmed with rapid diagnostic was not reported in any of the included studies**.**

No meta-analyses could be conducted for **influenza-associated complications** and no studies were identified for oseltamivir versus baloxavir, oseltamivir versus any non-antiviral treatment and baloxavir versus placebo.

First hospitalisation due to influenza symptoms and **length of hospitalisation**, was not reported in any of the included studies.

Adverse events were rare, with no statistically significant difference observed between oseltamivir and placebo (RR 0.96, 95% CI 0.82 to 1.12, low certainty, 3 RCT). No meta-analyses could be conducted for baloxavir versus placebo and no studies were identified for oseltamivir versus baloxavir and oseltamivir versus any non-antiviral treatment.

No meta-analyses could be conducted for **severe adverse events** and no studies were identified for oseltamivir versus baloxavir and oseltamivir versus any non-antiviral treatment.

Toxicities were not reported in any of the included studies.

For the prevention of influenza A and B, subgroup analyses were only computed for oseltamivir compared to placebo for the primary outcome mortality. No statistically significant difference resulted, regardless of post-exposure study inclusion.

Conclusion: The evidence suggests that in patients with influenza, oseltamivir reduces the absolute risk of influenza-associated complications from 13% to 8% compared to placebo, but has no statistically significant benefit on mortality and first hospitalisation. Oseltamivir reduces TTAS approximately by 1 day, and the risk for antibiotic use from 15% to 10% compared to placebo, while baloxavir reduces TTAS approximately by 1 day compared to placebo. There is no difference between oseltamivir and baloxavir regarding TTAS and antibiotic use. Adverse events and severe adverse events did not differ between oseltamivir and placebo but adverse events were higher with oseltamivir than with baloxavir.

The evidence also suggests that prevention with oseltamivir reduces the risk of laboratory-confirmed influenza from 14% to 8% compared to placebo, while mortality and adverse events were not statistically significantly different. No studies were identified for oseltamivir versus baloxavir or any non-antiviral treatment on influenza prevention.

Table of Contents

List of tables

Table of figures

Abbreviations and acronyms

BVS	Border veterinary service
CCGs	Clinical commissioning groups
CDC	Centers for Disease Control and Prevention
CEN	Cap-dependent endonuclease
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CNRI	National Reference Centre for Influenza (“Centre national de référence de l'Influenza”)
ELSO	Ethical, legal, social and organisational
FDHA	Federal Department of Home Affairs
FOPH	Federal Office of Public Health
FSVO	Federal Food Safety and Veterinary Office
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
h	Hours
HTA	Health Technology Assessment
ICSs	Integrated care systems
ITT	Intention-to-treat
ITTi	Intention-to-treat-infected
IQR	Interquartile range
NAIs	Neuraminidase inhibitors
NE	Not estimable
PCR	Polymerase chain reaction
PICO	Population, intervention, comparator, outcome
PP	Per-protocol
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis

qPCR	Quantitative polymerase chain reaction
RCT	Randomised controlled trial
REML	Restricted Maximum Likelihood
RNA	Ribonucleic acid
RoB	Risk of Bias
RoB 2	Risk of Bias 2 tool
ROB-ME	Risk of Bias due to Missing Evidence tool in a meta-analysis
SWiM	Synthesis Without Meta-analysis
TTAS	Time to alleviation of influenza symptoms
TTIIS	Time to improvement of influenza symptoms
WHO	World Health Organization

Objective of the report

The objective of this clinical evidence synthesis report is to generate a focused assessment of the clinical evidence of oseltamivir and baloxavir marboxil. The analytic methods applied to assess the value of using these health technologies, their execution and the results are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in this report include clinical effectiveness and safety. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1. Policy question and context

The topic entails the following policy question which will be informed by addressing the research questions (see ***Chapter 5***).

Should Switzerland maintain the current antiviral stockpile of oseltamivir (Tamiflu®) for influenza pandemic preparedness?

Influenza pandemics have historically posed significant threats to global public health, disrupting societal functions and causing widespread illness and mortality.[1] Antiviral drugs can be key in preventing the spread of infection and maintaining the stability of essential societal structures during the early phase of an influenza pandemic, until a specific vaccine becomes available.[2] The experience of the 2009 influenza A pandemic showed that demand for antiviral drugs can increase quickly and massively even in the case of a mild pandemic. To address foreseeable supply shortages during such volatile phases, Switzerland established a stockpile of oseltamivir (Tamiflu®) in 2012.[3] It has been called into question whether this stockpile should be maintained. To inform this strategic stockpiling decision for future influenza pandemics, the Section Emerging Infectious Diseases and International Cooperation of the Federal Office of Public Health (FOPH) has commissioned a clinical evidence synthesis on the efficacy and safety of oseltamivir (Tamiflu®) and baloxavir marboxil (baloxavir, Xofluza®).

2. Medical background

2.1 Description of influenza

Influenza is an acute respiratory tract infection caused by influenza viruses, spreading easily with respiratory droplets through coughs, sneezes and contaminated hands.[5] Seasonal influenza typically presents with the sudden onset of high fever and cough or sore throat, possibly accompanied by a pronounced feeling of illness and weakness, muscle, joint, head or generalised pain and gastrointestinal symptoms.[4,5] The symptoms generally appear 1-4 days after exposure.[5] While most individuals recover within a week without medical intervention, severe illness or death can occur, particularly in high-risk groups such as the elderly, young children, pregnant women, and those with chronic diseases or immunosuppressive conditions (e.g., untreated HIV, cancer, chemotherapy or long course of steroid treatments).[1] In industrialised countries, most influenza-related deaths occur in individuals aged 65 and older.[1]

2.2 Influenza pandemic

Seasonal influenza refers to the annual flu epidemic.[6] An epidemic is an increase in the number of cases of a specific disease above the usual level in a particular area and time period.[7] An influenza

pandemic is a worldwide spread of a new influenza virus that significantly differs from circulating seasonal influenza viruses, to which there is little or no pre-existing immunity in the human population.[6,8] Influenza pandemics are impossible to predict. The world has experienced four pandemics in the past century: 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), and 2009 (H1N1pdm09). Pandemic viruses can cause mild to severe illness or death, affecting both high-risk groups, similar to seasonal influenza, and healthy individuals, more severely than typical seasonal flu.[3,8]

2.3 Types of influenza

Influenza is a ribonucleic acid (RNA) virus belonging to the Orthomyxoviridae family. There are 4 types of influenza viruses: A, B, C and D. Types A and B are responsible for seasonal epidemics, and type A has previously caused several pandemics. Type A viruses are categorised into subtypes based on the protein combinations on their surface. The subtypes A(H1N1) and A(H3N2) are currently circulating among humans. Type B is not divided into subtypes but has 2 lineages: B/Yamagata and B/Victoria. Type C causes mild infections and has therefore a small public health impact, while type D does not infect humans but mainly cattle.[9]

2.4 Surveillance and diagnosis

In Switzerland, seasonal influenza is a notifiable disease in accordance with the Federal Department of Home Affairs (FDHA) Ordinance of 1 December 2015 “on the reporting of observations of communicable diseases in humans” (SR 818.101.126).[10,11] The dynamics of seasonal influenza are monitored by the Sentinella system, a network of general practitioners and paediatricians across Switzerland who report weekly data on influenza-like illnesses. Clinical data and nasal/throat swabs are collected by the National Reference Centre for Influenza (CNRI), which is part of the Geneva University Hospital, to confirm the presence of the influenza virus. The laboratory tests employed to confirm the diagnosis of influenza within this framework are Hemagglutination inhibition and Polymerase chain reaction (PCR) tests.[12] Seasonal influenza is typically diagnosed clinically based on symptoms and the epidemic context, with laboratory testing rarely performed.[4]

New subtypes with pandemic potential (HxNy) are also notifiable both for laboratory and clinical outcomes based on criteria set out in the reporting guidelines of the FOPH. The CNRI performs PCR testing to confirm influenza infections and identify subtypes (e.g., H1N1, H3N2) and genetic sequencing to detect mutations and assess potential antiviral resistance. The surveillance of specific subtypes such as avian influenza (e.g., H5N1, H7N9) is done in a One Health approach in collaboration with the border veterinary service (BVS) operated by the Federal Food Safety and Veterinary Office (FSVO).

2.5 Role of vaccination and antiviral drugs

Vaccination against viral diseases has been shown to be a cost-effective, efficient, and rapid method to control epidemics and pandemics.[13–15] However, influenza viruses undergo frequent

genetic changes.[16,17] This complicates the development of long-lasting vaccines and requires annual updates to flu vaccines to match circulating strains.[1] Antiviral drugs could contribute to preventing the spread of infection, reducing mortality, and ensuring the continued functioning and stability of essential societal structures until a specific vaccine becomes available.[2]

According to the World Health Organization (WHO), pandemic influenza preparedness must be a top priority for all Member States, considering the magnitude of the threat and the equal vulnerability of all countries.[8] Though the 2009 pandemic was moderate in its impact, targeted pandemic preparation is of great importance and must be developed systematically based on the experience gained. Pandemic preparedness should therefore be routinely reviewed even when there is no crisis. Stockpiling essential resources, such as antiviral drugs, vaccines, and medical supplies, is a vital component of pandemic preparedness.[18] It enables a rapid and effective response to emerging threats by reducing delays in the distribution of critical items during an outbreak.

2.6 Treatments

Several measures can help alleviate influenza symptoms. Maintaining hydration is essential to replace fluids lost due to fever. Antipyretics such as ibuprofen or acetaminophen can help reduce fever, prevent additional fluid loss, alleviate muscle pain and relieve chills, though they do not shorten the duration of the illness. Additionally, antiviral medications are available for the treatment of influenza A and B.[5] Oseltamivir and baloxavir are within the scope of the current technology assessment. These treatments, along with alternative therapies are described in ***Chapter 3.1*** and ***3.2***.

2.7 Burden of influenza

The impact of influenza on public health is significant, leading to widespread morbidity and mortality during peak seasons.[19] Influenza epidemics can lead to substantial productivity losses due to absenteeism, and sometimes hospitals are overwhelmed by patient surges.[1] In temperate zones, influenza viruses mainly circulate during the winter, leading to annual epidemics, with some exceptions, such as during the SARS-CoV-2 pandemic. In Switzerland, influenza seasons lead to 100’000-300’000 doctor visits, thousands of hospitalisations, and several hundred deaths per year.[20] It is estimated that, for adults alone, seasonal influenza healthcare costs fluctuated between CHF 44 million and CHF 77 million annually from 2017 to 2019.[21] Almost 80% of these costs were attributable to hospitalisations.[21] The difference in the number of influenza cases could be partially responsible for the large variation in costs between the years. For example, the percentage of patients testing positive for influenza viruses was 43% (2019/2020), 12% (2021/2022) and 23% (2022/2023), for patients with flu-like illness and/or suspected Covid-19.[4] During the last flu season, 13.8% of the reported suspected flu cases belonged to a group of people with an increased risk of complications and pneumonia was diagnosed in 3.1% of suspected cases.[4] Only 0.05% of the suspected cases received antiviral treatment and 11.8% had been vaccinated against the flu during the last season.[4]

3. Technology

3.1 Technology description

Oseltamivir and baloxavir are antiviral medications used for the prevention and treatment of influenza A and B. Oseltamivir is a neuraminidase inhibitor (NAI) that blocks the function of the neuraminidase enzyme, which is essential for the release of new viral particles from infected cells.[22,23] In contrast, baloxavir is a cap-dependent endonuclease (CEN) inhibitor, representing a newer class of antiviral agents targeting the polymerase acidic protein of the influenza virus, which is necessary for viral transcription.[24] This mechanism interferes with viral RNA transcription, preventing the virus from replicating effectively.[22]

Oseltamivir is available in the form of capsules and as a powder.[25] The dosage for treating adults and children over 12 years is one capsule (75mg) twice daily for 5 days. In case of a seasonal influenza wave, the recommended oral dose for prevention of influenza after close contact with an influenza-infected person or for persons at risk is one capsule (75mg) daily for 10 days for adults and children ≥ 13 years. For children ≤ 12 years old the dose depends on body weight.[25]

Baloxavir is available in the form of oral tablets and granules.[26] Adults, adolescents, and children weighing ≥ 20 kg who can swallow tablets are treated with a single dose of either 40 mg or 80 mg, depending on body weight. For a body weight < 20 kg, the recommended dose is 2 mg of oral granules per kg of body weight, administered as a single dose.[26]

Antiviral treatment should be taken as early as possible after the onset of symptoms.[5] However, according to guidelines from the WHO and the Swiss Society for Infectious Diseases, antiviral drugs should be used sparingly to avoid the development of resistant strains.[3,27,28] Preventive use is recommended for exposed individuals, such as healthcare workers (post-exposure prevention) and for at-risk individuals (pre-exposure prevention). Therapeutic use is advised for individuals with suspected or confirmed influenza, particularly for at-risk individuals and hospitalised patients.[3] In specific cases, antiviral drugs for pre- or post-exposure prevention can aid in outbreak control in certain populations.[29]

3.2 Alternative technologies

Another antiviral treatment for influenza A and B approved for use in Switzerland is the NAI zanamivir (Relenza®). Relenza® is authorised for the treatment of influenza in adults and children aged 7 years and older, as well as for prevention in adults and children aged 12 years and older.[25,26,30] The recommended treatment dosage is two oral inhalations (10 mg per inhalation) twice daily, totalling 20 mg/day, for a duration of 5 days. For prophylactic use, the dosage is 10 mg/day for 10 days, with the option to extend the regimen up to 28 days if necessary.[30] However, its use is contraindicated in patients with severe milk protein allergy and not recommended for individuals with underlying respiratory conditions such as asthma and COPD.[22] Relenza®'s production has been discontinued worldwide, and it is therefore not considered in this report.

Alternative technologies approved for use in Switzerland consist also of non-antiviral treatments, such as Echinaforce®. Echinaforce® is a standardised extract derived from Echinacea purpurea and is commonly used to support the immune system in preventing and managing respiratory tract infections, including influenza-like illnesses.[31,32] Additionally, analgesics and antipyretics, such as paracetamol and ibuprofen, are commonly used to reduce fever and relieve aches and pains associated with influenza. While these over-the-counter drugs help manage discomfort, they do not address the underlying viral infection. Products containing dextromethorphan or guaifenesin are used to manage cough symptoms, and nasal decongestants, such as pseudoephedrine or oxymetazoline, are used to relieve nasal congestion and improve breathing comfort.[33]

3.3 Regulatory status / provider

The approval of oseltamivir and baloxavir in Switzerland differs in terms of age groups, treatment duration, administration routes, and dosing. Oseltamivir is approved for both treatment and prevention in adults and children aged one year and older. Baloxavir is approved for the treatment of uncomplicated influenza in patients symptomatic for up to 48 hours, including children aged one year and older, healthy adults, and adolescents aged 12 years and older, as well as adults at high risk for influenza-related complications. For prevention, baloxavir is approved for use in adults and children aged one year and older. Neither oseltamivir nor baloxavir is listed on the pharmaceutical specialties list ("Spezialitätenliste") and drug costs are not covered by Switzerland's mandatory health insurance. Currently, Switzerland maintains a mandatory stockpile (compulsory reserve) that can be used to meet demands in case of a pandemic.[3]

Switzerland maintains two federally managed stockpiles of oseltamivir to address potential supply shortages in emergencies: the compulsory stockpile and, until 2019, the emergency reserve. These reserves are accessed when commercial supply is insufficient or cantonal stocks are depleted.[3] The compulsory stockpile provides oseltamivir to cantons on a quota basis, particularly for prophylactic use by healthcare personnel. The emergency reserve, managed by the Armed Forces Pharmacy, previously contained 40'000 packs of Tamiflu® (75 mg for adults) and 9'000 packs of Relenza® (5 mg for both children and adults), all of which expired in 2019. No new supplies were purchased, as the compulsory stockpile was deemed sufficient to provide the necessary flexibility.[3]

According to the Swiss Influenza Pandemic Plan of 2018, oseltamivir treatment should not be routinely given to patients with mild illness who are not in high-risk groups.[3] It should be considered for high-risk patients or those with severe illness, especially during periods of high influenza activity, provided influenza is highly suspected. Early treatment is recommended for patients at greater risk of complications or with severe symptoms. The prophylactic use of oseltamivir carries the risk of developing resistance in viral strains. Therefore, post-exposure prevention with oseltamivir should be reserved for patients expected to have a weak immune response, and those at very high risk of severe influenza complications.[3]

4. Population, Intervention, Comparator, Outcome (PICO)

The population, intervention, comparator and outcomes (PICO) are shown in ***Table 1*** and ***Table 2***. They are based on the policy questions and were further developed in consultation with a clinical expert in general internal medicine and ambulatory infectiology.

Table 1: PICO 1 - Therapeutic use

P:	**Patients with influenza A or B or influenza A-, B-like symptoms**	
I:	Oseltamivir (Tamiflu®)	Baloxavir (Xofluza®)
C:	Placebo Baloxavir (Xofluza®) Any non-antiviral treatment	Placebo Any non-antiviral treatment
O:	**Efficacy:** Primary Outcomes • Disease-specific and all-cause mortality • Influenza-associated symptoms or complications (e.g., fever, headache, pneumonia, bronchitis, otitis media) • First hospitalisation due to influenza symptoms Secondary Outcomes • Time to alleviation of influenza symptoms (TTAS) • Number of people with antibiotics use • Length of hospitalisation • Number of patients with re-consultations with a doctor (in outpatient setting) • Number of onward transmissions to household contacts (in outpatient setting) **Safety:** • Adverse drug reactions • Toxicities	

Table 2: PICO 2 - Post-exposure prevention

P:	**Persons receiving prophylactic treatment against influenza (e.g. healthcare personnel or persons at risk)**	
I:	Oseltamivir (Tamiflu®)	Baloxavir (Xofluza®)
C:	Placebo Baloxavir (Xofluza®) Any non-antiviral treatment	Placebo Any non-antiviral treatment
O:	**Efficacy:** Primary Outcomes • Disease-specific and all-cause mortality • Laboratory-confirmed influenza • Influenza confirmed with rapid diagnostic tests • Influenza-associated symptoms or complications (e.g. fever, headache, pneumonia, bronchitis, otitis media) • First hospitalisation due to influenza symptoms Secondary Outcomes • Length of hospitalisation **Safety:** • Adverse drug reactions • Toxicities	

5. Research questions

For the evaluation of oseltamivir and baloxavir the following research questions are addressed:

1. Are oseltamivir and baloxavir efficacious compared to each other, placebo or any non-antiviral treatment in patients with influenza A or B?
2. Are oseltamivir and baloxavir safe compared to each other, placebo or any non-antiviral treatment in patients with influenza A or B?
3. Are oseltamivir and baloxavir efficacious compared to each other, placebo or any non-antiviral treatment in persons receiving prophylactic treatment against influenza?
4. Are oseltamivir and baloxavir safe compared to each other, placebo or any non-antiviral treatment in persons receiving prophylactic treatment against influenza?

The evidence synthesis will address the efficacy and safety of oseltamivir and baloxavir. Costs, cost-effectiveness, budget impact as well as ethical, legal, social and organisational (ELSO) issues will not be addressed.

6. Methodology

The systematic literature review and meta-analysis related to the clinical efficacy and safety was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[34–36]

6.1 Databases and search strategy

The search strategy has been developed based on the PICO framework (see ***Chapter 4***) in collaboration with a medical librarian, following current best practice guidelines. The systematic literature search was conducted in the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Medline, Web of Science, clinicaltrials.gov and WHO International Clinical Trials Registry. The search strategy focused on the population and intervention components of PICO, while comparators or outcomes were not specified to avoid undue narrowing of the search results. Search limits were applied to include ongoing and only randomised controlled trials (RCTs) on humans. No restrictions were applied on the publication date. Several relevant systematic reviews, meta-analyses and network meta-analyses studies were considered when building the search strategy and were also used to validate its quality.[37–48] The detailed search strategy in each database is outlined in ***Appendix 12.1***. To identify additional issues, the international HTA database (INAHTA) and websites of prominent HTA agencies were also searched. All studies were imported to Covidence for study selection.[49]

6.2 Study selection

The inclusion and exclusion criteria were defined according to the PICO framework and are shown in ***Table 3***. All outcomes were considered if they were within the domains outlined in the PICO (***Chapter 4***). The country and the setting were not restricted. The study design was restricted to RCTs. Studies were eligible if they provide essential data for conducting a quantitative or narrative synthesis, ranging from published peer-reviewed journal articles to conference abstracts. The publication language had to be English, French, German or Italian.

Table 3: Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	Human PICO 1: Otherwise healthy patients or with comorbidities treated for influenza or influenza-like symptoms (incl. H1-H3, H5, H7, H9-H11) PICO 2: Healthy patients or with comorbidities receiving prophylactic treatment against influenza or influenza-like symptoms	Animal **Patients receiving the intervention for the treatment or prevention of other diseases, such as COVID.** PICO 2: healthy persons not exposed to influenza
Intervention	• Oseltamivir • Baloxavir	Any other intervention or combination therapy
Comparator	• Oseltamivir • Baloxavir • Placebo	Any other comparator or combination therapy

	• Any non-antiviral treatment approved in Switzerland (including standard care and no treatment)	
Outcomes	Efficacy and safety outcomes mentioned in ***Chapter 4***	• No efficacy or safety outcomes • Outcomes only on pharmacokinetics or pharmacodynamics
Study design	RCT Protocols of RCTs (including ongoing, stopped early, completed but not published in peer-reviewed journals with or without results)	Not RCT, Review, Meta-analysis Phase 1 RCT of healthy not exposed to influenza
Language	English, French, German or Italian	Not English, French, German or Italian
Country	No restrictions	—
Setting	No restrictions	—
Publication status	Published peer reviewed articles, conference abstracts, entries in clinical trial registries from ongoing, stopped or unpublished RCTs	For peer reviewed articles and conference abstracts: not published full text or the essential data could not be obtained

Abbreviation:
RCT: Randomised Controlled Trial

In a first step, the studies were title-and-abstract-screened by 2 reviewers independently according to the inclusion and exclusion criteria. In a second step, 2 reviewers independently reviewed full texts of studies retained from the first step. Disagreements were resolved by consensus and if consensus was not reached, a third reviewer was consulted. To increase consistency between reviewers, training sessions were held. A PRISMA flow diagram was created to illustrate the study selection results.

6.3 Assessment of quality of evidence

The methodological quality of RCTs included in the meta-analysis was critically appraised according to the Cochrane Risk of Bias 2 tool for randomised trials (RoB 2).[50,51] Risk of bias figures were generated. If a study adequately addressed the specific risk of bias domain (e.g. adequate generation of random sequence for randomisation), it was judged as “low risk of bias” in this domain. Description of an inadequate method was judged as “high risk of bias” and, if minor concerns appeared, as “some concerns in risk of bias”. The judgement of the most severe individual domain was assigned to the overall risk of bias. Outcomes judged as some concerns for multiple domains could lead to an overall high risk of bias if the concerns substantially lowered the confidence in the results. The assessment was performed in duplicate, and inconsistencies were solved by consensus. Where consensus was not reached, a third reviewer was consulted.

Bias due to missing evidence using the Risk of Bias due to Missing Evidence tool in a meta-analysis (ROB-ME) was not assessed.[52] Instead, a comprehensive evaluation of selective reporting was included in the risk of bias assessment for each outcome. Additionally, study protocols were reviewed and unpublished studies were systematically assessed, to ensure a thorough appraisal of potential reporting biases and missing evidence. Contour-enhanced funnel plots were not performed to assess publication bias or the effects of small sample sizes, as fewer than 10 studies per

outcome and comparison were available, which could compromise the reliability of these methods.[34,53–55]

To obtain an overall rating of confidence in the estimated effects, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied and the confidence in the meta-analysis results was rated in duplicate.[56] For PICO 1 the outcomes all-cause mortality, influenza-associated complications, first hospitalisation, TTAS, antibiotic use, serious adverse events and adverse events were assessed. For PICO 2 laboratory-confirmed influenza, influenza confirmed with rapid diagnostic tests, influenza-associated complications, length of hospitalisation, serious adverse events and adverse events were examined. The GRADE evidence table was derived using the online tool.[57] Disagreements between raters were solved by consensus. Where consensus was not found, a third reviewer was consulted.

6.4 Methodology data extraction, analysis and synthesis

6.4.1 Data extraction

Relevant data from the included studies were extracted by a single reviewer into a predefined Excel sheet, which was pilot-tested with selected studies retained after full-text screening. A second reviewer checked the extracted data against the original publication. Disagreements were resolved by consensus and if consensus was not reached, a third reviewer was consulted. To increase consistency between reviewers, training sessions were held.

There are different types of analyses used in clinical trials, each serving a specific purpose. In intention-to-treat (ITT) analysis, participants are analysed in the group to which they were originally assigned, regardless of treatment adherence, reflecting real-world effectiveness. Intention-to-treat infected (ITTi) analysis is a modified ITT approach that includes only a subset of randomised participants confirmed to have the influenza virus. In per protocol (PP) analysis, only participants who strictly adhered to the study protocol, such as completing the assigned treatment, are considered. These participants may have influenza-like symptoms or confirmed influenza. When studies reported results from both ITT and PP analyses, only ITT results were extracted. When studies reported results from both ITT and ITTi analyses, data from both analyses were extracted.

The Excel data extraction form included:

- Study characteristics (country, setting, study period, length of follow-up and study sponsor)
- Population (e.g., age and sex structure, diagnosis method, virus type (A/B), influenza severity, disease(s), sample size, comorbidities, risk groups, exposure)
- Intervention (e.g., administration method, dosage, administration time after onset of symptoms, frequency, treatment duration, drug resistance)
- Comparator (e.g., administration method, dosage, administration time after onset of symptoms, frequency, treatment duration)

- Actual results on safety and clinical efficacy (e.g., influenza associated complications, duration of symptoms, TTAS, time to resolution of fever, risk of mortality and first hospitalisation, duration of hospitalisation, re-consultation with a doctor, antibiotic use, drug-related adverse events and severe adverse events, time the outcome was assessed, transmission to household contacts, occurrence of resistance against the intervention)
- Information relevant to assess the quality of studies (i.e., information to perform the RoB, GRADE, ROB-ME. The quality assessment itself was performed outside of Covidence.)
- Additional comments (study limitations, definition of outcomes or issues which are not identifiable from other extracted data)

Details of ongoing, stopped or unpublished RCTs [1] found in clinical trial registries were extracted and summarised in a table:

- status (e.g. recruiting, not yet recruiting, stopped recruiting)
- country
- study period
- population
- intervention
- comparator
- outcomes
- estimated time of completion of the trial
- study sponsor

6.4.2 Data analysis and synthesis

The included studies were summarised in a table including information on the study characteristics and relevant outcomes, grouped by relevant patient subpopulations.

Separate pairwise meta-analyses were performed for each outcome within each PICO, type of analysis (ITT, ITTi, PP) and comparison when at least 2 published peer-reviewed studies reported the outcome. This approach was used to pool the estimates for the outcomes with the highest relevance for the patients. These are outcomes that are judged as critical outcomes to quantitatively summarise the estimated efficacy and safety in the included studies and are most frequently reported in RCTs. Additionally, only dosages recommended in Switzerland were included in the analysis. When meta-analysis was possible, forest plots were presented. Meta-analyses were conducted using the *metafor* package in R.[58] Continuous data were pooled using mean differences. Where means were not available, medians were transformed to means[59–61] and 95% confidence intervals (CI) or p-values were converted to standard deviations.[60,61] Binary data were pooled using risk ratios as the effect measure.[62] Uncertainty was expressed using 95% CI. Between studies variation was taken into account and Tau square was estimated by the Restricted Maximum

[1] Unpublished RCTs refer to studies that are published in trial registries but not in peer reviewed journals.

Likelihood (REML) method. When the number of studies is limited, heterogeneity measures such as I square and Tau square are subject to considerable uncertainty. Therefore, simple thresholds for identifying heterogeneity were not applied and prediction intervals were not calculated. For studies with no events in one or both arms, computation error may arise due to division by zero, which occurs when the calculations involve a zero count. To address this issue, studies with no events in both arms were excluded from the meta-analysis. They were also excluded because studies with no events in both arms do not provide any indication of either the direction or magnitude of the relative treatment effect. For studies with no events in one arm, a fixed value of 0.5 was added to all cells of the 2×2 table.[63] Sensitivity analyses using a different continuity correction (0.1) were conducted. Further sensitivity analysis was conducted for pre- and post-exposure prevention in PICO 2. Unless stated otherwise, the results presented are based on intention-to-treat analysis (ITT). Results are presented separately for "patients with influenza-like symptoms" and "patients with confirmed influenza".

The possible network meta-analysis mentioned in the protocol was not performed, as studies with direct comparisons of oseltamivir and baloxavir were available. Meta-regressions were also not conducted due to the limited number of studies available.

If meta-analyses were not feasible, the evidence was described narratively using the Synthesis Without Meta-analysis (SWiM) guideline.[64]

To identify possible effect modifiers for the outcomes mortality, influenza-associated complications, hospitalisation due to influenza symptoms, time to alleviation of influenza symptoms, fever and antibiotic use subgroup analyses were computed when at least two studies in each subgroup were available. First, subgroup analyses by timing of drug administration (within 48 hours after onset of symptoms, post-48 hours after onset of symptoms) were performed. Second in patients that were administered the drug within 48 hours the following subgroup analyses were conducted:

- Age groups (children, adolescents, adults, >65 years)
- High-risk groups (pregnant women, people who are immunosuppressed, elderly, people with a chronic Illness, people with multiple risks)

7. Results

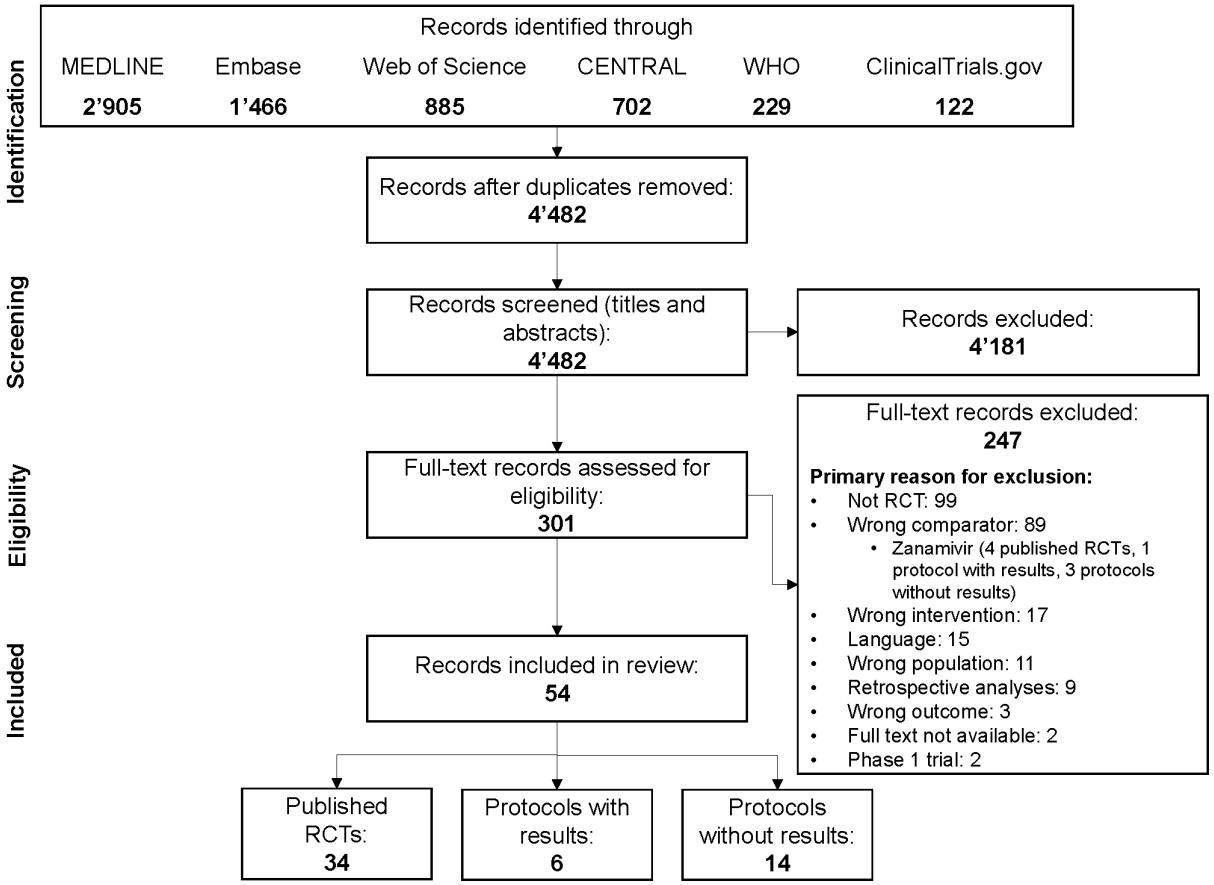
7.1 PRISMA flow diagram

In total, 4'482 unique records were identified through the literature searches. Of these, 4'181 were excluded based on their titles and abstracts (***Figure 1***). The full texts of the remaining 301 records were screened, resulting in the exclusion of 247 records. The most common reasons for exclusion were that the studies were not RCTs or had an ineligible comparator [2]. Fifty-four records were

[2] The high number of studies excluded due to the wrong comparator is attributable to the stepwise approach employed to determine the feasibility of conducting a network meta-analysis. Further details can be found in the study protocol.[65]

ultimately included for the assessment of clinical efficacy and safety, comprising 34 RCTs, 6 protocols with reported results, and 14 protocols without reported results.

Figure 1: PRISMA flow diagram



7.2 Study characteristics and quality assessment of included studies

7.2.1 Study characteristics of included RCTs

Of the 34 RCTs included, 27 addressed PICO 1 and 9 addressed PICO 2. The included RCTs were conducted in various countries, involving a total of 18'418 participants for PICO 1 (***Table 4***) and 4'195 participants for PICO 2 (***Table 5***). The most recent RCT for PICO 1 was published in 2024 and for PICO 2 in 2020, while the oldest RCT for both PICOs dates back to 1999.

PICO 1

Interventions and Comparators: Seventeen studies compared oseltamivir with placebo[66–82], 4 compared oseltamivir with baloxavir[66,67,83,84], 7 compared oseltamivir with non-antiviral treatments (such as usual primary care, Echinaforce®, or no treatment)[85–91] and 3 compared baloxavir with placebo[66,67,92].

Dosage: Most RCTs employed the standard dosage of oseltamivir, as detailed in the notes accompanying ***Table 4*** and ***Table 5.*** One RCT from 1999 assigned participants to 20, 100, or 200 mg twice daily, or 200 mg once daily[81]. Additionally, 3 RCTs from 2000 analysed a treatment regimen of 150 mg twice daily for 5 days[69,75,80]. For children, 3 RCTs administrated oseltamivir as a syrup

at a dosage of 2mg/kg twice daily[71,77,91]. Nearly all RCTs employed the standard dose of baloxavir, with the exception of one study, which assigned a single dose of 10 mg, 20 mg or 40 mg[67].

Administration time: Nineteen RCTs[66–69,71,72,74–77,83–89,91,92] administrated the treatment within 48 hours of symptom onset and 2 RCTs[70,73] within 120 hours. Two RCTs[78,82] analysed two groups, one provided treatment within 48 hours and one between 48 and 120 hours from symptom onset. In one RCT[79] the administration time varied between 44 and 93 hours, two RCTs [80,81] looked at the time from inoculation, while one RCT[90] did not report the administration time at all.
Population: Six RCTs for PICO 1 focused on patients with health risks[66,70,71,76,87,88], 7 on children[71,72,77,79,84,90,91], one on elderly individuals[76], and 15 included mixed populations of either only adults or individuals of all ages with diverse health states[67–69,73–75,78,80,82,83,85,86,89,92,93].
Gender: All RCTs recruited both women and men, with the proportion of women varying between 28% and 67%.

Setting: Most of the RCTs for PICO 1 were conducted in outpatient clinics[66,67,69–73,85,86,89], four in an inpatient setting[79,87,88,91], two in a community or household setting[78,82], and one in an emergency department[90].

Follow-up: The follow-up duration varied across studies, with most investigating periods of 20-28 days.

Funding: Thirteen RCTS[66,67,69,71,72,75–77,80,84,85,87,92] were industry-funded, 7 RCTs[68,70,78,79,82,86,88] were publicly funded, one RCT[83] did not receive any funding, one RCT[81] received funding from both industry and public institutions and 5 RCTs[73,74,89–91] did not report their funding source.

PICO 2

Interventions and Comparators: Eight studies compared oseltamivir with placebo[80,81,93–98] and one compared baloxavir with placebo[99].

Dosage: The prevention dosage varied across studies, with some using oseltamivir at 75 mg once daily for durations ranging from 1 to 112 days.[80,98] The one RCT on baloxavir prescribed 1 mg/kg for participants weighing <10 kg, 10 mg for those weighing 10 to 20 kg, 20 mg for 20 to 40 kg, 40 mg for 40 to 80 kg, and 80 mg for those weighing ≥80 kg.[99]

Population: Three RCTs focused on patients with health risks[94,95,97], two of which specifically targeted elderly individuals[95,97], and 6 RCTs included mixed populations of either only adults or individuals all ages with diverse health states[80,81,93,96,98,99].

Gender: All RCTs recruited both women and men, with the proportion of women varying between 31% and 79%.

Setting: Two RCTs were conducted in nursing homes[95,97], one in a community or household setting[96], one in outpatient clinics[99], and one in an inpatient setting[98].

Timing of prevention: Two RCTs provided pre-exposure prevention[93,98], while 3 focused on post-exposure prevention[80,97,99].

Follow-up: The follow-up duration varied across studies, ranging from 8 days[93] to 16 weeks[94,98].

Funding: Five RCTS[80,94–96,99] were industry-funded, 2 RCTs[97,98] were publicly funded, and 2 RCTs[81,93] received funding from both industry and public institutions.

Table 4: Evidence table for RCTs on PICO 1

First author year	Country Funding	Enrolment period Follow-up	Setting Sample size	Diagnosis method Virus Type	Age group Risk group	Intervention (dosage) Comparator (dosage)	Administration time[1]	Mean age (SD) Sex (% women)
Baker et al. 2020[84]	USA, Poland, Spain, Costa Rica, Mexico and Russia	20.11.2018 - 27.08.2019	NR	PCR/ laboratory-confirmed	Children	Oseltamivir (standard)	within 48 hours	I: 6 (3), C: 6 (3)
	F. Hoffmann-La Roche AG	29 days	176	Influenza A or B	All	Baloxavir (standard)		I: 55%, C: 52%
Beigel et al. 2020[68]	Thailand, USA, Argentina	01.01.2012 - 01.10.2017	NR	Several	Adults	Oseltamivir (standard)	within 48 hours	I: 37, C: 35 (median)
	National Institute of Health and federal funds from the National Cancer Institute	28 days	558	Influenza A or B	All	Placebo		I: 66%, C: 59%
Butler et al. 2020[86]	15 European countries	15.01.2016 - 12.04.2018	Outpatient clinics	Symptoms-based	All	Oseltamivir (standard)	within 48 hours	NR
	European Commission	28 days	3259	Influenza A- or B-like symptoms	All	Usual primary care		NR
Ceyhan et al. 2012[90]	Turkey	01.01.2011 - 01.03.2011	Emergency department	Symptoms-based	Children	Oseltamivir (standard)	NR	NR
	NR	7 days	300	Influenza A- or B-like symptoms	All	No treatment		NR
Dawood et al. 2016[79]	El Salvador, Panama	01.09.2012 & 01.04.2013 - 01.10.2012 / 01.10.2013	Inpatient	PCR/ laboratory-confirmed	Children	Oseltamivir (standard)	within 44-93 hours	NR
	CDC	7 days after discharge	683	Influenza A or B	NR	Placebo		NR

First author year	Country	Enrolment period	Setting	Diagnosis method	Age group	Intervention (dosage)	Administration time[1]	Mean age (SD)
	Funding	Follow-up	Sample size	Virus Type	Risk group	Comparator (dosage)		Sex (% women)
Dharan et al. 2011[73]	USA	19.01.2009 - 11.02.2009	Outpatient clinics	PCR/ laboratory-confirmed	All	Oseltamivir (standard)	within 120 hours	I: 12, C: 5 (median)
	NR	14 days	19	Influenza A	All	Placebo		I: 58%, C: 28%
Fry et al. 2014[82]	Bangladesh	11.05.2008 - 31.12.2010	Community/ households	Rapid antigen test	All	Oseltamivir (standard)	two groups: 1) <=48 hours and 2) 48-120 hours	**I: 5, C: 5 (median)**
	CDC	14 days	1190	Influenza A or B	NR	Placebo		**I: 47%, C: 48%**
Fry et al. 2015[78]	Bangladesh	11.05.2008 - 31.12.2010	Community/ households	Rapid antigen test	All	Oseltamivir (standard)	two groups: 1) <=48 hours and 2) 48-120 hours	I: 5, C: 5 (median)
	CDC	7 days after symptoms' resolvent	1190	Influenza A or B	All	Placebo		I: 47%, C: 48%
Hayden et al. 1999[81]	USA	01.06.1997 - 01.07.1997	NR	PCR/ laboratory-confirmed	Adults	Oseltamivir (20/100/200 mg twice or 200 mg once daily)	28 hours after inoculation	Overall: 21 (median)
	F. Hoffmann-La Roche AG and National Cancer Institute, National Institutes of Health	8 days	80	Influenza A	All	Placebo		NR
Hayden et al. 2000[80]	USA, UK, New Zealand	NR	NR	PCR/ laboratory-confirmed	Adults	Oseltamivir (75 mg/150 mg twice daily)	24 hours after inoculation	NR
	F. Hoffmann-La Roche AG	8 days on study site and 3-4 weeks after discharge	197	Influenza B	All	Placebo		NR
Hayden et al. 2018[67]	Japan and USA	Phase 2: 01.12.2015 - 01.03.2016 Phase 3: 01.12.2016 - 01.03.2017	Outpatient clinics	Phase 2: Rapid antigen test Phase 3: PCR/ laboratory-confirmed	Adults	Phase 2: Baloxavir (10/20/40 mg once daily) - Placebo Phase 3: Oseltamivir (standard) - Baloxavir (standard) - Placebo	within 48 hours	Phase 2: B: 36-38 (median; based on dosage), P: 37 (median) Phase 3: O: 35, B: 32, P: 33 (median)
	Shionogi & Co., Ltd.	22 days	Phase 2: 400 Phase 3: 1436	Influenza A or B	All			Phase 2: B: 32%-42% (based on

First author year	Country Funding	Enrolment period Follow-up	Setting Sample size	Diagnosis method Virus Type	Age group Risk group	Intervention (dosage) Comparator (dosage)	Administration time[1]	Mean age (SD) Sex (% women)
								dosage), P: 39% Phase 3: O: 42%, B: 49%, P: 48%
Heinonen et al. 2010[72]	Finland F. Hoffmann-La Roche AG and Turku University Hospital Foundation	14.01.2008 - 26.03.2009 5-8 days	Outpatient clinics 409	PCR/ laboratory-confirmed Influenza A or B	Children All	Oseltamivir (standard) Placebo	within 24 hours	I: 6 (3.2), C: 6 (2.9) I: 58%, C: 28%
Ison et al. 2020[66]	Japan, South Korea, Philippines, Taiwan, USA, Europe (Belgium, Bulgaria, Germany, Spain, UK, Hungary, Latvia, Poland, and Romania), and areas in Australia, New Zealand, and South Africa Shionogi & Co., Ltd.	11.01.2017 - 30.03.2018 22 days	Outpatient clinics 2184	PCR/ laboratory-confirmed Influenza A or B	All With multiple risks	Oseltamivir (standard), Baloxavir (standard) Placebo	within 48 hours	O: 51 (17), B: 52 (17), P: 52 (17) O: 51%, B: 50%, P: 53%
Johnston et al. 2005[71]	many F. Hoffmann-La Roche AG	1998-1999 28 days	Outpatient clinics 335	PCR/ laboratory-confirmed Influenza A or B	Children With asthma	Oseltamivir (standard) Placebo	within 48 hours	I: 9, C: 9 (median) I: 35%, C: 38%
Li et al. 2004[74]	China NR	01.01.2001 - 01.04.2001 21 days	NR 478	PCR/ laboratory-confirmed / Symptoms-based Influenza A or B /	Adults All	Oseltamivir (standard) Placebo	within 36 hours	I: 32 (12), C: 30 (11) I: 53%, C: 47%

First author year	Country Funding	Enrolment period Follow-up	Setting Sample size	Diagnosis method Virus Type	Age group Risk group	Intervention (dosage) Comparator (dosage)	Administration time[1]	Mean age (SD) Sex (% women)
				Influenza A- or B-like symptoms				
Lin et al. 2006[87]	China F. Hoffmann-La Roche AG	2002 - 2003 21 days	Inpatient 56	PCR/ laboratory-confirmed Influenza A or B	All With chronic illness	Oseltamivir (standard) Symptomatic treatment	within 24 hours	I: 48 (1), C: 52 (16) I: 37%, C: 45%
Markovski et al. 2002[89]	North Macedonia NR	01.12.2001 - 01.04.2002 NR	Outpatient clinics 41	PCR/ laboratory-confirmed Influenza A or B	Adults All	Oseltamivir (standard) No treatment	within 48 hours	NR NR
Martin et al. 2001[76]	NR F. Hoffmann-La Roche AG	NR 21 days	NR 1138	PCR/ laboratory-confirmed NR	All/ Elderly With chronic illness/ Elderly	Oseltamivir (standard) Placebo	within 36 hours	Chronic illness: I: 54, C: 50 (median) Elderly: I: 73, C: 73 (median) Chronic illness: I: 57%, C: 55% Elderly: I: 58%, C: 56%
McLean et al. 2015[70]	USA CDC	2007 - 2011 14 days	Outpatient clinics 193	PCR/ laboratory-confirmed Influenza A or B	All With multiple risks	Oseltamivir (standard) Placebo	within 120 hours	I: 18, C: 17 (median) I: 57%, C: 67%
Nicholson et al. 2000[75]	Europe, Canada, China F. Hoffmann-La Roche AG	01.01.1998 - 01.03.1998 21 days	NR 726	PCR/ laboratory-confirmed / Symptoms-based Influenza A or B / Influenza A- or B-like symptoms	Adults All	Oseltamivir (75 mg/150 mg twice daily) Placebo	within 36 hours	I: 38 (11) -37 (12) (based on dosage), C: 33 I: 47%-50% (based on dosage), C: 50%
Qiu et al. 2024[83]	China No financial	01.01.2022 - 01.03.2022 5 days	NR 200	PCR/ laboratory-confirmed Influenza A	All All	Oseltamivir (standard) Baloxavir (standard)	within 48 hours	I: 44 (17), C: 40 (17) I: 52%, C: 49%

First author year	Country Funding	Enrolment period Follow-up	Setting Sample size	Diagnosis method Virus Type	Age group Risk group	Intervention (dosage) Comparator (dosage)	Administration time[1]	Mean age (SD) Sex (% women)
	support was received							
Ramirez et al. 2018[88]	USA CDC	2010 - 2013 30 days	Inpatient 1107	PCR/ laboratory-confirmed / Symptoms-based Influenza A or B / Influenza A- or B-like symptoms	All With multiple risks	Oseltamivir (standard) Standard care	within 24 hours	I: 62, C: 62 (median) I:45%, C: 44%
Raus et al. 2015[85]	Czech Republic A. Vogel Bioforce AG	22.11.2011 - 29.04.2013 10 days	Outpatient clinics 473	Symptoms-based Influenza A- or B-like symptoms	All All	Oseltamivir (standard) Echinaforce	within 48 hours	I: 37 (13), C: 38 (14) I: 54%, C: 46%
Sato et al. 2005[91]	Japan NR	01.12.2002 - 01.04.2003 NR	Inpatient 63	Rapid antigen test Influenza A and B	Children All	Oseltamivir (2 mg/kg twice daily) No antiviral agent	within 48 hours	Influenza A: I: 3 (2), C: 5 (2) Influenza B: I: 5 (3), C: 4 (3) NR
Treanor et al. 2000[69]	USA F. Hoffmann-La Roche AG	01.01.1998 - 01.03.1998 21 days	Outpatient clinics 629	PCR/ laboratory-confirmed / Symptoms-based Influenza A or B	Adults All	Oseltamivir (75 mg/150 mg twice daily) Placebo	within 36 hours	I: 32 (11) -33 (10) (based on dosage), C: 33 I: 45%-53% (based on dosage), C: 54%
Whitley et al. 2001[77]	USA and Canada F. Hoffmann-La Roche AG	1998 -1999 28 days	NR 698	PCR/ laboratory-confirmed Influenza A or B	Children All	Oseltamivir (2 mg/kg twice daily) Placebo	within 48 hours	I: 5, C: 5 (median) I: 50%, C: 49%
Watanabe et al. 2019[92]	Japan Shionogi & Co., Ltd.	01.12.2015 - 01.04.2016 14 days	NR 200	PCR/ laboratory-confirmed NR	NR All	Baloxavir (standard) Placebo	within 48 hours	NR NR

Abbreviations:
B: baloxavir, C: comparator, CDC: Centers for Disease Control and Prevention, I: intervention, NR: not reported, O: oseltamivir, P: placebo, PCR: Polymerase chain reaction, SD: standard deviation
Notes:
Standard dose for oseltamivir: 30 mg twice daily for those weighting ≤15 kg, 45 mg for 15–23 kg, 60 mg for 23–40 kg, and 75 mg for >40 kg, or 15 mg/mL in liquid form for children weighting ≤88 pounds, 3 mg/kg twice daily for infants
Standard dose for baloxavir: 20 mg single dose for those weighting 20-40 kg, 40 mg for 40-80 kg, 80 mg for ≥80 kg or 2 mg/kg for <20 kg in children
[1]Time between symptom onset and medication administration

Table 5: Evidence table for RCTs on PICO 2

First author year	Country Funding	Enrolment period Follow-up	Setting Sample size	Diagnosis method Virus Type	Age group Risk group	Intervention (dosage) Comparator (dosage)	Mean age (SD) Sex (% women)
Anekthananon et al. 2013[98]	Thailand National Institute of Allergy and Infectious Diseases (NSAID) & University of Oxford	01.10.2009 - 01.04.2010 16 weeks	Inpatient 194	Pre-exposure	Adults All	Oseltamivir (75 mg once daily for 112 days) Placebo	I: 32, C: 30 (median) I: 73%, C: 69%
Hayden et al. 1999[81]	USA F. Hoffmann-La Roche AG and National Cancer Institute, National Institutes of Health	01.06.1997 - 01.07.1997 8 days	NR 37	Pre-exposure	Adults All	Oseltamivir (100 mg once/twice daily for 5 days) Placebo	Overall: 21 (median) NR
Hayden et al. 1999[93]	USA F. Hoffmann-La Roche AG and National Cancer Institute, National Institutes of Health	1997 - 1998 8 weeks	NR 1039	NR	Adults All	Oseltamivir (75 mg once daily for 7 days) Placebo	I: 34 (NR), C: 35 (NR) I: 61%, C: 64%
Hayden et al. 2000[80]	USA, UK, New Zealand F. Hoffmann-La Roche AG	NR 8 days on study site and 3-4 weeks after discharge	NR 58	Post-exposure	Adults All	Oseltamivir (75 mg once for 1/2 days) Placebo	NR NR
Ikematsu et al. 2020[99]	Japan	01.11.2018 - 01.03.2019	Outpatient clinics 749	Post-exposure	All All	Baloxavir (1 mg/kg for weight < 10 kg, 10 mg for 10 ≤ weight < 20 kg, 20 mg for 20	I: 34 (16), C: 34 (17) I: 79%, C: 77%

First author year	Country Funding	Enrolment period Follow-up	Setting Sample size	Diagnosis method Virus Type	Age group Risk group	Intervention (dosage) Comparator (dosage)	Mean age (SD) Sex (% women)
	Shionogi & Co., Ltd.	10 days				≤ weight < 40, 40 mg for 40 ≤ weight < 80 kg, 80 mg for weight ≥ 80 kg) Placebo	
Ison et al. 2012[94]	USA, Israel, Europe F. Hoffmann-La Roche AG	17.01.2007 - 03.06.2008 112 days	NR 475	NR	All Immuno-suppressed	Oseltamivir (standard once daily for 84 days) Placebo	I: 49 (NR), C: 49 (NR) I: 31%, C: 36%
Peters et al. 2001[95]	USA, France, Netherlands, Belgium, UK F. Hoffmann-La Roche AG	1998 - 1999 8 weeks	Nursing home 548	NR	Elderly	Oseltamivir (75 mg once daily for 42 days) Placebo	I: 81 (NR), C: 82 (NR) I: 68%, C: 70%
van der Sande et al. 2014[97]	the Netherlands Dutch Ministry of Health	2009 – 2013 NR	Nursing home 140	Post-exposure	Elderly	Oseltamivir (75 mg once daily for 10 days) Placebo	I: 84 (8), C: 79 (9) I: 72%, C: 62%
Welliver et al. 2001[96]	Belgium, Canada, Denmark, Finland, Germany, Netherlands, Norway, Switzerland, UK, USA F. Hoffmann-La Roche AG	1998 - 1999 25 days	Community/ households 955	NR	Adults All	Oseltamivir (75 mg once daily for 7 days) Placebo	I: 33 (NR), C: 34 (NR) I: 51%, C: 51%

Abbreviations:

C: comparator, CDC: Centers for Disease Control and Prevention, I: intervention, NR: not reported, PCR: Polymerase chain reaction, SD: standard deviation

Notes:

Standard dose for oseltamivir: 30 mg twice daily for those weighting ≤15 kg, 45 mg for 15–23 kg, 60 mg for 23–40 kg, and 75 mg for >40 kg, or 15 mg/mL in liquid form for children weighting ≤88 pounds, 3 mg/kg twice daily for infants

Standard dose for baloxavir: 20 mg single dose for those weighting 20-40 kg, 40 mg for 40-80 kg, 80 mg for ≥80 kg or 2 mg/kg for <20 kg in children

[1]Time between symptom onset and medication administration

7.2.2 Study characteristics of included protocols

Out of the 20 included RCT protocols that were published in trial registries but not in peer-reviewed journals, 17 addressed PICO 1 (***Table 6***) and 3 addressed PICO 2 (***Table 7***). Overall, 9 RCTs were completed, 5 have been stopped early, and 3 were ongoing, with 2 currently in the recruitment phase. The status of 3 trials remained unknown. Among the RCTs stopped early, one was industry-funded, while the sponsor for two studies was not reported. Furthermore, the results for 6 RCTs were published in trial registries but not in peer-reviewed journals. These findings are presented in ***Chapter 7.6.***

Regarding the interventions, 9 protocols compared oseltamivir with placebo, 3 compared oseltamivir with baloxavir, 2 compared oseltamivir, baloxavir, and placebo, and 1 compared oseltamivir, baloxavir, the combination of oseltamivir and baloxavir, and no intervention. Additionally, 3 protocols compared oseltamivir with usual primary care (including paracetamol), and one compared baloxavir with placebo. One protocol focused on oseltamivir but did not report the comparator.

Table 6: Characteristics of included protocols for PICO 1

Trial ID	Trial Status Trial Phase	Registra- tion/start date	Funding	Setting	Age	Virus type	Intervention(s) Comparator(s)	Outcomes
NCT00436124	Stopped Phase IV	15.02.2007	F. Hoffmann- La Roche AG	NR	18-64	Influenza A and B	Oseltamivir NR	Viral shedding Serum and intracellular concentrations of inflam- matory cytokines Duration of illness Health and functional status Extent and severity of symptoms Incidence of resistant viruses Adverse events
EUCTR2007-004734-17	Completed NR	19.09.2007	Terho Heik- kinen	NR	1-3	Influenza A and B	Oseltamivir Placebo	NR
NCT01249833	Completed Phase IV	26.11.2010	Trial Manage- ment Group Inc.	NR	18-65	Influenza A and B	Oseltamivir and standard of care treatment standard of care alone	Attention Working Memory Processing Speed Mood Assessment
EUCTR2006-006263-23-IT	Stopped Phase IV	05.01.2012	NR	NR	NR	Influenza A and B	Oseltamivir Placebo	Viral shedding Serum and cytoplasmatic inflammatory cytokine concentration Patient's health and functional status Resistance
EUCTR2013-001983-52-GB, NCT01980966	Completed Phase II	19.09.2013	Genentech, Inc.	Hospital	18-45	Severe influenza A	Oseltamivir Placebo	Viral area under the concentration-time curve (AUC) of nasopharyngeal viral load by quantitative Polymerase Chain Reaction (qPCR) Adverse events Lung function Anti-therapeutic antibodies Pharmacokinetics AUC of nasopharyngeal viral load Peak viral load (qPCR and cell culture) Duration of viral shedding Duration of Grade 2 or worse symptoms
EUCTR2014-004471-23-SE	Completed Phase I	18.06.2015	University of Oxford	Primary care	All	Influenza A and B	Oseltamivir and standard of care treatment	Time to return to usual daily activity Cost effectiveness Incidence of hospital admissions

Trial ID	Trial Status Trial Phase	Registra- tion/start date	Funding	Setting	Age	Virus type	Intervention(s) Comparator(s)	Outcomes
							Standard of care alone	Complications related to influenza-like illness (ILI) Repeat attendance at the GP Time to alleviation of ILI symptoms Incidence of new or worsening symptoms Time to initial reduction in severity of symptoms Duration of symptoms that are moderately severe or worse Use of additional symptomatic and prescribed medication, including antibiotics Other
NCT02561169	Stopped Phase IV	22.09.2015	McMaster Uni- versity	Outpatient hospital, community centre, medi- cal centre, hospital emergency department	18-65	Influenza A and B	Oseltamivir Placebo	Length of non-elective hospitalisation Non-elective Hospitalisations New antimicrobial prescription Need for mechanical ventilation Admission to intensive or critical care unit Duration of mechanical ventilation Pneumonia Acute Sinusitis Adverse Events Death Duration of stay in intensive or critical care unit Medical visits for acute respiratory illness Lower respiratory tract infection (LRTI)
NCT03754686	Unknown status Phase IV	25.11.2018	Rambam Health Care Campus	Tertiary hos- pital	≥18	Influenza-like Ill- ness	Oseltamivir Paracetamol	Clinical stability Time to clinical stability
UMIN000035028	Completed NR	27.11.2018	Kyoto Chubu Medical Center Department of Pediatrics	NR	≤15	Influenza A and B	Oseltamivir Baloxavir	Time to resolution of fever Number of days absent from school or preschool Number of asthmatic symptoms Number of pneumonia Number of gastrointestinal symptoms Number of abnormal behaviours Drug adherence
EUCTR2018-004056- 37-ES, NCT03969212	Completed Phase III	29.05.2019	F. Hoffmann- La Roche AG	NR	5-64	Influenza A and B	Baloxavir Placebo	Virological Transmission by Day 5/9 Symptomatic Transmission by Day 5/9 Any Virological Infection by Day 9 Any Symptomatic Infection by Day 9

Trial ID	Trial Status Trial Phase	Registra- tion/start date	Funding	Setting	Age	Virus type	Intervention(s) Comparator(s)	Outcomes
								Adverse Events Palatability and Acceptability Response
jRCTs071200034	Completed NR	05.10.2020	Mukae Hiroshi	NR	≥75	Influenza A and B	Oseltamivir Baloxavir	Time to improvement of influenza symptoms Time to alleviation of the seven influenza symptoms Time to improvement of the four general symptoms Time to improvement of the three respiratory symptoms Time to resolution of fever to normal temperature Resolution of fever to normal temperature Body temperature Influenza virus serum antibody titers Time to resolution of gastrointestinal symptoms Time to improvement of each symptom of influenza Time to return to pre-influenza health Influenza-related complications Household infection rate for influenza after the start of the study Other
NCT05648448	Recruiting Phase II	22.02.2023	University of Oxford	NR	18-60	Influenza A and B	Oseltamivir Baloxavir Oseltamivir/ Baloxavir No intervention	Rate of viral clearance Time to symptom alleviation Fever duration Rates of hospitalisation Development of influenza-related complications
NCT06507813	Recruiting Phase III	28.06.2024	Jiaxing AnDi-Con Biotech Co.,Ltd	NR	2-11	Influenza A and B	Oseltamivir Baloxavir Placebo	Adverse Events Serious Adverse Events Plasma Concentrations of ADC189 and ADC189-I07 Time to Resolution of Influenza Symptoms
CN-00311642 (Proceeding of an annual meeting by Hayden et al. 1998[100])	NR	NR	NR	NR	18-65	Influenza A and B	Oseltamivir Placebo	Time to alleviation of illness Duration of illness Severity of illness Incidence of secondary complications Acetaminophen use Health status

Trial ID	Trial Status Trial Phase	Registra- tion/start date	Funding	Setting	Age	Virus type	Intervention(s) Comparator(s)	Outcomes
								Daily activity Sleep quality
CTRI/2019/12/022490	Stopped Phase III	NR	NR	NR	NR	Influenza A	Oseltamivir Placebo	NR
NR (Congress paper by Kawaguchi et al. 2018[101])	Completed Phase III	NR	Shionogi & Co., Ltd.	NR	12–64	Influenza B	Oseltamivir Baloxavir Placebo	Time to alleviation of symptoms (TTAS Viral titres
NR (Congress paper by Zaug et al. 2001[102])	NR	NR	F. Hoffman-La Roche Ltd.	NR	>13	Influenza A and B	Oseltamivir Placebo	Duration of illness Titres Complications

Abbreviations:
NR: not reported, qPCR: quantitative Polymerase chain reaction

Table 7: Characteristics of included protocols for PICO 2

Trial ID	Trial Status Trial Phase	Registra- tion/start date	Funding	Setting	Age	Virus type	Intervention(s) Comparator(s)	Outcomes
NL-OMON33181, EUCTR2006-000749-21-NL	Completed NR	01.09.2009	ZonMw;RIVM	Nursing homes	18-99	Post-exposure	Oseltamivir Placebo	Newly laboratory confirmed influenza Resistance Cost-effectiveness Potential ethical and logistical restrictions
NCT02282384	Stopped Phase IV	10.2014	McMaster Uni-versity	Outpatient	18-90	NR	Oseltamivir Placebo	Non-elective admission to hospital Lower respiratory tract infection other
NCT05012189	Active, not re-cruiting Phase IV	12.08.2021	Insight Thera-peutics, LLC	Nursing homes	18-120	NR	Oseltamivir Baloxavir	Total number of ILI cases Outbreak duration Facility-level data on antiviral courses of treatment Hospitalisations Mortality

Abbreviations:
NR: not reported

7.2.3 Risk of Bias

Figure 2 shows the risk of bias across all included RCTs and outcomes which were analysed using the ITT approach. The overall bias was judged to be of 'some concern' for almost all outcomes. The domain 'selection of the reported result' was judged as having some concerns in most studies because no pre-specified analysis plan was available for some studies or secondary outcomes were not pre-specified in the protocol. The risk of bias concerning the domain 'measurement of the outcome' was assessed as low in most of the studies. One study was open-label and the outcome adverse events was reported by the patients[87] and in another study the information about blinding of the participants and assessors was missing.[91] Therefore, the outcome in these studies was rated as having high risk of bias. For the domain 'missing outcome data', risk of bias was low in most of the studies. Several outcomes were rated as having some concerns due to slightly less than 95% of participant data being available, or because the number of participants with missing outcome data exceeded the observed number of events (e.g. death, hospitalisation). Three studies had a significant amount of unexplained missing data or missingness in the outcome, which was probably depending on its true value.[76,85,86] The domain 'deviations from intended interventions' was mostly rated as having low risk. Three outcomes were rated as high risk of bias, because in the ITT analyses several participants who had received treatment were excluded.[73,85,86] The 'randomisation process' was assessed as having low risk of bias in the majority of studies.

Figure 3 shows the risk of bias across all included RCTs and outcomes which were analysed using the per-protocol approach. The overall bias and the domains 'missing outcome data' and 'deviations from intended interventions' were rated as having high risk of bias because excluded participants who did not meet the per-protocol criteria might have affected the outcome values and a relevant number of participants had missing values.[85,86]

The detailed risk of bias assessments for each outcome of interest of the included RCTs are presented in the Appendix in **Table 54** to ***Table 58***.

Regarding PICO 1, the overall risk of bias across all outcomes analysed using the intention-to-treat approach was predominantly assessed as having ‘some concerns’. This judgment was mainly influenced by the domains ‘missing outcome data’ and ‘selection of the reported result’. The primary reasons were that missing data slightly exceeded the 5% threshold and that no pre-specified analysis plan was available for the included RCTs or secondary outcomes were not pre-specified in the protocol.

For PICO 1, the overall risk of bias of all outcomes analysed using the per-protocol approach was assessed as high. This was primarily due to serious concerns related to the domains of 'deviations from intended interventions' and 'missing outcome data'.

For PICO 2 the overall risk of bias across all outcomes analysed using the intention-to-treat approach was assessed as having 'some concerns'. This assessment was largely driven by issues within the domains of 'randomisation process' and 'selection of the reported result'. Specifically, the randomisation process was not described and no protocol was available or secondary outcomes were not pre-specified.

Figure 2: Risk of bias across all studies and outcomes as percentage for intention-to-treat analysis

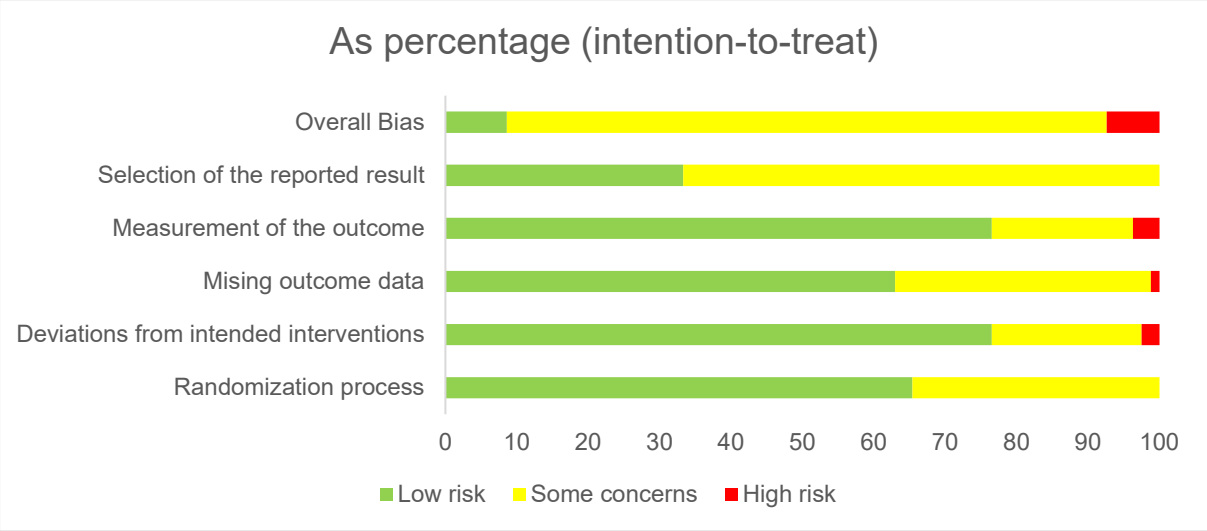
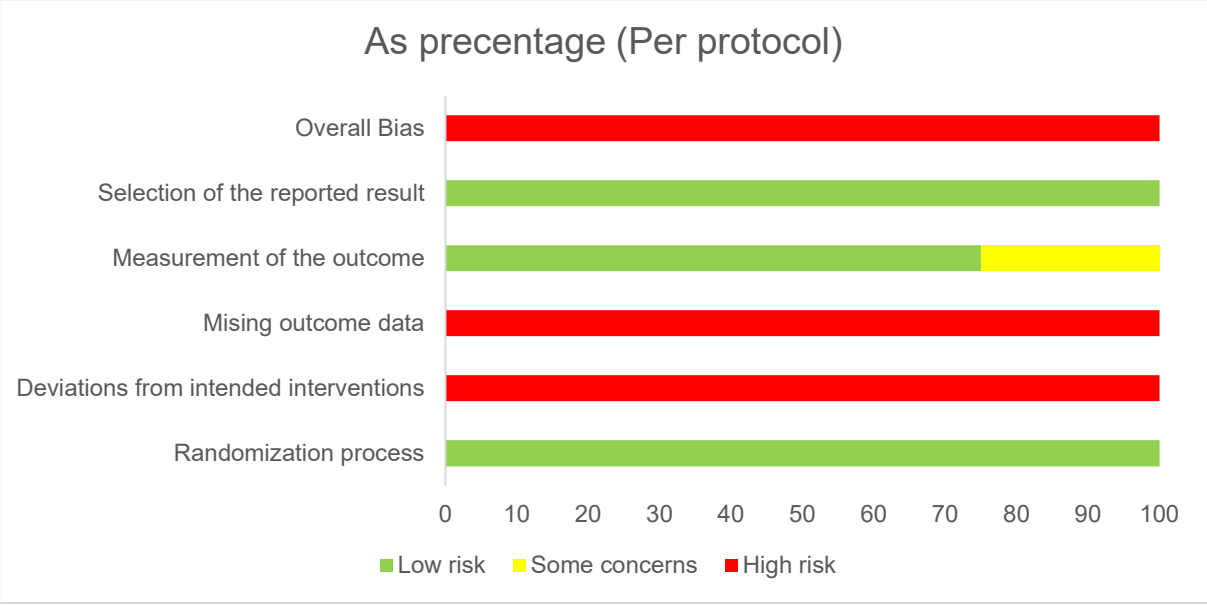


Figure 3: Risk of bias across all studies and outcomes as percentage for per-protocol analysis



7.3 Findings efficacy

The following section shows the results for all efficacy outcomes, including subgroup and sensitivity analyses. The results for each outcome are reported for the different comparisons mentioned in ***Chapter 4,*** except for the comparison between baloxavir and any non-antiviral treatment, which was not assessed in any of the included studies. First, the outcomes for which meta-analyses could

be conducted are shown, followed by those summarised narratively. Meta-analyses were performed separately for patients with influenza-like symptoms and patients with confirmed influenza.

The outcome influenza-associated symptoms was not reported consistently in the included RCTs and therefore the outcomes “time to improvement of influenza symptoms” and “time to resolution of fever” were additionally included as secondary outcome. ***Table 59*** in the Appendix provides an overview of the evidence retrieved from the systematic literature review, along with the methods used for synthesis.

7.3.1 PICO 1: Primary outcomes

7.3.1.1 Disease-specific and all-cause mortality

7.3.1.1.1 Oseltamivir versus placebo

Two RCTs[66,79] that assessed all cause or disease specific mortality for oseltamivir compared to placebo in patients with influenza-like symptoms were included in the meta-analysis. Dawood et al. 2016[79] analysed children from 0 to 9 years hospitalised with influenza and Ison et al. 2020[66] examined high-risk adolescent and adult outpatients with uncomplicated influenza. Mortality was not statistically significantly different between oseltamivir and placebo in patients with influenza-like symptoms. The pooled estimated RR was 3.00 (95% CI 0.31 to 28.82, ***Figure 4***).

Two other RCTs[67,71] reported zero events in both arms and were therefore not included in the meta-analysis (***Table 8***).

No study reported mortality for this comparison in patients with confirmed influenza.

Figure 4: Meta-analysis on mortality comparing oseltamivir versus placebo in patients with influenza-like symptoms

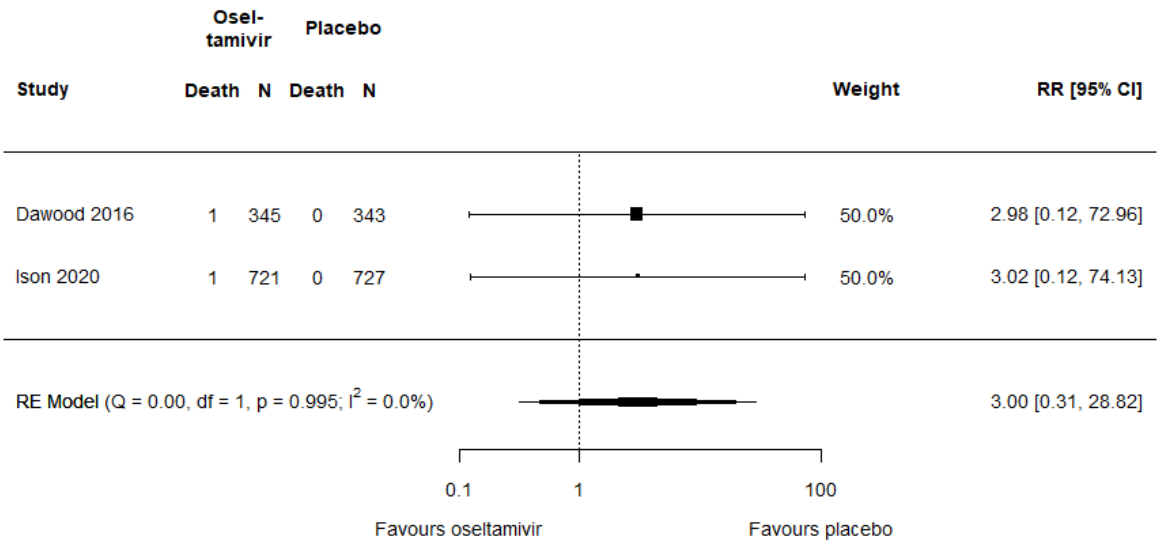


Table 8: Synthesis without meta-analysis on mortality comparing oseltamivir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Johnston 2005[71]	In patients with influenza-like symptoms	Children with asthma	0 (N=170)	0 (N=164)	NE
Hayden 2018[67]	Not reported	Adults and adolescents, not high-risk	0 (N=513)	0 (N=309)	NE

Abbreviations:
NE: Not estimable

7.3.1.1.2 Oseltamivir versus baloxavir

Two RCTs[66,84] assessed mortality for oseltamivir compared to baloxavir in patients with influenza-like symptoms (***Table 9***). One of them reported zero events in both arms and therefore no meta-analysis was conducted, while the other found no statisticlly significant difference. Another RCT[67] also reported zero events but did not specify the type of analysis used.

No study reported mortality for this comparison in patients with confirmed influenza.

Table 9: Synthesis without meta-analysis on mortality comparing oseltamivir versus baloxavir

Study	Type of analysis	Population	Intervention	Comparator	Effect
Ison 2020[66]	In patients with influenza-like symptoms	High-risk adolescent and adult patients with uncomplicated influenza	1 (N=721)	0 (N=730)	RR=3.04 ,95% CI 0.12 to 74.44[1]
Baker 2020[84]	In patients with influenza-like symptoms	Children, not high-risk	0 (N=58)	0 (N=115)	NE
Hayden 2018[67]	Not reported	Adults and adolescents, not high-risk	0 (N=513)	0 (N=610)	NE

Abbreviations:
CI: confidence interval, RR: relative risk, NE: Not estimable
Notes:
[1]Calculated by the authors of this report

7.3.1.1.3 Oseltamivir versus any non-antiviral treatment

Only one RCT[88] assessed mortality for oseltamivir compared to any non-antiviral treatment in patients with influenza-like symptoms but the effect was not statistically significant (***Table 10***).

No study reported mortality for this comparison in patients with confirmed influenza.

Table 10: Synthesis without meta-analysis on mortality comparing oseltamivir versus any non-antiviral treatment

Study	Type of analysis	Population	Intervention	Comparator	Effect
Ramirez 2018[88]	In patients with influenza-like symptoms	Adults hospitalised with influenza infection	22 (N=551)	27 (N=556)	RR=0.82, 95% CI 0.47 to 1.43[1]

Abbreviations:
CI: confidence interval, RR: relative risk

Notes:
[1]Calculated by the authors of this report

7.3.1.1.4 Baloxavir versus placebo

Two studies[66,67] assessed mortality for baloxavir compared to placebo and both studies reported zero events in both arms (***Table 11***). One study analysed patients with influenza-like symptoms, while the other did not report this information.

No study reported mortality for this comparison in patients with confirmed influenza.

Table 11: Synthesis without meta-analysis on mortality comparing baloxavir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Ison 2020[66]	In patients with influenza-like symptoms	High-risk adolescent and adult patients with uncomplicated influenza	0 (N=730)	0 (N=727)	NE
Hayden 2018[67]	Not reported	Adults and adolescents, not high-risk	0 (N=610)	0 (N=309)	NE

Abbreviations:
NE: Not estimable

7.3.1.2 Number of people with influenza-associated complications

7.3.1.2.1 Oseltamivir versus placebo

Five RCTs[66,69,74,75,77] that assessed the number of people with influenza-associated complications for oseltamivir compared to placebo in patients with confirmed influenza were included in the meta-analysis. The number of people with influenza-associated complications was statistically significantly lower with oseltamivir than with placebo in patients with confirmed influenza. The pooled estimated RR was 0.60 (95% CI 0.47 to 0.78, ***Figure 5***).

Ison et al. 2020[66] examined high-risk (people with multiple health risks) adolescent and adult outpatients with uncomplicated influenza, Treanor et al.2000[69], Li et al. 2004[74] and Nicholson et al. 2000[75] adults without risk and Whitley et al. 2001[77] children.

One RCT[75] reported influenza-associated complications in patients with influenza-like symptoms (***Table 12***), finding no statically significant difference between oseltamivir and placebo.

Figure 5: Meta-analysis on influenza-associated complications comparing oseltamivir versus placebo in patients with confirmed influenza

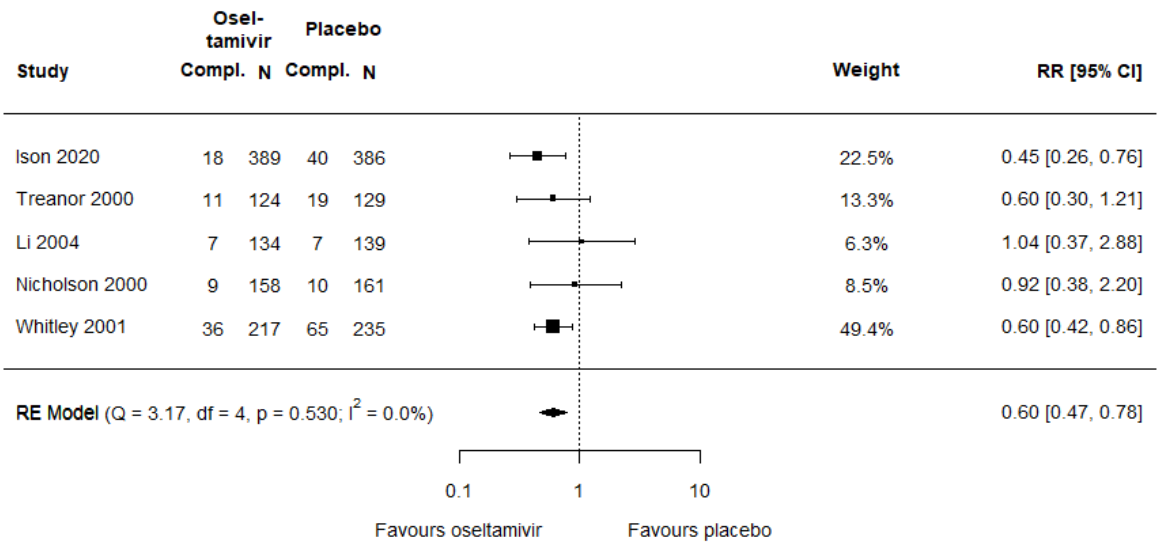


Table 12: Synthesis without meta-analysis on influenza-associated complications comparing oseltamivir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Nicholson 2000[75]	In patients with influenza-like symptoms	Adults, not high-risk	16 (N=241)	13 (N=235)	RR=1.20, 95% CI 0.59 to 2.44[1]

Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.3.1.2.2 Oseltamivir versus baloxavir

Two RCTs[66,84] assessed the number of people with influenza-associated complications for oseltamivir compared to baloxavir, with both finding no statistically significant difference (***Table 13***). One study analysed patients with influenza-like symptoms, while the other analysed those with confirmed influenza. The two studies also analysed different populations, with Baker et al. 2020[85] focusing on children and Ison et al. 2020[66] on high-risk adolescent and adult patients with multiple health risks and uncomplicated influenza.

Table 13: Synthesis without meta-analysis on number of influenza-associated complications comparing oseltamivir versus baloxavir

Study	Type of analysis	Population	Intervention	Comparator	Effect
Baker 2020[84]	In patients with influenza-like symptoms	Children, not high-risk	3 (N=43)	6 (N=80)	RR=0.93, 95% CI 0.24 to 3.54[1]
Ison 2020[66]	In patients with confirmed influenza	High-risk adolescent and adult patients with uncomplicated influenza	18 (N=389)	11 (N=388)	RR=1.63, 95% CI 0.78 to 3.41[1]

Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.3.1.2.3 Oseltamivir versus any non-antiviral treatment

Two RCTs[85,87] assessed the number of people with influenza-associated complications for oseltamivir compared to any non-antiviral treatment (***Table 14***). Raus et al. 2015[85] analysed patients with influenza-like symptoms and found no statistically significant difference between the two treatments. Lin et al. 2006[87] analysed patients with confirmed influenza and showed a statistically significant lower RR in the oseltamivir group. The two studies analysed different populations, with Lin et al. 2006[87] focusing on high-risk population.

Table 14: Synthesis without meta-analysis on number of influenza-associated complications comparing oseltamivir versus any non-antiviral treatment

Study	Type of analysis	Population	Intervention	Comparator	Effect
Raus 2015[85]	In patients with influenza-like symptoms[2]	All ages, no high risk	14 (N=217)	5 (N=203)	RR=2.62, 95% CI 0.96 to 7.14[1]
Lin 2006[87]	In patients with confirmed influenza	All ages, high-risk population	3 (N=27)	13 (N=29)	RR=0.25, 95% CI 0.08 to 0.78[1]

Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report
[2]PP analysis

7.3.1.2.4 Baloxavir versus placebo

Two RCTs[66,92] assessed the number of people with influenza-associated complications for baloxavir compared to placebo (***Table 15***). Watanabe et al. 2019[92] analysed patients with influenza-like symptoms and found no statistically significant difference between the two treatments. Ison et al. 2020[66] analysed patients with confirmed influenza and showed a statistically significant lower RR in the baloxavir group. The two studies analysed different populations, with Ison et al. 2020[66] focusing on high-risk adolescent and adult patients.

Table 15: Synthesis without meta-analysis on number of influenza-associated complications comparing baloxavir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Watanabe 2019[92]	In patients with influenza-like symptoms	Not high-risk adult outpatients	2 (N=100)	1 (N=100)	RR=2.00, 95% CI 0.18 to 21.71[1]
Ison 2020[66]	In patients with confirmed influenza	High-risk adolescent and adult patients with uncomplicated influenza	11 (N=388)	40 (N=386)	RR=0.27, 95% CI 0.14 to 0.53[1]

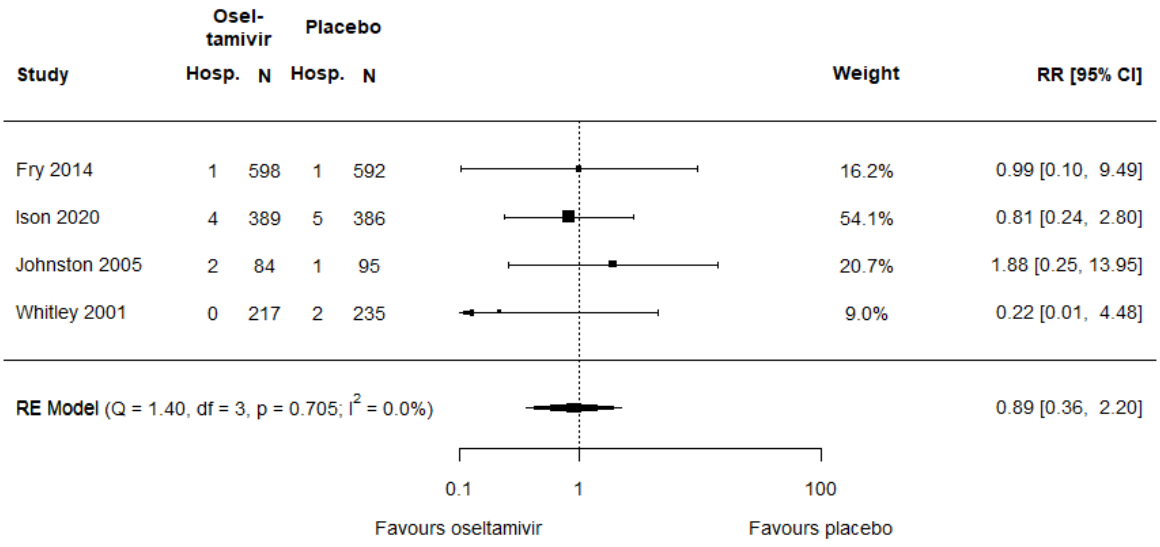
Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.3.1.3 First hospitalisation due to influenza symptoms

7.3.1.3.1 Oseltamivir versus placebo

Four RCTs[66,71,77,82] that assessed the number of people hospitalised due to influenza symptoms for oseltamivir compared to placebo patients with confirmed influenza were included in the meta-analysis. The number of people hospitalised due to influenza was not statistically significantly different. The pooled estimated RR was 0.89 (95% CI 0.36 to 2.20, ***Figure 6***).

Figure 6: Meta-analysis on first hospitalisation comparing oseltamivir versus placebo in outpatients with confirmed influenza



Fry et al. 2014[82] studied influenza patients of all ages, Ison et al. 2020[66] focused on high-risk adolescents and adults with uncomplicated influenza, Johnston et al. 2005[71] examined children with asthma, and Whitley et al. 2001[77] investigated children without comorbidities.

Additionally, two RCTs[72,73] analysing patients with confirmed influenza reported zero events in both arms and were therefore not included in the meta-analysis (***Table 16***). One RCT[72] also reported results for patients with influenza-like symptoms but found no statistically significant difference between the two treatments.

Table 16: Synthesis without meta-analysis on number of hospitalisations due to influenza symptoms comparing oseltamivir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Heinonen 2010[72]	In patients with influenza-like symptoms	Children aged 1-3 years	1 (N=202)	0 (N=204)	RR=3.03, 95% CI 0.12 to 73.93[1]
Dharan 2011[73]	In patients with confirmed influenza	Patients with oseltamivir-resistant seasonal influenza A	0 (N=12)	0 (N=7)	NE
Heinonen 2010[72]	In patients with confirmed influenza	Children aged 1-3 years	0 (N=37)	0 (N=61)	NE
Hayden 2018[67]	Not reported	Adults and adolescents, not high-risk	1 (N=NI)	0 (N=NI)	NE

Abbreviations:
CI: confidence interval, NE: Not estimable, NI: no information, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.3.1.3.2 Oseltamivir versus baloxavir

Three RCTs[66,67,84] assessed the number of hospitalisations due to influenza symptoms for oseltamivir compared to baloxavir (***Table 17***). One RCT[84] analysing patients with influenza-like symptoms reported zero events in both arms, while the other two RCTs[66,67] found no statistically significant difference between the two treatments. Among these, one study analysed patients with confirmed influenza, while the other did not specify the type of analysis used.

Table 17: Synthesis without meta-analysis on number of hospitalisations due to influenza symptoms comparing oseltamivir versus baloxavir

Study	Type of analysis	Population	Intervention	Comparator	Effect
Baker 2020[84]	In patients with influenza-like symptoms	Children, not high-risk	0 (N=58)	0 (N=115)	NE
Ison 2020[66]	In patients with confirmed influenza	High-risk adolescent and adult patients with uncomplicated influenza	4 (N=389)	3 (N=388)	RR=1.28, 95% CI 0.32 to 5.15[1]
Hayden 2018[67]	Not reported	Adults and adolescents, not high-risk	1 (N=NI)	0 (N=NI)	NE

Abbreviations:
CI: confidence interval, NE: not estimable, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.3.1.3.3 Oseltamivir versus any non-antiviral treatment

Four RCTs[85–87,89] assessed the number of hospitalisations due to influenza symptoms for oseltamivir compared to any non-antiviral treatment (***Table 18***). Three RCTs[86,87,89] found no statistically significant difference, while one RCT[85] analysing patients with influenza-like symptoms reported zero events in both arms. Among the 3 RCTs showing no statistically significant difference, one anlysed patients with influenza-like symptoms, one analysed patients with confirmed influenza, and one did not specify the type of analysis used.

Table 18: Synthesis without meta-analysis on number of hospitalisations due to influenza symptoms comparing oseltamivir versus any non-antiviral treatment

Study	Type of analysis	Population	Intervention	Comparator	Effect
Raus 2015[85]	In patients with influenza-like symptoms[2]	All ages, no high risk	0 (N=217)	0 (N=203)	NE
Butler 2020[86]	In patients with influenza-like symptoms[2]	All ages, no high risk	19 (N=1426)	22 (N=1393)	RR=0.98, 95% CI 0.27 to 3.60[1]
Lin 2006[87]	In patients with confirmed influenza	All ages, high-risk population	2 (N=27)	5 (N=29)	RR=0.49, 95% CI 0.12 to 1.98[1]
Markovski 2002[89]	Not reported	Adults	2 (N=17)	7 (N=24)	RR=0.46, 95% CI 0.13 to 1.69[1]

Abbreviations:
CI: confidence interval, NE: not estimable, RR: relative risk
Notes:
[1]Calculated by the authors of this report
[2]PP analysis

7.3.1.3.4 Baloxavir versus placebo

No study reported first hospitalisation due to influenza symptoms for this comparison in patients with influenza-like symptoms.

Two RCTs[66,67] assessed the number of hospitalisations due to influenza symptoms for baloxavir compared to placebo (***Table 19***). Ison et al. 2020[66] analysing patients with confirmed influenza found no statistically significant difference, while Hayden et al. 2018[67], who did not specify the type of analysis used, reported zero events in both arms.

Table **19**: **Synthesis without meta-analysis on number of hospitalisations due to influenza symptoms comparing baloxavir versus placebo**

Study	Type of analysis	Population	Intervention	Comparator	Effect
Ison 2020[66]	In patients with confirmed influenza	High-risk adolescent and adult patients with uncomplicated influenza	3 (N=388)	5 (N=386)	RR=0.63, 95% CI 0.17 to 2.40[1]
Hayden 2018[67]	Not reported	Adults and adolescents, not high-risk	0 (N=610)	0 (N=309)	NE

Abbreviations:

CI: confidence interval, NE: not estimable, RR: relative risk
Notes:
[1]Calculated by the authors of this report

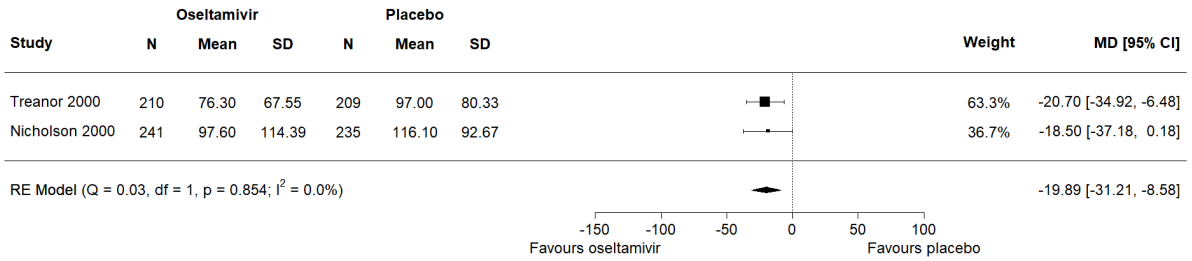
7.3.2 PICO 1: Secondary outcomes

7.3.2.1 Time to alleviation of influenza symptoms (TTAS)

7.3.2.1.1 Oseltamivir versus placebo

Two RCTs[69,75] that assessed the TTAS for oseltamivir compared to placebo in patients with influenza-like symptoms were included in the meta-analysis. The mean TTAS was statistically significantly shorter with oseltamivir than with placebo in patients with influenza-like symptoms. The pooled estimated mean difference was -19.89 hours (95% CI -31.21 to -8.58, ***Figure 7***). Both studies assessed adults without risks.

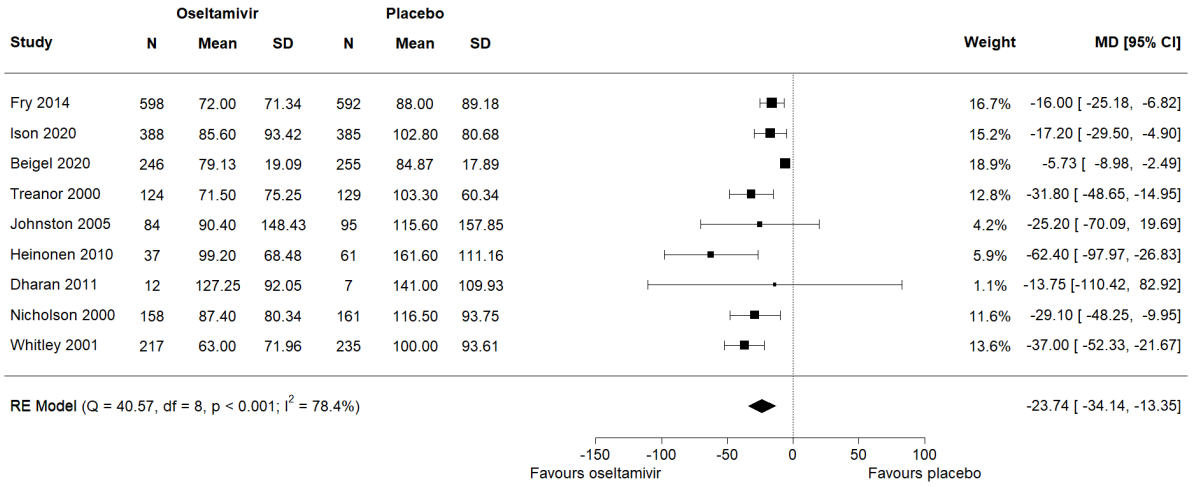
Figure 7: Meta-analysis on time to alleviation of influenza symptoms (in hours) comparing oseltamivir versus placebo in patients with influenza-like symptoms



Nine RCTs[66,68,69,71–73,75,77,82] that assessed TTAS for oseltamivir compared to placebo in patients with confirmed influenza were included in the meta-analysis. The mean TTAS was statistically significantly lower with oseltamivir than with placebo in patients with confirmed influenza. The pooled estimated mean difference was -23.74 hours (95% CI -34.14 to -13.35, ***Figure 8***).

Whitley et al. 2001[77] and Heinonen et al. 2010[72] investigated children without comorbidities, Johnston et al. 2005[71] examined children with asthma, Ison et al. 2020[66] focused on high-risk adolescents and adults, Nicholson et al. 2000[75], Beigel et al. 2020[68] and Treanor et al. 2000[69] assessed adults without risks, Fry et al. 2014[82] studied influenza patients of all ages and Dharan et al. 2011[73] investigated patients with oseltamivir-resistant seasonal influenza A.

Figure 8: Meta-analysis on time to alleviation of influenza symptoms (in hours) comparing oseltamivir versus placebo in patients with confirmed influenza



An additional study by Martin et al. 2001[76] also assessed TTAS in patients with confirmed influenza. However, it did not provide any dispersion measure and was therefore not included in the meta-analysis (***Table 20***). The study focused on high-risk patients and on elderly patients and showed in both populations results favouring oseltamivir.

Table 20: Synthesis without meta-analysis on time to alleviation of influenza symptoms comparing oseltamivir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Martin 2001[76]	In patients with confirmed influenza	High-risk patients	96.06h (N=118)	117.3h (N=133)	NE
Martin 2001[76]	In patients with confirmed influenza	Elderly patients	115.0h (N=222)	132.3h (N=254)	NE

Abbreviations:
NE: not estimable

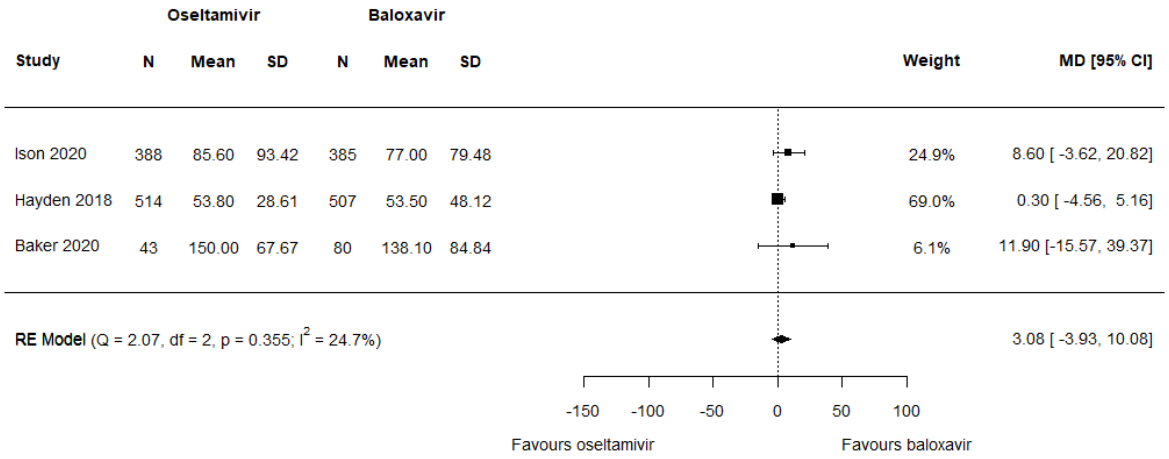
7.3.2.1.2 Oseltamivir versus baloxavir

No study reported TTAS for this comparison in patients with influenza-like symptoms.

Three RCTs[66,67,84] that assessed the TTAS for oseltamivir compared to baloxavir in patients with confirmed influenza were included in the meta-analysis. The mean TTAS was not statistically significantly different with oseltamivir than with baloxavir in patients with confirmed influenza. The pooled estimated mean difference was 3.08 hours (95% CI -3.93 to 10.08, ***Figure 9***).

Hayden et al. 2018[67] studied adolescents and adults without risks, Ison et al. 2020[66] focused on high-risk adolescents and adults and Baker et al. 2020[84] assessed children.

Figure 9: Meta-analysis on time to alleviation of influenza symptoms (in hours) comparing oseltamivir versus baloxavir in patients with confirmed influenza



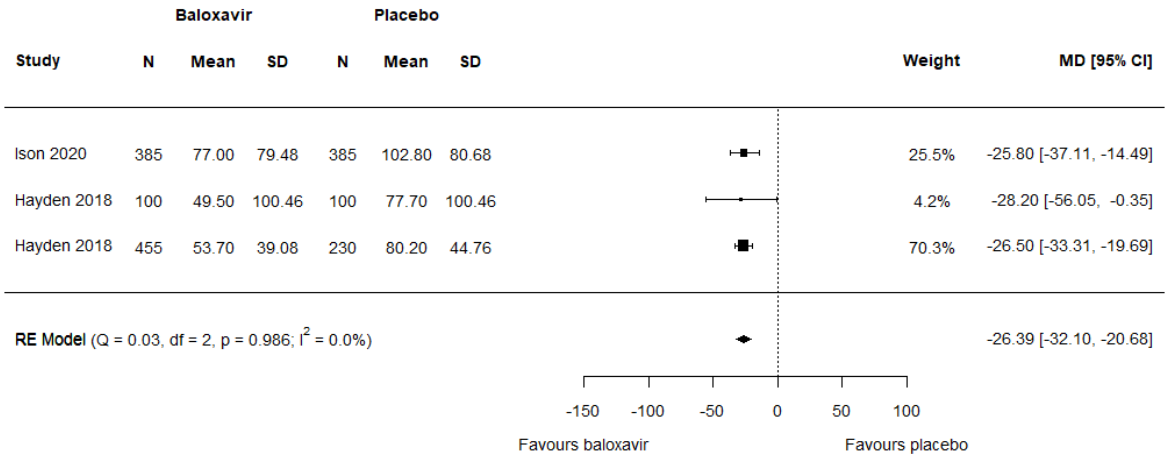
7.3.2.1.3 Oseltamivir versus any non-antiviral treatment

No study was identified that analysed TTAS for oseltamivir compared to any non-antiviral treatment.

7.3.2.1.4 Baloxavir versus placebo

Two RCTs[66,67] that assessed the TTAS for baloxavir compared to placebo in patients with confirmed influenza were included in the meta-analysis. The mean TTAS was statistically significantly shorter with baloxavir than with placebo in patients with confirmed influenza. The pooled estimated mean difference was -26.39 hours (95% CI -32.10 to -20.68, ***Figure 10***).

Figure 10: Meta-analysis on time to alleviation of influenza symptoms (in hours) comparing baloxavir versus placebo in patients with confirmed influenza



Ison et al. 2020[66] analysed high-risk adolescents and adults and Hayden et al. 2018[67] studied adolescents and adults without risks. Hayden et al 2018[67] reported the results of the phase 2 trial (with 100 patients in each group) and the results of the phase 3 trial.

Furthermore, two RCTs analysed patients with influenza-like symptoms and found favourable results for baloxavir (***Table 21***). In Watanabe et al. 2019[92] the effect was statistically significant, while in Hayden et al. 2018[67] the significance level could not be calculated.

Table 21: Synthesis without meta-analysis of time to alleviation of influenza symptoms comparing baloxavir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Hayden 2018[67]	In patients with influenza-like symptoms	Adults and adolescents, not high-risk	65.4h (N=610)	88.6h (N=309)	NE
Watanabe 2019[92]	In patients with influenza-like symptoms	Not high-risk	49.5h (95% CI 44.5 to 64.4, N=100)	77.7h (95% CI 67.6 to 88.7, N=100)	Mean difference -28.20, 95% CI -39.77 to -16.63[1]

Abbreviations:
CI: confidence interval, NE: not estimable
Notes:
[1]Calculated by the authors of this report

7.3.2.2 Time to improvement of influenza symptoms (TTIIS)

7.3.2.2.1 Oseltamivir versus placebo

No study reported TTIIS for this comparison in patients with influenza-like symptoms.

Only one RCT[66] assessed the TTIIS for oseltamivir compared to placebo in patients with confirmed influenza and showed statistically significant favourable results for oseltamivir (***Table 22***).

Table 22: Synthesis without meta-analysis of duration on time to improvement of influenza symptoms comparing oseltamivir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Ison 2020[66]	In patients with confirmed influenza	High-risk adolescent and adult patients with uncomplicated influenza	81h (95% CI 69.4 to 91.5, N=389)	102.3 (95% CI 92.7 to 113.1, N=386)	Mean difference -21.30, 95% CI -33.30 to -9.30[1]

Abbreviations:
CI: confidence interval
Notes:
[1]Calculated by the authors of this report

7.3.2.2.2 Oseltamivir versus baloxavir

No study reported TTIIS for this comparison in patients with influenza-like symptoms.

Only one RCT[66] assessed the TTIIS for oseltamivir compared to baloxavir in patients with confirmed influenza and found no statistically significant difference (***Table 23***).

Table 23: Synthesis without meta-analysis of duration on time to improvement of influenza symptoms comparing oseltamivir versus baloxavir

Study	Type of analysis	Population	Intervention	Comparator	Effect
Ison 2020[66]	In patients with confirmed influenza	High-risk adolescent and adult patients with uncomplicated influenza	81h (95% CI 69.4 to 91.5, N=389)	73.2h (95% CI 67.2 to 85.1, N=388)	Median difference 7.7h, 95% CI –7.9 to 22.7

Abbreviations:
CI: confidence interval

7.3.2.2.3 Oseltamivir versus any non-antiviral treatment

No study was identified that analysed TTIIS for oseltamivir compared to any non-antiviral treatment.

7.3.2.2.4 Baloxavir versus placebo

No study reported TTIIS for this comparison in patients with influenza-like symptoms.

Only one RCT[66] assessed the TTIIS for baloxavir compared to placebo in patients with confirmed influenza and showed favourable results for baloxavir (***Table 24***).

Table 24: without meta-analysis of duration of time to improvement of influenza symptoms, baloxavir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Ison 2020[66]	In patients with confirmed influenza	High-risk adolescent and adult patients with uncomplicated influenza	73.2h (95% CI 67.2 to 85.1, N=388)	102.3h (95% CI 92.7 to 113.1, N=386)	Mean difference -29.10 h, 95% CI -39.93 to -18.27[1]

Abbreviations:
CI: confidence interval
Notes:
[1]Calculated by the authors of this report

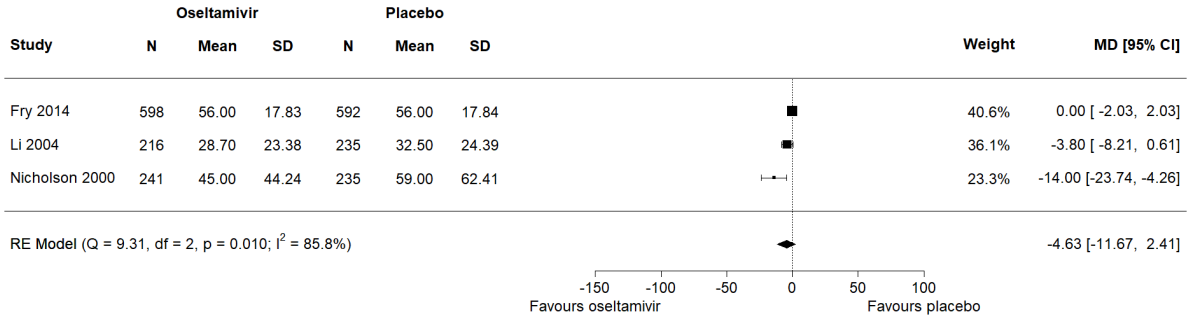
7.3.2.3 Time to resolution of fever

7.3.2.3.1 Oseltamivir versus placebo

Three RCTs[74,75,82] that reported the time to resolution of fever in the oseltamivir compared to placebo arm in patients with influenza-like symptoms were included in the meta-analysis. The mean time to resolution of fever was not statistically significantly different with oseltamivir than with placebo in patients with influenza-like symptoms. The pooled estimated mean difference was -4.63 hours (95% CI -11.67 to 2.41, ***Figure 11***).

Nicholson et al. 2000[75] and Li et al. 2004[74] assessed adults without risks and Fry et al. 2014[82] studied influenza patients of all ages.

Figure 11: Meta-analysis on time to resolution of fever (in hours) comparing oseltamivir versus placebo in patients with influenza-like symptoms



Seven RCTs[66,69,72,74–77] that assessed the time to resolution of fever for oseltamivir compared to placebo in patients with confirmed influenza were included in the meta-analysis. The mean time to resolution of fever was statistically significantly shorter with oseltamivir than with placebo in patients with confirmed influenza. The pooled estimated mean difference was -20.50 hours (95% CI -25.98 to -15.02, ***Figure 12).***

Whitley et al. 2001[77] and Heinonen et al. 2010[72] investigated children without comorbidities, Martin et al. 2001[76] and Ison et al. 2020[66] focused on high-risk adolescents and adults, Nicholson et al. 2000[75], Li et al. 2004[74] and Treanor et al. 2000[69] assessed adults without risks. Martin et al. 2001[76] also analysed elderly patients (***Table 25***).

Figure 12: Meta-analysis on time to resolution of fever (in hours) comparing oseltamivir versus placebo in patients with confirmed influenza

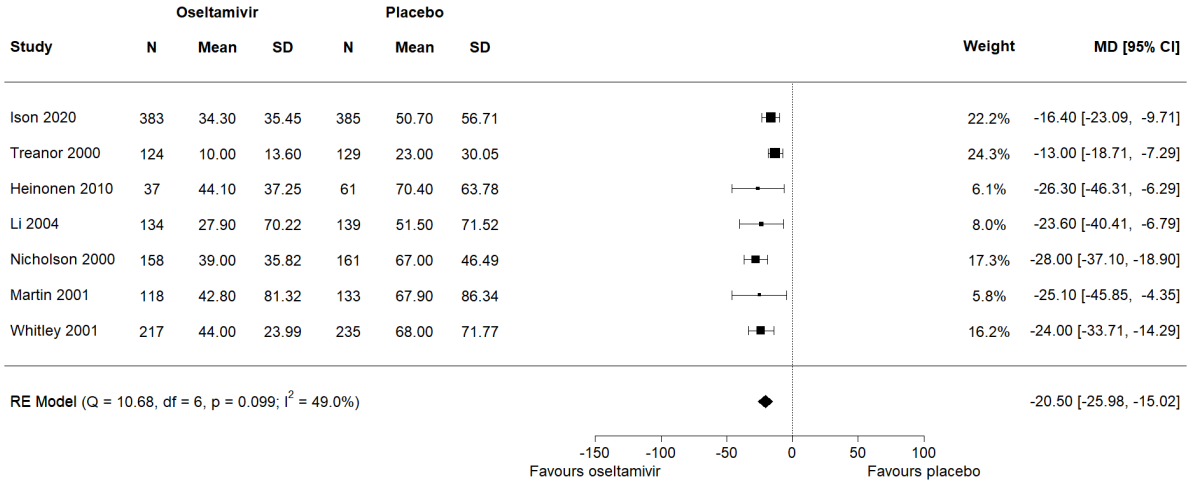


Table 25: Synthesis without meta-analysis on time to resolution of fever comparing oseltamivir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Martin 2001[76]	In patients with confirmed influenza	Elderly patients	66.9h (N=222)	89.5h (N=254)	Mean difference-25.10, 95% CI -45.85 to -4.351

Abbreviations:

CI: confidence interval
Notes:
[1]Calculated by the authors of this report

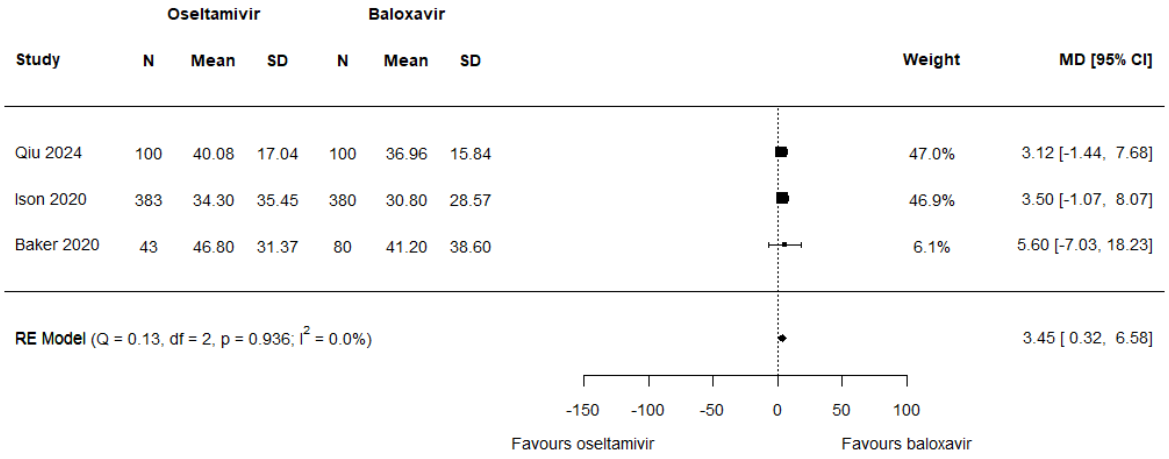
7.3.2.3.2 Oseltamivir versus baloxavir

No study reported time to resolution of fever for this comparison in patients with influenza-like symptoms.

Three RCTs[66,83,84] that assessed the time to resolution of fever for oseltamivir compared to baloxavir in patients with confirmed influenza were included in the meta-analysis. The mean time to resolution of fever was statistically significantly longer with oseltamivir than with baloxavir in patients with confirmed influenza. The pooled estimated mean difference was 3.45 hours (95% CI 0.32 to 6.58, ***Figure 13***).

Qiu et al. 2024[83] studied influenza patients of all ages, Ison et al. 2020[66] focused on high-risk adolescents and adults and Baker et al. 2020[84] assessed children.

Figure 13: Meta-analysis on time to resolution of fever (in hours) comparing oseltamivir versus baloxavir in patients with confirmed influenza

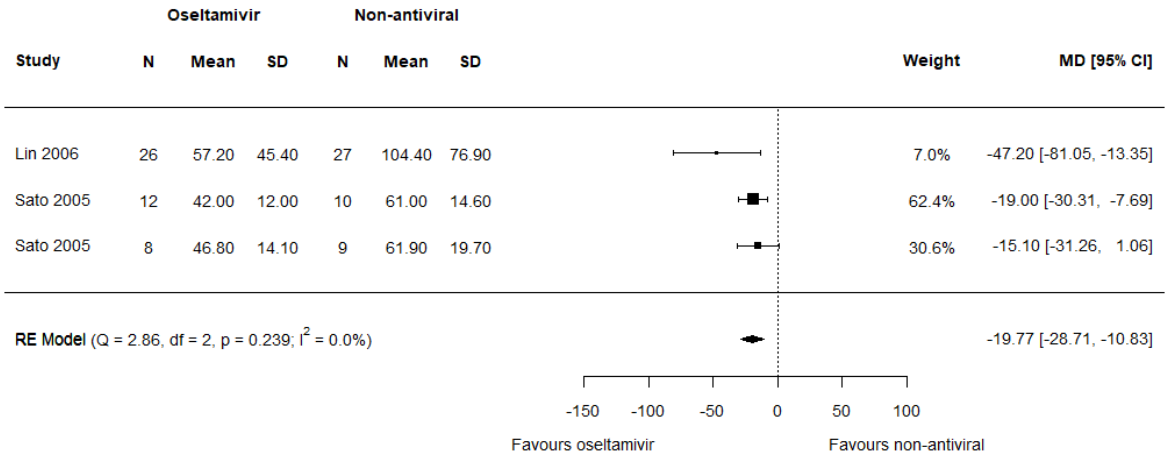


7.3.2.3.3 Oseltamivir versus any non-antiviral treatment

Two RCTs[87,91] that assessed the time to resolution of fever for oseltamivir compared to any non-antiviral treatment in patients with confirmed influenza were included in the meta-analysis. The mean time to resolution of fever was statistically significantly shorter with oseltamivir than with any non-antiviral treatment in patients with confirmed influenza. The pooled estimated mean difference was -19.77 hours (95% CI -28.71 to -10.83, ***Figure 14***).

Lin et al. 2006[87] investigated high-risk patients, Sato et al. 2005[91] analysed children with influenza A and Influenza B separately.

Figure 14: Meta-analysis on resolution of fever (in hours) comparing oseltamivir versus non-antiviral in patients with confirmed influenza



Furthermore, Raus et al. 2015[85] assessed the time to resolution of fever for oseltamivir compared to any non-antiviral treatment for patients with influenza-like symptoms using the PP analysis and found no difference between the two treatments (***Table 26***).

Table 26: Synthesis without meta-analysis on time to resolution of fever comparing oseltamivir versus any non-antiviral treatment

Study	Type of analysis	Population	Intervention	Comparator	Effect
Raus 2015[85]	In patients with influenza-like symptoms2	All ages, no high risk	48h (N=217)	48h (N=203)	NE

Abbreviations:
NE: not estimable
Notes:
[2]PP analysis

7.3.2.3.4 Baloxavir versus placebo

Two RCTs[66,92] assessed the time to resolution of fever for baloxavir compared to placebo, one in patients with influenza-like symptoms and one in patients with confirmed influenza (***Table 27***). Both studies found statistically significant favourable results for baloxavir.

Table 27: Synthesis without meta-analysis on time to resolution of fever comparing baloxavir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Watanabe 2019[92]	In patients with influenza-like symptoms	Not high-risk	28.9h (95% CI 24.5 to 34.7, N=100)	45.3h (95% CI 35.6 to 54.0, N=100)	Mean difference -16.40, 95% CI -24.79 to -8.01[1]
Ison 2020[66]	In patients with confirmed influenza	High-risk adolescent and adult patients with uncomplicated influenza	30.8h (95% CI 28.2 to 35.4, N=380)	50.7h (95% CI 44.6 to 58.8, N=385)	Mean difference -19.90, 95% CI -26.25 to -13.55[1]

Abbreviations:

CI: confidence interval
Notes:
[1]Calculated by the authors of this report

7.3.2.4 Number of people with antibiotic use

7.3.2.4.1 Oseltamivir versus placebo

Six RCTs[66,69,74,75,77,79] that assessed the antibiotic use for oseltamivir compared to placebo in patients with confirmed influenza were included in the meta-analysis. The number of patients that used antibiotics was statistically significantly lower with oseltamivir than with placebo in patients with confirmed influenza. The pooled estimated RR was 0.67 (95% CI 0.54 to 0.84, ***Figure 15***).

Whitley et al. 2001[77] investigated children without comorbidities, Dawood et al. 2016[79] focused on hospitalised children, Ison et al. 2020[66] focused on high-risk adolescents and adults and Nicholson et al. 2000[75], Li et al. 2004[74] and Treanor et al. 2000[69] assessed adults without risks.

In addition, one RCT[75] analysed patients with influenza-like symptoms and found no statistically significant difference between the two treatments (***Table 28***).

Figure 15: Meta-analysis on the antibiotic use comparing oseltamivir versus placebo in patients with confirmed influenza

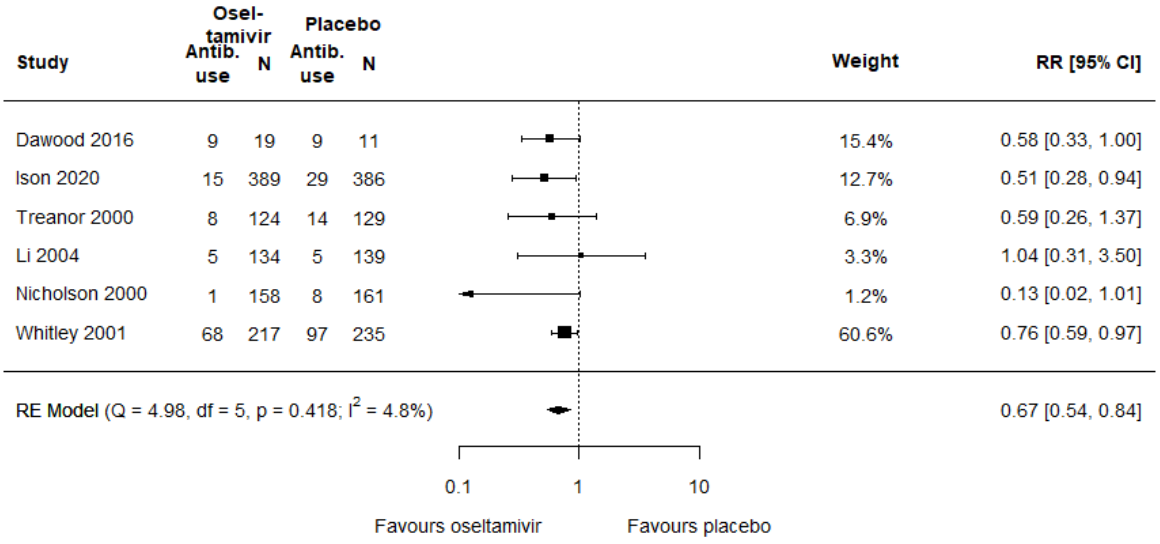


Table 28: Synthesis without meta-analysis on time to resolution of fever comparing oseltamivir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Nicholson 2000[75]	In patients with influenza-like symptoms	Adults, not high-risk	6 (N=241)	10 (N=235)	RR=0.59, 95% CI 0.22 to 1.581

Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report

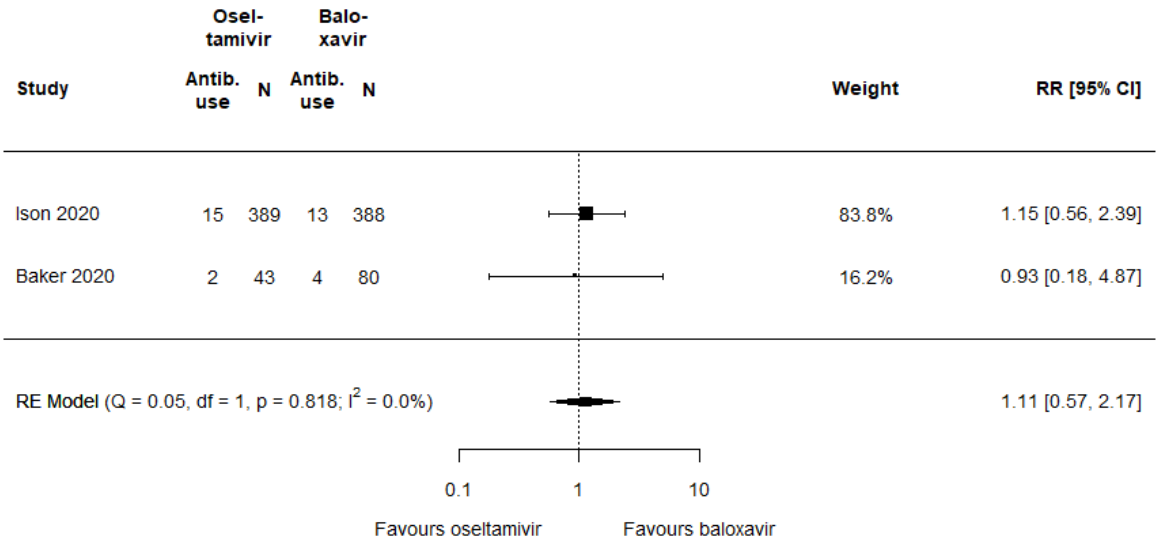
7.3.2.4.2 Oseltamivir versus baloxavir

No study reported antibiotic use for this comparison in patients with influenza-like symptoms.

Two RCTs[66,84] that assessed the antibiotic use for oseltamivir compared to baloxavir in patients with confirmed influenza were included in the meta-analysis. The number of patients that used antibiotics was not statistically significantly different with oseltamivir than with baloxavir in patients with confirmed influenza. The pooled estimated RR was 1.11 (95% CI 0.57 to 2.17, ***Figure 16***).

Ison et al. 2020[66] investigated high-risk adolescents and adults and Baker et al. 2020[84] children without risks.

Figure 16: Meta-analysis on antibiotic use comparing oseltamivir versus baloxavir in patients with confirmed influenza



7.3.2.4.3 Oseltamivir versus any non-antiviral treatment

Two RCTs[85,86] that assessed the antibiotic use for oseltamivir compared to non-antiviral treatment in patients with influenza-like symptoms for the PP population were included in the meta-analysis. The number of patients that used antibiotics was statistically significantly lower with oseltamivir than with any non-antiviral treatment. The pooled estimated RR was 0.70 (95% CI 0.58 to 0.86, ***Figure 17***).

In addition, Lin et al. 2006[87] analysed patients with confirmed influenza and showed also favourable results for oseltamivir compared to any non-antiviral treatment (***Table 29***).

Figure 17: Meta-analysis on antibiotic use comparing oseltamivir versus any non-antiviral in the per protocol population

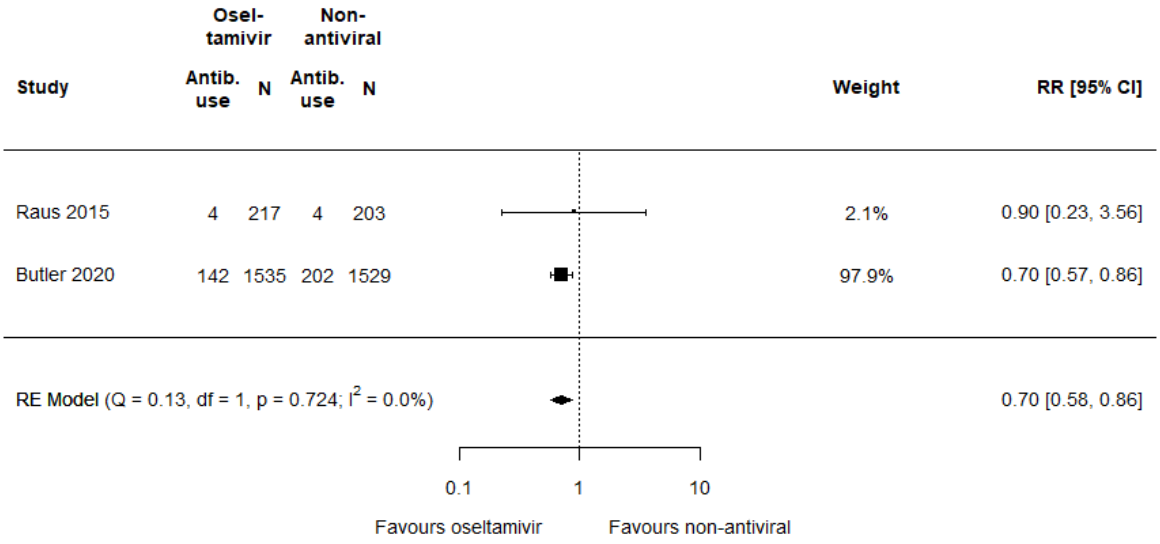


Table 29: Synthesis without meta-analysis of number of people with antibiotic use, placebo versus any non-antiviral treatment

Study	Type of analysis	Population	Intervention	Comparator	Effect
Lin 2006[87]	In patients with confirmed influenza	All ages, high-risk population	10 (N=27)	20 (N=29)	RR=0.54, 95% CI 0.31 to 0.93[1]

Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.3.2.4.4 Baloxavir versus placebo

No study reported antibiotic use for this comparison in patients with influenza-like symptoms.

Only one RCT[66] assessed the number of people with antibiotic use for baloxavir compared to placebo and found statistically significant favourable results for baloxavir (***Table 30***).

Table 30: Synthesis without meta-analysis on number of people with antibiotic use comparing baloxavir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Ison 2020[66]	In patients with confirmed influenza	High-risk adolescent and adult patients with uncomplicated influenza	13 (N=388)	29 (N=386)	RR=0.45, 95% CI 0.24 to 0.84[1]

Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.3.2.5 Length of hospitalisation

7.3.2.5.1 Oseltamivir versus placebo

No study was identified that analysed the length of hospitalisation for oseltamivir compared to placebo.

7.3.2.5.2 Oseltamivir versus baloxavir

No study was identified that analysed the length of hospitalisation for oseltamivir compared to baloxavir.

7.3.2.5.3 Oseltamivir versus any non-antiviral treatment

Only one RCT[88] assessed the hospitalisation length for oseltamivir compared to any non-antiviral treatment, both in patients with influenza-like symptoms and those with confirmed influenza (***Table 31***). The significance level for both analyses could not be calculated. The median time from illness onset to enrolment was 5 days (IQR: 5 days) for both study groups, while the median time from illness onset to oseltamivir administration was 6 days.

Table 31: Synthesis without meta-analysis on length of hospitalisation comparing oseltamivir versus any non-antiviral treatment

Study	Type of analysis	Population	Intervention	Comparator	Effect
Ramirez 2018[88]	In patients with influenza-like symptoms	Adults hospitalised with influenza infection	4 days (N=551)	4 days (N=556)	NE
Ramirez 2018[88]	In patients with confirmed influenza	Adults hospitalised with influenza infection	3 days (N=29)	4 days (N=45)	NE

Abbreviations:
NE: not estimable

7.3.2.5.4 Baloxavir versus placebo

No study was identified that analysed the length of hospitalisation for baloxavir compared to placebo.

7.3.2.6 Number of patients with re-consultations with a doctor

7.3.2.6.1 Oseltamivir versus placebo

No study was identified that analysed the number of patients with re-consultations with a doctor for oseltamivir compared to placebo.

7.3.2.6.2 Oseltamivir versus baloxavir

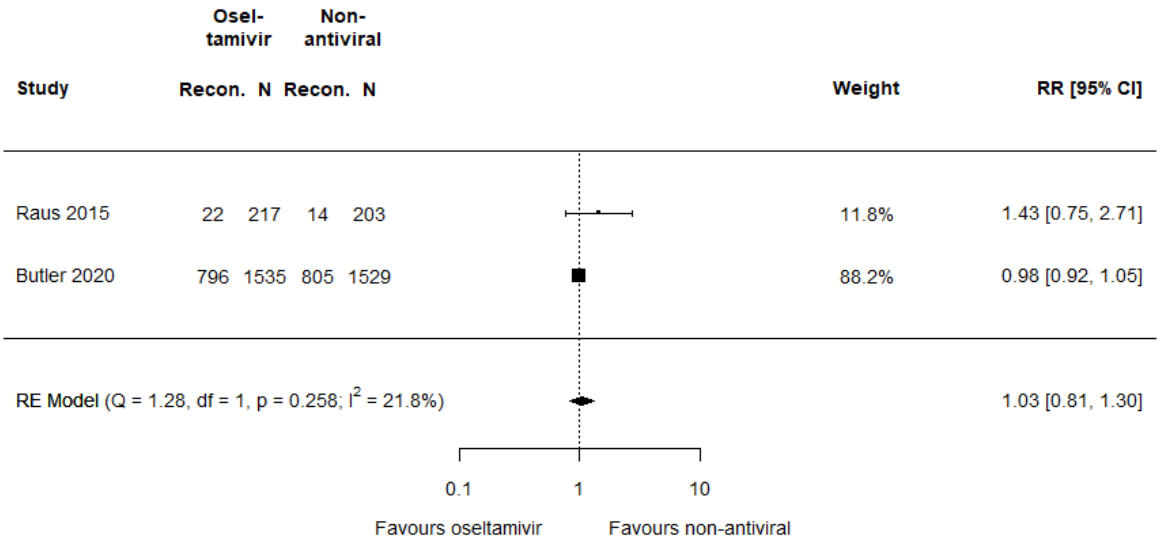
No study was identified that analysed the number of patients with re-consultations with a doctor for oseltamivir compared to baloxavir.

7.3.2.6.3 Oseltamivir versus any non-antiviral treatment

Two RCTs[85,86] that assessed the re-consultations with a doctor for oseltamivir compared to non-antiviral treatment in patients with influenza-like symptoms in the per protocol (PP) population were included in the meta-analysis. The number of re-consultations with a doctor was not statistically significantly different with oseltamivir than with any non-antiviral treatment in patients with influenza-like symptoms. The pooled estimated RR was 1.03 (95% CI 0.81 to 1.30, ***Figure 18***).

No study reported re-consultations with a doctor for this comparison in patients with confirmed influenza.

Figure 18: Meta-analysis on the re-consultations with a doctor comparing oseltamivir versus non-antiviral in patients with influenza-like symptoms in the per protocol population



7.3.2.6.4 Baloxavir versus placebo

No study was identified that analysed the number of patients with re-consultations with a doctor for baloxavir compared to placebo.

7.3.2.7 Number of onward transmissions to household contacts (symptoms- and test-based)

7.3.2.7.1 Oseltamivir versus placebo

Only one RCT[78] assessed the number of onward transmissions to household contacts for oseltamivir compared to placebo in patients with influenza-like symptoms (***Table 32***). It showed a statistically significant lower proportion of new infections within households for oseltamivir. However, the number of PCR-confirmed influenza infections in household members did not statistically significantly differ between the treatment groups.

No study reported number of onward transmissions to household contacts for this comparison in patients with confirmed influenza.

Table 32: Synthesis without meta-analysis on number of onward transmissions to household contacts comparing oseltamivir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Fry 2015[78]	In patients with influenza-like symptoms	All ages, not high-risk	87 household members with illness (N=1816; 5%)	110 household members with illness (N=1647; 7%)	OR 0.68 (95% CI 0.47 to 0.98, p = 0.041)
Fry 2015[78]	In patients with influenza-like symptoms	All ages, not high-risk	37 household members with PCR-confirmed influenza (N=1816; 2%)	47 household members with PCR-confirmed influenza (N=1647; 7%)	OR 0.68 (95% CI 0.30 to 1.56, p = 0.362)

Abbreviations:
CI: confidence interval, PCR: Polymerase chain reaction, OR: odds ratio

7.3.2.7.2 Oseltamivir versus baloxavir

No study was identified that analysed the number of onward transmissions to household contacts for oseltamivir compared to baloxavir.

7.3.2.7.3 Oseltamivir versus any non-antiviral treatment

Only one RCT[86] assessed the number of onward transmissions to household contacts for oseltamivir compared to any non-antiviral treatment and found a 6%-point lower proportion of new infections within households for oseltamivir (***Table 33***).

No study reported number of onward transmissions to household contacts for this comparison in patients with confirmed influenza.

Table 33: Synthesis without meta-analysis on number of onward transmissions to household contacts comparing oseltamivir versus any non-antiviral treatment

Study	Type of analysis	Population	Intervention	Comparator	Effect
Butler 2020[86]	Patients with influenza-like symptoms[2]	All ages, no high risk	485 households with infections (N=1237; 39%)	553 households with infections (N=1222; 45%)	Difference: 6.0% (95% CI 2.1% to 10.0%)

Abbreviations:
CI: confidence interval, PP: per-protocol
Notes:
[2]PP analysis

7.3.2.7.4 Baloxavir versus placebo

No study was identified that analysed the number of onward transmissions to household contacts for baloxavir compared to placebo.

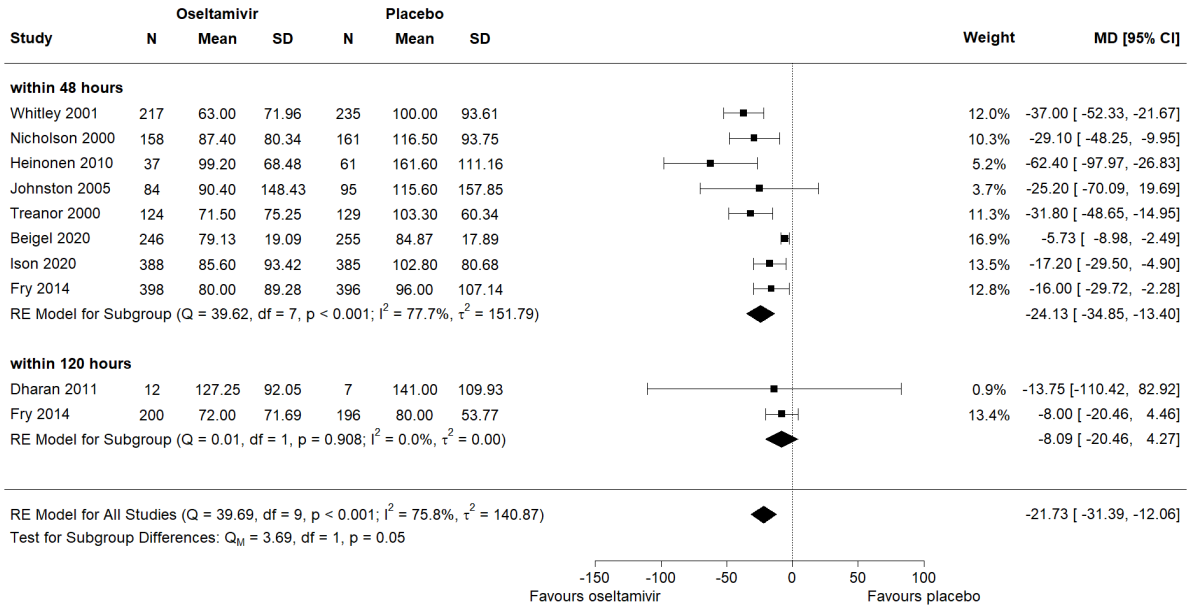
7.3.3 PICO 1: Subgroup analyses

For the primary outcomes it was not possible to compute subgroup analyses. For the secondary outcomes TTAS and time to resolution of fever it was possible to compute subgroup analyses for

oseltamivir compared to placebo in patients with confirmed influenza. None of the included studies reported results for immunosuppressed patients or pregnant women and only one study[76] reported results on the elderly. Therefore, these high-risk groups were not included in subgroup analyses. A distinction between influenza A and B was also rarely made in the included RCTs. Only 4 focused on influenza A (two compared oseltamivir with placebo, one compared oseltamivir with baloxavir and one compared oseltamivir with any non-antiviral treatment), while only one study examined influenza B (comparing oseltamivir with any non-antiviral treatment). Due to this limited data, no subgroup analysis was performed to differentiate between influenza A and B.

Nine RCTs[66,68,69,71–73,75,77,82] that assessed the TTAS for oseltamivir compared to placebo in patients with confirmed influenza were included in the meta-analysis, stratified by time of drug administration. The mean TTAS was statistically significantly shorter with oseltamivir than with placebo in the group that received the drug within 48 hours after symptom onset but not in the group that received it within 120 hours after symptom onset. The pooled estimated mean difference was -24.13 hours (95% CI -34.85 to -13.4) in the within 48 hours group and -8.09 hours (95% CI -20.46 to 4.27) in the within 120 hours group (***Figure 19***). There are no statistically significant differences in effect sizes among the time of drug administration groups (test for subgroup differences p=0.05).

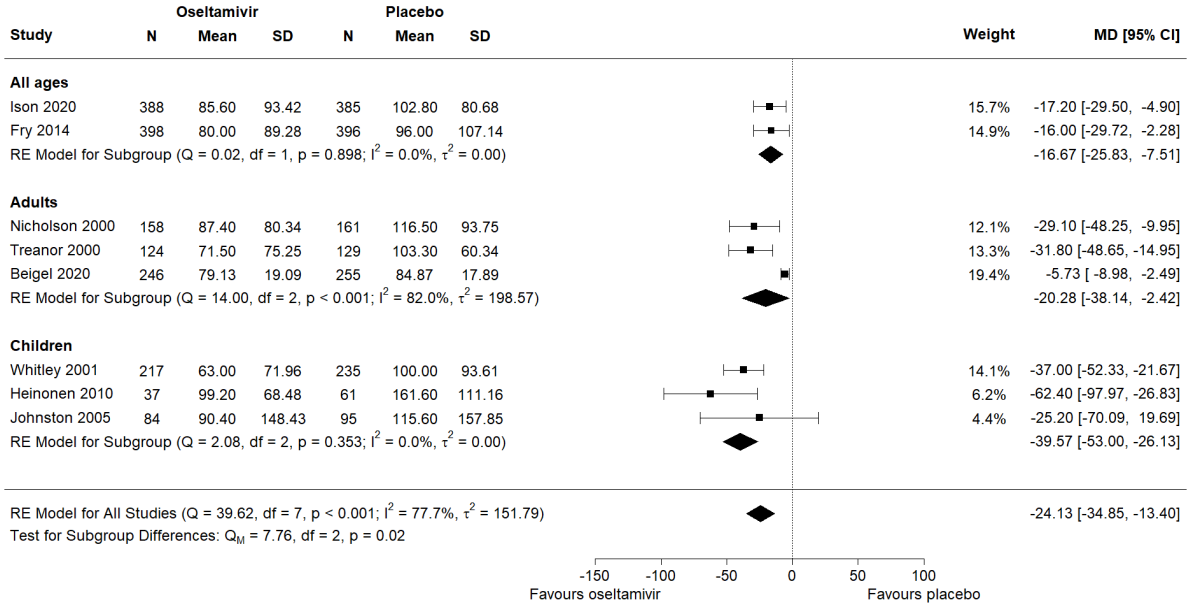
Figure 19: Meta-analysis on time to alleviation of influenza symptoms (in hours) comparing oseltamivir versus placebo in patients with confirmed influenza by time of drug administration



Eight RCTs[66,68,69,71,72,75,77,82] that assessed the TTAS for oseltamivir compared to placebo in patients with confirmed influenza that were administered the drug within 48 hours were included in the meta-analysis, stratified by age group. The mean TTAS was statistically significantly shorter with oseltamivir than with placebo in the group including all ages, in the adult group and in the children group. The pooled estimated mean difference was -16.67 hours (95% CI -25.83 to -7.51) in the all-ages group, -20.28 hours (95% CI -38.14 to -2.42) in the adults group and -39.57 hours

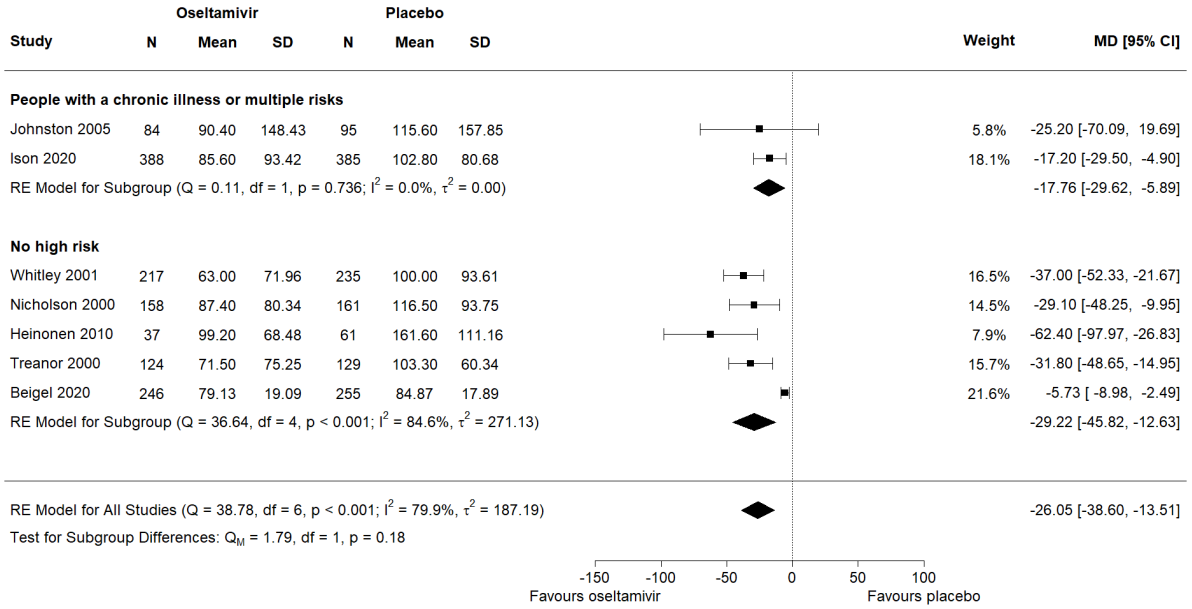
(95% CI -53.00 to -26.13) in the children group (***Figure 20***). The difference in effect sizes among the age groups is statistically significant (test for subgroup differences p=0.02).

Figure 20: Meta-analysis on time to alleviation of influenza symptoms (in hours) comparing oseltamivir versus placebo in patients with confirmed influenza that were administered the drug within 48 hours by age group



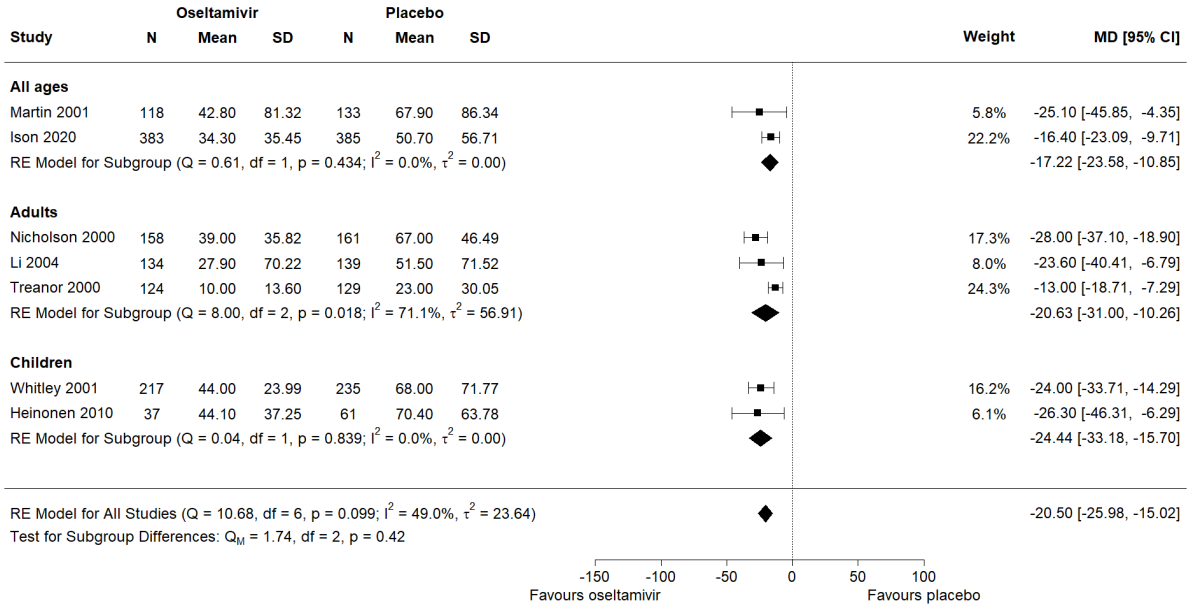
Seven RCTs[66,68,69,71,72,75,77] that assess the TTAS for oseltamivir compared to placebo in patients with confirmed influenza that were administered the drug within 48 hours were included in the meta-analysis, stratified by risk group. One study[82] which did not report the risk group was excluded. The mean TTAS was statistically significantly shorter with oseltamivir than with placebo in the group of people with a chronic illness or multiple risks as well as in the no high risk group. The pooled estimated mean difference was -17.76 hours (95% CI -29.62 to -5.89) in the group of people with a chronic illness or multiple risks, and -29.22 hours (95% CI -45.82 to -12.63) in the no high risk group (***Figure 21***). There are no statistically significant differences in effect sizes among the risk groups (test for subgroup differences p=0.18).

Figure 21: Meta-analysis on time to alleviation of influenza symptoms (in hours) comparing oseltamivir versus placebo in patients with confirmed influenza that were administered the drug within 48 hours by risk group



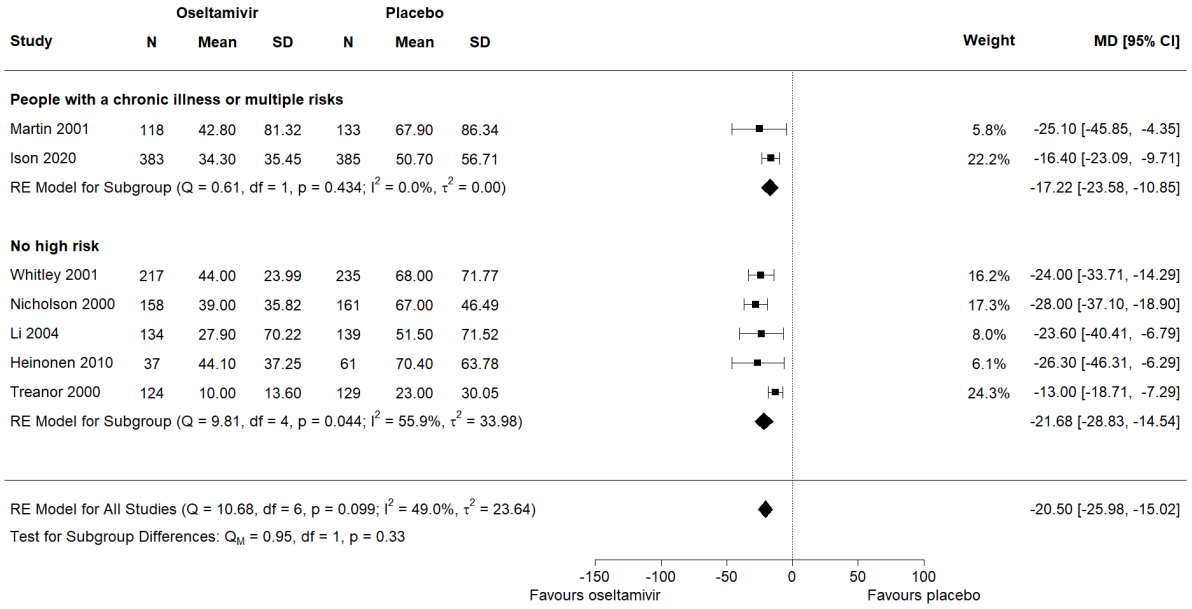
Seven RCTs[66,69,72,74–77] that assessed the time to resolution of fever for oseltamivir compared to placebo in patients with confirmed influenza that were administered the drug within 48 hours were included in the meta-analysis by age group. The mean time to resolution of fever was statistically significantly shorter with oseltamivir than with placebo in the all-ages group, in the adults' group and in the children group. The pooled estimated mean difference was -17.22 (95% CI -23.58 to -10.85) in the all ages group, -20.63 (95% CI -31.00 to -10.26) in the adults group and -24.44 (95% CI -33.18 to -15.70) in the children group (***Figure 22***). There are no statistically significant differences in effect sizes among the age groups (test for subgroup differences p=0.42).

Figure 22: Meta-analysis on time to resolution of fever (in hours) comparing oseltamivir versus placebo in patients with confirmed influenza that were administered the drug within 48 hours by age group



Seven RCTs[66,69,72,74–77] that assessed the time to resolution of fever for oseltamivir compared to placebo in patients with confirmed influenza that were administered the drug within 48 hours were included in the meta-analysis by risk group. The mean time to resolution of fever was statistically significantly shorter with oseltamivir than with placebo in the group of people with a chronic illness or multiple risks as well as in the no high risk group. The pooled estimated mean difference was -17.22 hours (95% CI -23.58 to -10.85) in the group of people with a chronic illness or multiple risks and -21.68 hours (95% CI -28.83 to -14.54) in the no high risk group (***Figure 23***). There are no statistically significant differences in effect sizes among the risk groups (test for subgroup differences p=0.33).

Figure 23: Meta-analysis on time to resolution of fever (in hours) comparing oseltamivir versus placebo in patients with confirmed influenza that were administered the drug within 48 hours by risk group



7.3.4 PICO 2: Primary outcomes

Of the 9 studies addressing the research questions of PICO 2, 8 studies[80,81,93–98] compared oseltamivir with placebo and one[99] compared baloxavir with placebo. No studies were identified that compared oseltamivir with baloxavir or any non-antiviral treatment.

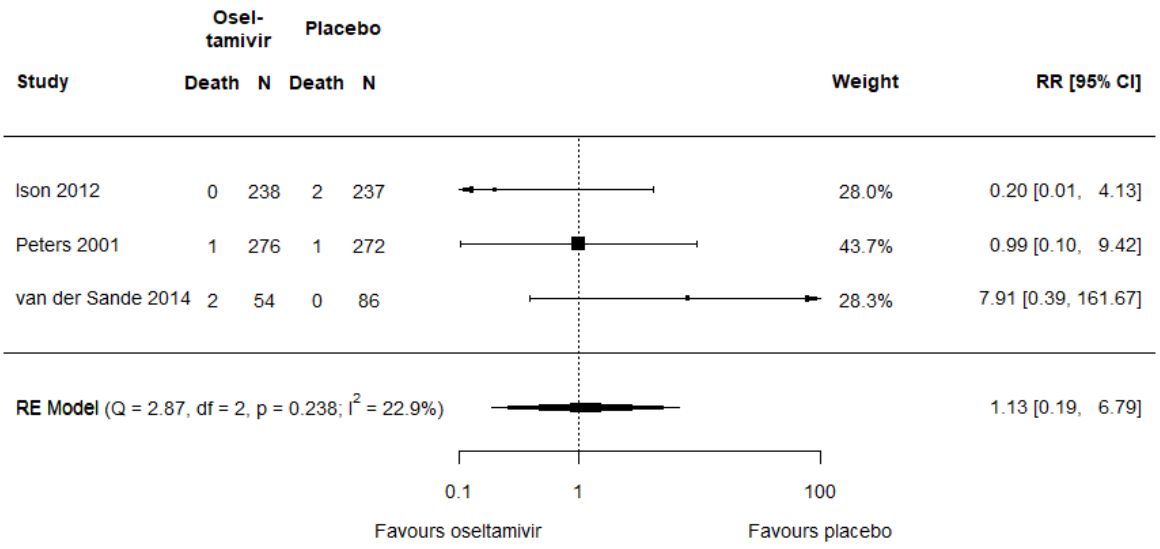
7.3.4.1 Disease-specific and all-cause mortality

7.3.4.1.1 Oseltamivir versus placebo

Three RCTs[94,95,97] that assessed mortality for oseltamivir compared to placebo were included in the meta-analysis. Mortality was not statistically significantly different with oseltamivir than placebo. The pooled estimated RR was 1.13 (95% CI 0.19 to 6.79, ***Figure 24***).

Ison et al. 2012[94] examined transplant recipients, van der Sande et al. 2014[97] examined elderly with a post-exposure administration and Peters et al. 2001[95] focused on vaccinated frail older population.

Figure 24: Meta-analysis on mortality comparing oseltamivir versus placebo



7.3.4.1.2 Baloxavir versus placebo

Only one RCT[99] assessed mortality for baloxavir compared to placebo and found zero events in both arms (***Table 34***).

Table 34: Synthesis without meta-analysis on mortality comparing baloxavir versus placebo

Study	Population	Intervention	Comparator	Effect
Ikematsu 2020[99]	All ages, not high-risk, post-exposure admin-istration	0 (N=374)	0 (N=375)	NE

Abbreviations:
NE: not estimable

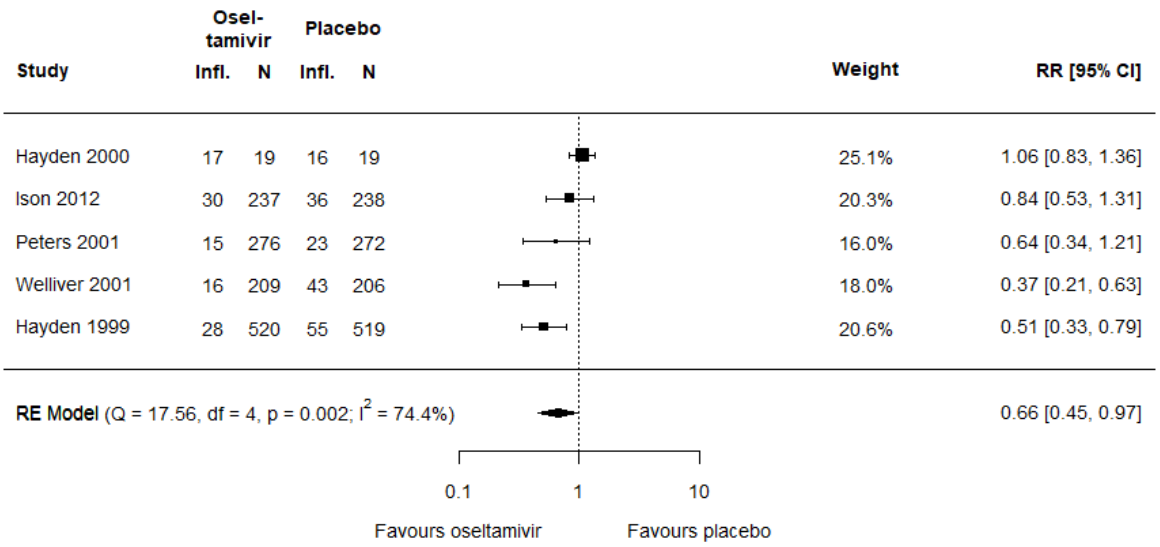
7.3.4.2 Number of people with laboratory-confirmed influenza

7.3.4.2.1 Oseltamivir versus placebo

Five RCTs[80,93–96] that assessed the number of people with laboratory-confirmed influenza for oseltamivir compared to placebo were included in the meta-analysis. The number of people with laboratory-confirmed influenza was statistically significantly lower with oseltamivir than placebo. The pooled estimated RR was 0.66 (95% CI 0.45 to 0.97, ***Figure 25***).

Hayden et al. 1999[93] and Welliver et al. 2001[96] studied adults without risks, Hayden et al. 2000[80] focused on influenza B, Ison et al. 2012[94] examined transplant recipients and Peters et al. 2001[95] examined vaccinated frail older population.

Figure 25: Meta-analysis on laboratory-confirmed influenza comparingoseltamivir versus placebo



7.3.4.2.2 Baloxavir versus placebo

Only one RCT[99] assessed the number of people with laboratory-confirmed influenza for baloxavir compared to placebo, reporting statistically significantly favourable results for baloxavir (***Table 35***).

Table 35: Synthesis without meta-analysis on laboratory-confirmed influenza comparing baloxavir versus placebo

Study	Population	Intervention	Comparator	Effect
Ikematsu 2020[99]	All ages, not high-risk, post-exposure admin-istration	7 (N=374)	51 (N=375)	RR=0.14; 95% CI 0.06 to 0.30; p < 0.001

Abbreviations:
CI: confidence interval, RR: relative risk

7.3.4.3 Influenza confirmed with rapid diagnostic tests

None of the included studies assessed the effect on influenza confirmed with rapid diagnostic tests.

7.3.4.4 Number of people with influenza-associated complications

7.3.4.4.1 Oseltamivir versus placebo

Only one RCT[95] assessed the number of people with influenza-associated complications with osel-tamivir compared to placebo and showed no statistically significant difference between the two treatments (***Table 36***).

Table 36: Synthesis without meta-analysis of number on influenza-associated complications comparing oseltamivir versus placebo

Study	Population	Intervention	Comparator	Effect
Peters 2001[95]	Vaccinated frail older population	1 (N=276)	7 (N=272)	RR=0.14 ,95% CI 0.02 to 1.14[1]

Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.3.4.4.2 Baloxavir versus placebo

No study was identified that analysed the number of influenza-associated complications for baloxavir compared to placebo.

7.3.4.5 First hospitalisation due to influenza symptoms

None of the included studies assessed the effect on hospitalisation due to influenza symptoms.

7.3.5 PICO 2: Secondary outcomes

7.3.5.1 Length of hospitalisation

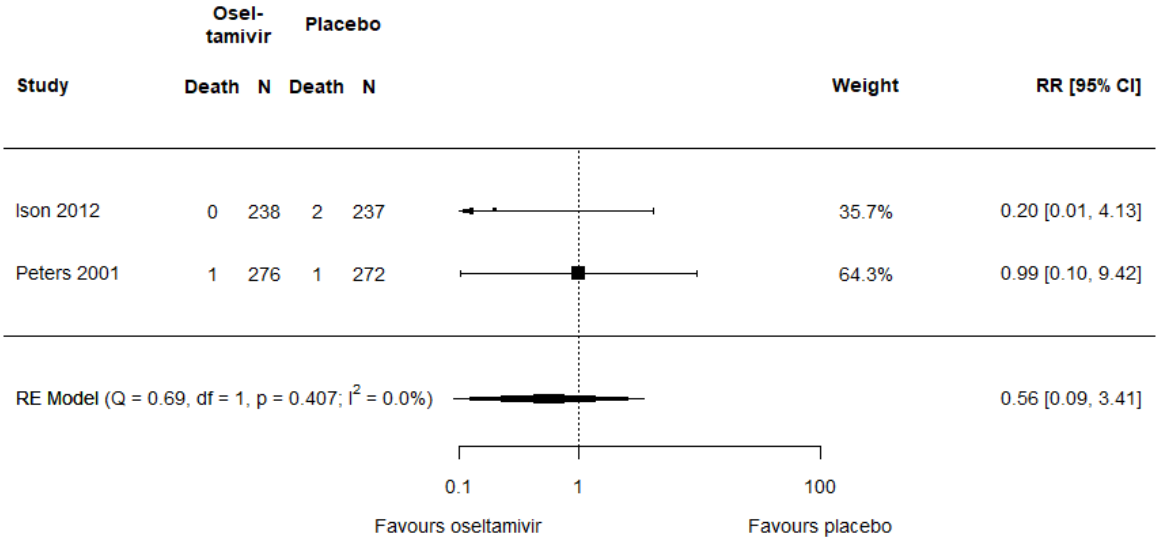
None of the included studies assessed the effect on the length of hospitalisation due to influenza symptoms.

7.3.6 PICO 2: Subgroup analyses

For the primary outcomes it was not possible to compute subgroup analyses except for oseltamivir versus placebo. For the secondary outcome it was not possible to compute subgroup analyses.

The exclusion of the post-exposure study[97] showed that mortality was not statistically significantly different with oseltamivir than placebo. The pooled estimated RR was 0.56 (95% CI 0.09 to 3.41, ***Figure 26***). Ison et al. 2012[94] and Peters et al. 2001[95] did not report the time of exposure.

Figure 26: Meta-analysis on mortality comparing oseltamivir versus placebo, without study reporting post-exposure



7.3.7 Sensitivity analyses

The meta-analyses showing the results using a continuity correction of 0.1 instead of 0.5 are in the ***Appendix 12.2.3*** and ***12.2.4***. The direction of effects and statistical significance remain the same when using a continuity correction of 0.1 as compared to 0.5.

7.4 Findings safety

7.4.1 PICO 1

7.4.1.1 Adverse events

Where available, the number of people with adverse events related to the treatment was analysed; otherwise, the total number of people with adverse events was assessed.

7.4.1.1.1 Oseltamivir versus placebo

Four RCTs[67,71,74,79] that assessed the adverse events for oseltamivir compared to placebo in patients with influenza-like symptoms were included in the meta-analysis. The number of adverse events was not statistically significantly different with oseltamivir than placebo in patients with influenza-like symptoms. The pooled estimated RR was 1.12 (95% CI 0.84 to 1.49, ***Figure 27***).

Dawood et al. 2016[79] focused on hospitalised children, while Johnston et al. 2005[71] studied children with asthma. Hayden et al. 2018[67] and Li et al. 2004[74] examined adults without risk factors, with Hayden et al. 2018[67] also including adolescents. Studies reporting only specific adverse events (e.g., nausea, vomiting) in patients with influenza-like symptoms are summarised ***Table 37***.

No study reported adverse events for this comparison in patients with confirmed influenza.

Figure 27: Meta-analysis on adverse events comparing oseltamivir versus placebo in patients with influenza-like symptoms

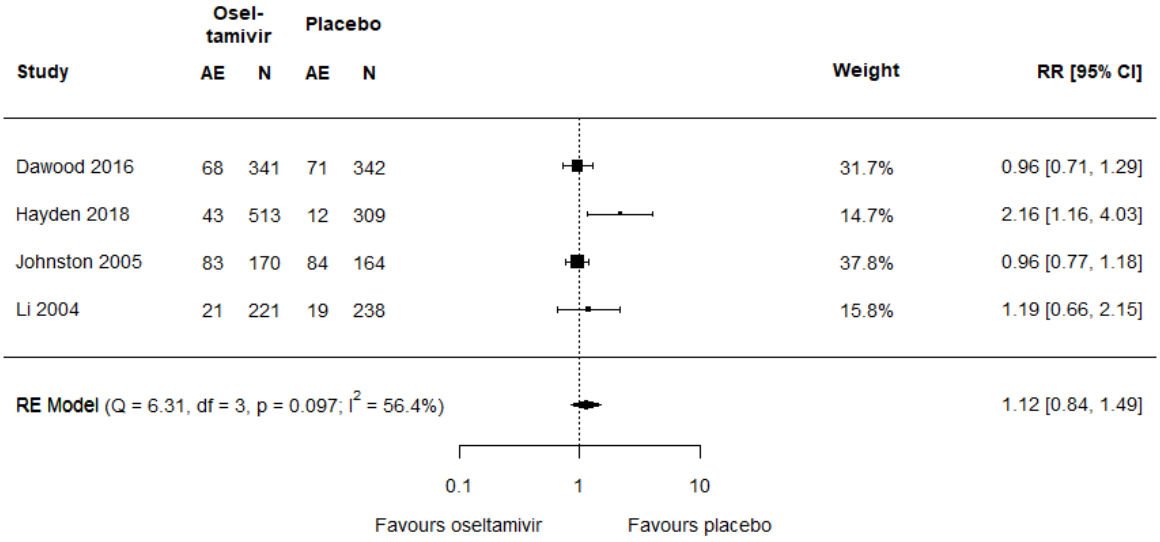


Table 37: Synthesis without meta-analysis on adverse events comparing oseltamivir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Fry 2014[82]	In patients with influenza-like symptoms	Children and adolescents	Nausea: 4 Diarrhoea:45 Vomiting: 31 N=522	Nausea: 2 Diarrhoea:65 Vomiting: 17 N=528	p = 0.45 p = 0.05 p = 0.039
Fry 2014[82]	In patients with influenza-like symptoms	Adults	Nausea: 5 Diarrhoea:2 Vomiting: 4 N=76	Nausea: 1 Diarrhoea:2 Vomiting: 2 N=64	p = 0.22 p = 1.00 p = 0.69
Hayden 2000[80]	In patients with influenza-like symptoms	Healthy adults with influenza B	Nausea: 8 Vomiting: 4 N=78	Nausea: 3 Vomiting: 1 N=39	NE
Treanor 2000[69]	In patients with influenza-like symptoms	Adults, not high-risk	Nausea: 35 Vomiting: 27 N=206	Nausea: 15 Vomiting: 7 N=204	p = 0.002 p < 0.001
Heinonen 2010[72]	In patients with influenza-like symptoms	Children aged 1-3 years	Vomiting:59 Diarrhoea: 71 N=202	Vomiting: 38 Diarrhoea: 73 N=204	p = 0.01 p = 0.89
Martin 2001[76]	In patients with influenza-like symptoms	High-risk patients	Nausea: 19 Vomiting: 9 Diarrhoea: 8 N=199	Nausea: 13 Vomiting: 6 Diarrhoea: 23 N=202	NE
Martin 2001[76]	In patients with influenza-like symptoms	Elderly patients	Nausea: 21 Vomiting: 17 Diarrhoea: 9 N=362	Nausea: 27 Vomiting: 11 Diarrhoea: 19 N=373	NE

Abbreviations:
NE: not estimable

7.4.1.1.2 Oseltamivir versus baloxavir

Two RCTs[67,84] that assessed the adverse events for oseltamivir compared to baloxavir in patients with influenza-like symptoms were included in the meta-analysis. The number of adverse events was statistically significantly higher with oseltamivir than baloxavir. The pooled estimated RR was 2.00 (95% CI 1.29 to 3.12, ***Figure 28***).

Hayden et al. 2018[67] studied adolescents and adults without risks and Baker et al. 2020[84] assessed children.

Furthermore, two RCTs[66,83] analysed patients with confirmed influenza and found no statistically significant differences between the two treatments (***Table 38***).

Figure 28: Meta-analysis showing adverse events of oseltamivir versus baloxavir in patients with influenza-like symptoms

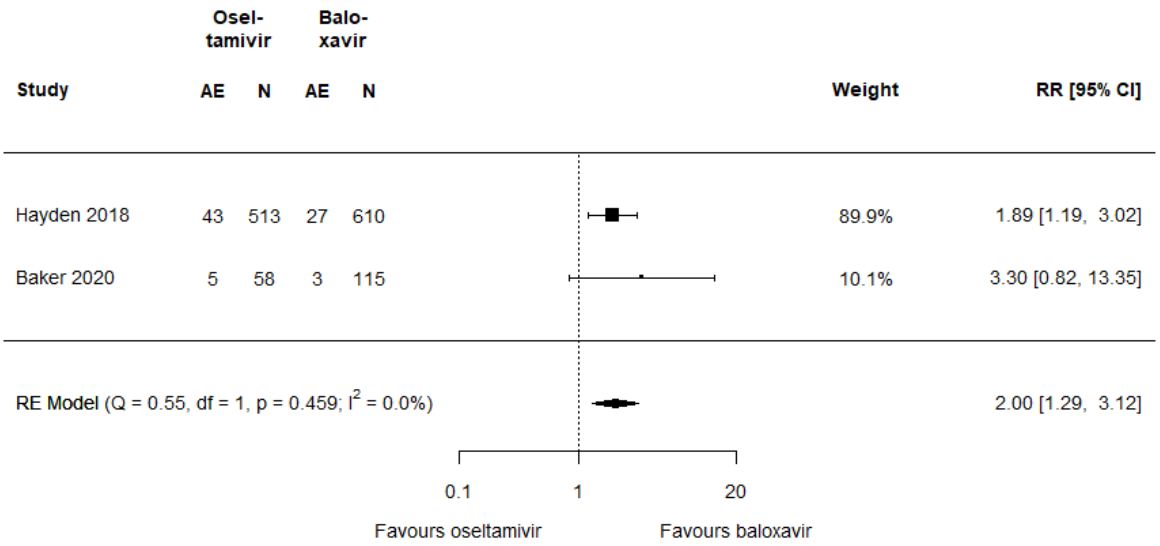


Table 38: Synthesis without meta-analysis on adverse events comparing oseltamivir versus baloxavir

Study	Type of analysis	Population	Intervention	Comparator	Effect
Qiu 2024[83]	In patients with confirmed influenza	Not high-risk patients with influenza A	13 (N=100)	8 (N=100)	RR=1.63, 95% CI 0.70 to 3.75[1]
Ison 2020[66]	In patients with confirmed influenza2	High-risk adolescent and adult patients with uncomplicated influenza	57 (N=721)	41 (N=730)	RR=1.41, 95% CI 0.95 to 2.07**1**

Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report
[2]PP analysis

7.4.1.1.3 Oseltamivir versus any non-antiviral treatment

Two RCTs[85,87] that assessed the adverse events for oseltamivir compared to any non-antiviral treatment in patients with influenza-like symptoms were included in the meta-analysis. The number of adverse events was not statistically significantly different with oseltamivir than any non-antiviral treatment in patients with influenza-like symptoms. The pooled estimated RR was 1.51 (95% CI 0.48 to 4.74, ***Figure 29***).

Raus et al. 2015[85] analysed all patients with influenza-like symptoms and Lin et al. 2006[87] investigated high-risk patients.

The result of one RCT[89] that did not specify the type of analysis used is presented in ***Table 39***. The estimated effect is not statistically significant.

No study reported adverse events for this comparison in patients with confirmed influenza.

Figure 29: Meta-analysis on adverse events comparing oseltamivir versus any non-antiviral treatment in patients with influenza-like symptoms

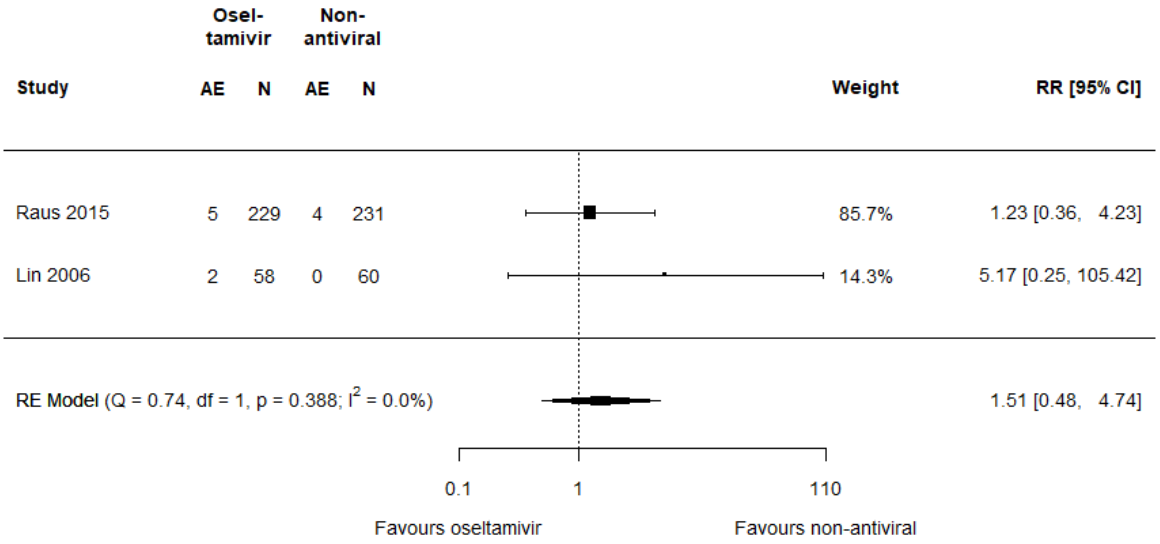


Table 39: Synthesis without meta-analysis on adverse events comparing oseltamivir versus any non-antiviral treatment

Study	Type of analysis	Population	Intervention	Comparator	Effect
Markovski 2002[89]	Not reported	Adults hospitalised with influenza infection	1 (N=17)	0 (N=24)	RR=4.17, 95% CI 0.18 to 96.53[1]

Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.4.1.1.4 Baloxavir versus placebo

Two RCTs[66,67] assessed the adverse events for baloxavir compared to placebo and found no statistically significant difference between the two treatments (***Table 40***). One study analysed patients with influenza-like symptoms, while the other analysed those with confirmed influenza.

Table 40: Synthesis without meta-analysis on adverse events comparing baloxavir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Hayden 2018[67] Phase 2 study	In patients with influenza-like symptoms	Adults and adolescents, not high-risk	26 (N=100)	29 (N=100)	RR=0.90, 95% CI 0.57 to 1.41[1]
Hayden 2018[67] Phase 3 study	In patients with influenza-like symptoms	Adults and adolescents, not high-risk	27 (N=610)	12 (N=309)	RR=1.14,95% CI 0.59 to 2.22[1]
Ison 2020[66]	In patients with confirmed influenza[2]	High-risk adolescent and adult patients with uncomplicated influenza	41 (N=730)	60 (N=727)	RR=0.68, 95% CI 0.46 to 1.00[1]

Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report
[2]PP analysis

7.4.1.2 Severe adverse events

Where available, the number of people with severe adverse events related to the treatment was analysed; otherwise, the total number of people with severe adverse events was assessed.

7.4.1.2.1 Oseltamivir versus placebo

Four RCTs[71,72,79,82] that assessed the severe adverse events for oseltamivir compared to placebo in patients with influenza-like symptoms were included in the meta-analysis. The number of severe adverse events was not statistically significantly different with oseltamivir than placebo in patients with influenza-like symptoms. The pooled estimated RR was 0.96 (95% CI 0.46 to 2.02, ***Figure 30***).

Heinonen et al. 2010[72] investigated children without comorbidities, Dawood et al. 2016[79] focused on hospitalised children, and Johnston et al. 2005[71] studied children with asthma. Fry et al. 2014[82] examined influenza patients across all age groups.

Additionally, 5 RCTs[67,69,74,77,80] analysing patients with influenza-like symptoms reported zero events in both arms and were therefore not included in the meta-analysis (***Table 41***). One RCT[66] analysing patient with confirmed influenza using the PP analysis also did not find a statistical significant difference between the two treatments.

Figure 30: Meta-analysis on severe adverse events comparing oseltamivir versus placebo in patients with influenza-like symptoms

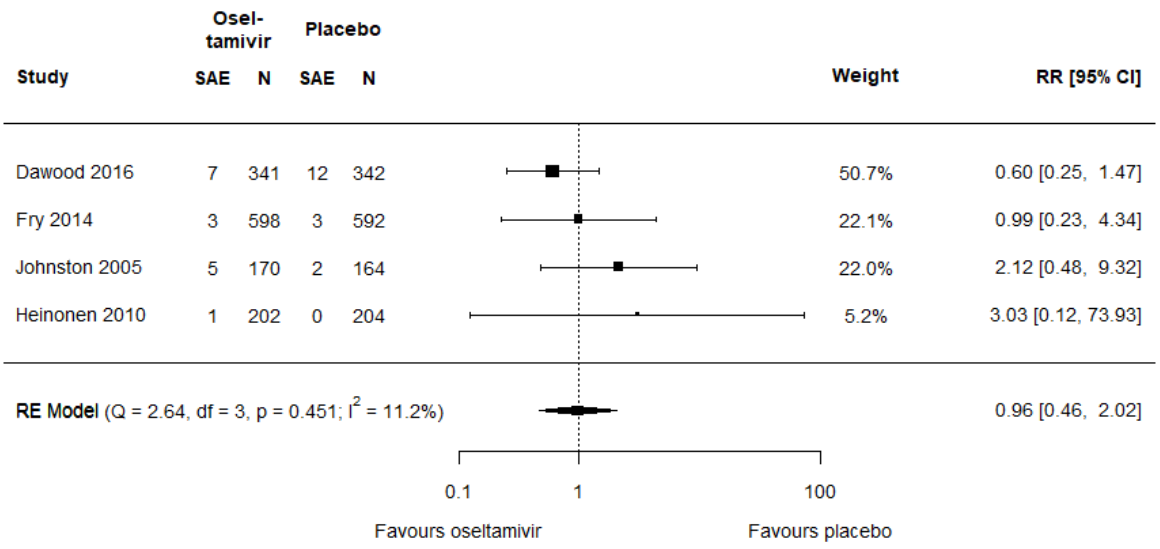


Table 41: Synthesis without meta-analysis on severe adverse events comparing oseltamivir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Hayden 2000[80]	In patients with influenza-like symptoms	Healthy adults with influenza B	0 (N=78)	0 (N=39)	NE
Hayden 2018[67]	In patients with influenza-like symptoms	Adults and adolescents, not high-risk	0 (N=513)	0 (N=309)	NE
Treanor 2000[69]	In patients with influenza-like symptoms	Adults, not high-risk	0 (=206)	0 (N=204)	NE
Li 2004[74]	In patients with influenza-like symptoms	Adults, not high-risk	0 (N=221)	0 (N=238)	NE
Whitley 2001[77]	In patients with influenza-like symptoms	Children, not high-risk	0 (N=344)	0 (N=351)	**NE**
Ison 2020[66]	In patients with confirmed influenza2	High-risk adolescent and adult patients with uncomplicated influenza	2 (N=721)	2 (N=727)	RR=1.01, 95% CI 0.18 to 5.80[1]

Abbreviations:
CI: confidence interval, NE: not estimable, RR: relative risk
Notes:
[1]Calculated by the authors of this report
[2]PP analysis

7.4.1.2.2 Oseltamivir versus baloxavir

Two RCTs[67,84] assessed the number of people with severe adverse events for oseltamivir compared to baloxavir in patients with influenza-like symptoms (***Table 42***). One study reported zero

events in both arms, while the other found no statistically significant difference between the two treatments. Two studies[66,67] assessed the number of people with severe adverse events for oseltamivir compared to baloxavir in patients with confirmed influenza (***Table 42***). Similarly, one study reported zero events in both arms, while the other found no statistically significant difference between the two treatments.

Table 42: Synthesis without meta-analysis on severe adverse events comparing oseltamivir versus baloxavir

Study	Type of analysis	Population	Intervention	Comparator	Effect
Baker 2020[84]	In patients with influenza-like symptoms	Children, not high-risk	0 (N=58)	0 (N=115)	NE
Hayden 2018[67]	In patients with influenza-like symptoms	Adults and adolescents, not high-risk	0 (N=513)	2 (N=610)	RR=0.24, 95% CI 0.01 to 4.94[1]
Ison 2020[66]	In patients with confirmed influenza[2]	High-risk adolescent and adult patients with uncomplicated influenza	2 (N=721)	0 (N=730)	RR=5.06, 95% CI 0.24 to 105.26[1]
Qiu 2024[83]	In patients with confirmed influenza	Not high-risk patients with influenza A	0 (N=100)	0 (N=100)	NE

Abbreviations:
CI: confidence interval, NE: not estimable, RR: relative risk
Notes:
[1]Calculated by the authors of this report
[2]PP analysis

7.4.1.2.3 Oseltamivir versus any non-antiviral treatment

Only one RCT[85] assessed the number of people with severe adverse events for oseltamivir compared to any non-antiviral treatment in patients with influenza-like symptoms and reported zero events in both arms (***Table 43***).

No study reported severe adverse events for this comparison in patients with confirmed influenza.

Table 43: Synthesis without meta-analysis on severe adverse events comparing oseltamivir versus any-non antiviral treatment

Study	Type of analysis	Population	Intervention	Comparator	Effect
Raus 2015[85]	In patients with influenza-like symptoms	All ages, no high risk	0 (N=229)	0 (N=231)	NE

Abbreviations:
NE: not estimable

7.4.1.2.4 Baloxavir versus placebo

Two RCTs[66,67] assessed the number of people with severe adverse events for baloxavir compared to placebo and found no statistically significant differences between the two treatments (***Table 44***).

One study analysed patients with influenza-like symptoms, while the other analysed those with confirmed influenza.

Table 44: Synthesis without meta-analysis on severe adverse events comparing baloxavir versus placebo

Study	Type of analysis	Population	Intervention	Comparator	Effect
Hayden 2018[67] Phase 2 study	In patients with influenza-like symptoms	Adults and adolescents, not high-risk	0 (N=100)	0 (N=100)	NE
Hayden 2018[67] Phase 3 study	In patients with influenza-like symptoms	Adults and adolescents, not high-risk	2 (N=610)	0 (N=309)	RR=2.54, 95% CI 0.12 to 52.68[1]
Ison 2020[66]	In patients with confirmed influenza2	High-risk adolescent and adult patients with uncomplicated influenza	0 (N=730)	2 (N=727)	RR=0.20, 95% CI 0.01 to 4.14**1**

Abbreviations:
CI: confidence interval, ITT: intention-to-treat, NE: not estimable, RR: relative risk
Notes:
[1]Calculated by the authors of this report
[2]PP analysis

7.4.1.3 Toxicities

None of the included studies assessed the effect on toxicities.

7.4.2 PICO 2

No studies were identified that compared oseltamivir with baloxavir or any non-antiviral treatment.

7.4.2.1 Adverse events

7.4.2.1.1 Oseltamivir versus placebo

Three RCTs[80,94,98] that assessed the number of people with adverse events for oseltamivir compared to placebo were included in the meta-analysis. The number of adverse events was not statistically significantly different with oseltamivir than placebo. The pooled estimated RR was 0.96 (95% CI 0.82 to 1.12, ***Figure 31***).

Hayden et al. 2000[80] examined adults with influenza B, Ison et al. 2012[94] focused on transplant recipients and Anekthananon et al. 2013[98] investigated health workers.

Furthermore, two additional RCTs[95,97] assessed adverse effects for oseltamivir compared to placebo (***Table 45***). Peters et al. 2001[95] analysed the ITT population and reported only specific adverse events (e.g., nausea, vomiting). Van der Sande et al. 2014[97] analysed the PP population and found no statistically significant difference in the RR between the two treatments.

Figure 31: Meta-analysis on adverse events comparing oseltamivir versus placebo

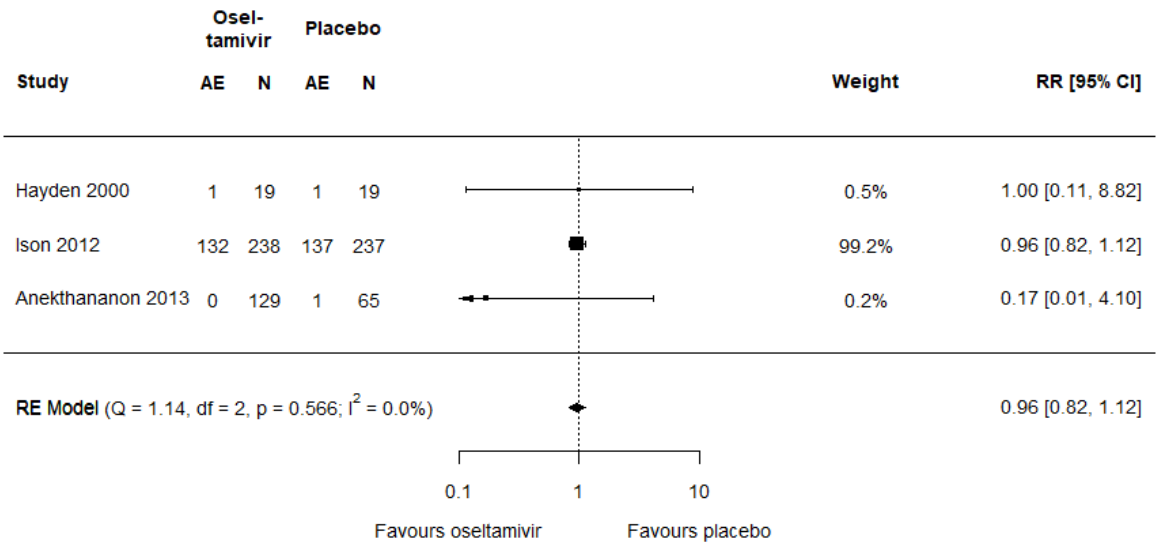


Table 45: Synthesis without meta-analysis on adverse events comparing oseltamivir versus placebo

Study	Population	Intervention	Comparator	Effect
Peters 2001[95]	Vaccinated frail older population	Nausea: 12 Diarrhoea: 9 Vomiting: 5 N=276	Nausea: 11 Diarrhoea:11 Vomiting: 4 N=272	NE
Van der Sande 2014[97]	Elderly, post-exposure prevention	2 (N=36)	5 (N=63)	RR=0.79, 95% CI 0.19 to 3.32[1]

Abbreviations:
CI: confidence interval, NE: not estimable, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.4.2.1.2 Baloxavir versus placebo

Only one RCT[99] assessed the number of people with adverse events for baloxavir compared to placebo and found no statistically significant difference between these two treatments (***Table 46***).

Table 46: Synthesis without meta-analysis on adverse events comparing baloxavir versus placebo

Study	Population	Intervention	Comparator	Effect
Ikematsu 2020[99]	All ages, not high-risk, post-exposure admin-istration	7 (N=374)	6 (N=375)	RR=1.17, 95% CI 0.40 to 3.45[1]

Abbreviations:
CI: confidence interval, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.4.2.2 Severe adverse events

7.4.2.2.1 Oseltamivir versus placebo

Four RCTs[80,94,96,98] assessed the number of people with severe adverse events for oseltamivir compared to placebo, three of which reported zero events in both arms, while the other found no statistically significant difference between the two treatments (***Table 47***).

Table 47: Synthesis without meta-analysis on severe adverse events comparing oseltamivir versus placebo

Study	Population	Intervention	Comparator	Effect
Hayden 2000[80]	Adults with influenza B, not high-risk	0 (N=19)	0 (N=19)	NE
Ison 2012[94]	Transplant recipients	18 (N=238)	23 (N=237)	RR=0.78, 95% CI 0.44 to 1.40[1]
Welliver 2001[96]	Adults, not high-risk	0 (N=493)	0 (N=462)	NE
Anekthananon 2013[98]	Health workers (adults, not high risk)	0 (N=129)	0 (N=65)	NE

Abbreviations:
CI: confidence interval, NE: not estimable, RR: relative risk
Notes:
[1]Calculated by the authors of this report

7.4.2.2.2 Baloxavir versus placebo

Only one RCT[99] assessed severe adverse events for baloxavir compared to placebo and reported zero events in both arms (***Table 48***).

Table 48: Synthesis without meta-analysis on severe adverse events comparing baloxavir versus placebo

Study	Population	Intervention	Comparator	Effect
Ikematsu 2020[99]	All ages, not high-risk, post-exposure administration	0 (N=374)	0 (N=375)	NE

Abbreviations:
NE: not estimable

7.4.2.3 Toxicities

None of the included studies assessed the effect on toxicities.

7.4.3 Sensitivity analyses

The meta-analyses showing the results using a continuity correction of 0.1 instead of 0.5 are in the ***Appendix 12.2.5*** and ***12.2.6.*** The direction of effects and statistical significance remain the same when using a continuity correction of 0.1 as compared to 0.5.

7.5 GRADE Summary of Findings Table

The results of the most relevant outcomes from the systematic review, meta-analysis, and GRADE assessment on the clinical efficacy and safety are summarised in Table 49 to Table 52 for the different interventions and comparators for PICO 1 and PICO2.

PICO 1: Primary outcomes

The certainty of evidence of the primary outcomes are presented in ***Table 49***.

Disease specific and all-cause mortality in patients with influenza-like symptoms

The certainty of evidence was rated as low for all comparisons. Indirectness was downgraded for all comparisons because studies analysed specific population groups limiting generalisability to all influenza A or B patients. Imprecision was downgraded for all comparisons due to wide confidence intervals and/or a very low or low event rate, combined with an insufficient sample size, resulting in the optimal information size not being met.

Influenza-associated complications (pneumonia, bronchitis, otitis media)

For the comparison of oseltamivir vs. placebo, the certainty of evidence was rated as moderate due to a downgrade for indirectness, as the studies focused on specific population groups, limiting the generalisability to all influenza A or B patients. For the comparison of oseltamivir vs. baloxavir, the certainty of evidence was rated as low because indirectness (specific population groups analysed limiting generalisability) and imprecision (optimal information size not met) were downgraded. For the comparison of oseltamivir vs. any non-antiviral treatment, the certainty of evidence was also rated as very low (patients with influenza-like symptoms) or low (patients with confirmed influenza). The certainty of evidence for the comparison of baloxavir vs. placebo was low. Inconsistency (inconsistent populations) and indirectness (specific population groups analysed limiting generalisability) were downgraded.

First hospitalisation in outpatients

The certainty of evidence was moderate for the comparison of oseltamivir vs. placebo and low for the comparison of oseltamivir vs. baloxavir and any non-antiviral treatment (confirmed influenza) as well as for baloxavir vs. placebo. For influenza-like symptoms, the certainty of evidence comparing oseltamivir vs. any non-antiviral treatment was very low. In all comparisons imprecision was downgraded because of wide confidence intervals and/or a very low or low event rate, combined with an insufficient sample size, resulting in the optimal information size not being met. Additionally, for the comparisons of oseltamivir vs. baloxavir and baloxavir vs. placebo, indirectness was downgraded, because specific population groups analysed limiting generalisability. For the comparison of oseltamivir vs. any non-antiviral treatment, risk of bias was downgraded because deviations from the intended interventions and missing outcome data were noticed.

PICO 1: Secondary outcomes

The certainty of evidence of the secondary outcomes are presented in ***Table 50***.

Time to alleviation of symptoms (TTAS)

The certainty of evidence was rated as low for the comparison of oseltamivir vs. placebo in patients with confirmed influenza as well as for oseltamivir vs. baloxavir in patients with confirmed influenza. The certainty of evidence was rated as moderate for the comparison of oseltamivir vs. placebo in patients with influenza-like symptoms and for baloxavir vs. placebo in patients with confirmed influenza. The main reason for downgrading was indirectness (specific population groups analysed limiting generalisability) in all comparisons and inconsistency (unexplained heterogeneity or inconsistent populations) in two comparisons.

Number of people with antibiotics use

The certainty of evidence was rated as moderate for the comparison of oseltamivir vs. placebo, as very low for the comparison of oseltamivir vs. baloxavir, and as low for the comparison of oseltamivir vs. any non-antiviral treatment in patients with confirmed influenza as well as for oseltamivir vs. baloxavir in patients with confirmed influenza. The main reason for downgrading was indirectness (specific population groups analysed limiting generalisability) in all comparisons and imprecision in two comparisons. Risk of bias and inconsistency were downgraded in one comparison each.

Severe adverse events

The certainty of evidence was rated as low for all comparisons. In all comparisons, indirectness and imprecision were downgraded because the studies focused on specific population groups, limiting generalisability and wide confidence intervals and/or a very low or low event rate, combined with an insufficient sample size, resulting in the optimal information size not being met.

Adverse events

The certainty of evidence was rated as very low for the comparison of oseltamivir vs. placebo and oseltamivir vs. any non-antiviral treatment and as low for the comparison of oseltamivir vs. baloxavir and baloxavir vs. placebo. In all comparisons indirectness (specific population groups analysed limiting generalisability) and imprecision (wide confidence intervals) were downgraded. Furthermore, inconsistency (oseltamivir vs. placebo) and risk of bias (oseltamivir vs. any non-antiviral treatment) were downgraded.

PICO 2: Primary outcomes

The certainty of evidence of the primary outcomes are presented in ***Table 51.*** Eight studies for the comparison of oseltamivir vs. placebo and one for the comparison of baloxavir vs. placebo were available. There were no studies comparing oseltamivir vs. baloxavir or oseltamivir vs. any non-antiviral treatment.

Disease-specific and all-cause mortality

The certainty of evidence was rated as low for both comparisons oseltamivir vs. placebo and baloxavir vs. placebo. Indirectness and imprecision were downgraded because specific population

groups were analysed limiting generalisability and optimal information size was not met due to very low event rate.

Laboratory-confirmed influenza

For the comparison of oseltamivir vs. placebo, the certainty of evidence was rated as low. Inconsistency was downgraded due to unexplained heterogeneity and indirectness was downgraded because the studies focused on specific populations limiting generalisability. For the comparison of baloxavir vs. placebo, the certainty of evidence was rated as moderate. The study analysed a specific population group and therefore, indirectness was downgraded.

Influenza confirmed with rapid diagnostic test

There were no studies that used rapid diagnostic tests to confirm influenza.

Influenza-associated complications

Only one study analysed influenza-associated complications and looked at the comparison of oseltamivir vs. placebo. The certainty of evidence was rated as very low because the study analysed a specific population group (downgrade of indirectness) and the event rate were very low and optimal information size was not met (downgrade of imprecision). Furthermore, publication bias was suspected because only one of the 8 studies identified for this comparison reported on influenza-associated complications.

PICO 2: Secondary outcomes

The certainty of evidence of the secondary outcomes are presented in ***Table 52***.

Length of hospitalisation

There were no studies analysing the length of hospitalisation.

Severe adverse events

The certainty of evidence was rated as very low for the comparison of oseltamivir vs. placebo. Inconsistency (inconsistent population), indirectness (specific population groups analysed limiting generalisability) and imprecision (very low event rate resulting that optimal information size was not met) were downgraded. Comparing baloxavir vs. placebo, the certainty of evidence was low due to downgrading of indirectness and imprecision (same reasons as mentioned before).

Adverse events

The certainty of evidence was rated as low for both comparisons. Inconsistent population across the studies (inconsistency), specific population groups (indirectness) and low event rates combined with insufficient sample size (imprecision) were the reasons for downgrading.

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Table 49: Summary of findings table – PICO 1– Primary outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
Disease-specific and all-cause mortality in patients with influenza-like symptoms (follow-up: range 12 days to 22 days)								**Oseltamivir vs. Placebo**				
2	randomised trials	not serious	not serious	serious[a]	serious[b]	1 RCT industry funded*	2/1066 (0.2%)	0/1070 (0.0%)	**RR 3.00** (0.31 to 28.82)	**0 fewer per 1'000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low[a,b]	CRITICAL
Disease-specific and all-cause mortality in patients with influenza-like symptoms (follow-up: range 22 days to 29 days)								**Oseltamivir vs. Baloxavir**				
3	randomised trials	not serious	not serious	serious[c]	serious[d]	all RCTs industry funded*	A pooled effect measure was not calculated because 2 RCTs reported zero events in both groups. In the other RCT, the risk was not significantly different: RR 3.04 (0.12 to 74.44).				⨁⨁◯◯ Low[c,d]	CRITICAL
Disease-specific and all-cause mortality in patients with influenza-like symptoms (follow-up: mean 30 days)								**Oseltamivir vs. any non-antiviral treatment**				
1	randomised trials	not serious	not serious[e]	serious[f]	serious[b,d]	none	22/551 (4.0%)	27/556 (4.9%)	no pooled effect Effect for single study: RR 0.82 (0.47 to 1.43)		⨁⨁◯◯ Low[b,d,e,f]	CRITICAL
Disease-specific and all-cause mortality in patients with influenza-like symptoms (follow-up: mean 22 days)								**Baloxavir vs. Placebo**				
2	randomised trials	not serious	not serious	serious[g]	serious[d]	all RCTs industry funded*	A pooled effect measure was not calculated because the 2 RCTs reported zero events in both groups.				⨁⨁◯◯ Low[d,g]	CRITICAL
Influenza-associated complications in patients with confirmed influenza (pneumonia, bronchitis, otitis media) (follow-up: range 21 days to 28 days)								**Oseltamivir vs. Placebo**				
5	randomised trials	not serious	not serious	serious[h]	not serious	4 RCTs industry funded*	81/1022 (7.9%)	141/1050 (13.4%)	**RR 0.60** (0.47 to 0.78)	**54 fewer per 1'000** (from 71 fewer to 30 fewer)	⨁⨁⨁◯ Moderate[h]	CRITICAL
Influenza-associated complications in patients with influenza-like symptoms (pneumonia, bronchitis, otitis media) (follow-up: mean 21 days)								**Oseltamivir vs. Placebo**				
1	randomised trials	not serious	not serious[e]	serious[i]	serious[b,d]	RCT industry funded*	16/241 (6.6%)	13/235(5.5%)	no pooled effect Effect for single study: RR 1.20 (0.59 to 2.44)		⨁⨁◯◯ Low[b,d,e,i]	CRITICAL
Influenza-associated complications in patients with influenza-like symptoms (pneumonia, bronchitis, otitis media) (follow-up: mean 29 days)								**Oseltamivir vs. Baloxvir**				
1	randomised trials	not serious	not serious[e]	serious[i]	serious[d]	RCT industry funded*	3/43 (7.0%)	6/80 (7.5%)	no pooled effect Effect for single study: RR 0.93 (0.24 to 3.54)		⨁⨁◯◯ Low[d,e,j]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
Influenza-associated complications in patients with confirmed influenza (pneumonia, bronchitis, otitis media) (follow-up: mean 22 days)								**Oseltamivir vs. Baloxavir**				
1	randomised trials	not serious	not serious[e]	serious[k]	serious[d]	RCT industry funded*	18/389 (4.6%)	11/388 (2.8%)	no pooled effect Effect for single study: RR 1.63 (0.78 to 3.41)		⨁⨁◯◯ Low[d,e,k]	CRITICAL
Influenza-associated complications in patients with influenza-like symptoms (pneumonia, bronchitis, otitis media) (follow-up: mean 10 days)								**Oseltamivir vs. any non-antiviral treatment**				
1	randomised trials	serious[l]	not serious[e]	serious[m]	serious[c]	RCT industry funded*	14/217 (6.5%)	5/203 (2.5%)	no pooled effect Effect for single study: RR 2.62 (0.96 to 7.14)		⨁◯◯◯ Very low[c,e,l,m]	CRITICAL
Influenza-associated complications in patients with confirmed influenza (pneumonia, bronchitis, otitis media) (follow-up: mean 21 days)								**Oseltamivir vs. any non-antiviral treatment**				
1	randomised trials	not serious	not serious[e]	serious[n]	serious[d]	RCT industry funded*	3/27 (11.1%)	13/29 (44.8%)	no pooled effect Effect for single study: RR 0.25 (0.08 to 0.78)		⨁⨁◯◯ Low[d,e,n]	CRITICAL
Influenza-associated complications in patients with influenza-like symptoms (pneumonia, bronchitis, otitis media) (follow-up: mean 14 days)								**Baloxavir vs. Placebo**				
1	randomised trials	not serious	not serious[e]	serious[o]	serious[b,d]	RCT industry funded*	2/100 (2.0%)	1/100 (1.0%)	no pooled effect Effect for single study: RR 2.00 (0.18 to 21.71)		⨁⨁◯◯ Low[b,d,e,o]	CRITICAL
Influenza-associated complications in patients with confirmed influenza (pneumonia, bronchitis, otitis media) (follow-up: mean 22 days)								**Baloxavir vs. Placebo**				
1	randomised trials	not serious	not serious[e]	serious[p]	serious[b]	RCT industry funded*	11/388 (2.8%)	40/386 (10.4%)	no pooled effect Effect for single study: RR 0.27 (0.14 to 0.53)		⨁⨁◯◯ Low[b,e,p]	CRITICAL
First hospitalisation in outpatients with confirmed influenza (follow-up: range 14 days to 28 days)								**Oseltamivir vs. Placebo**				
4	randomised trials	not serious	not serious	not serious	serious[b,d]	3 RCTs industry funded*	7/1288 (0.5%)	9/1308 (0.7%)	**RR 0.89** (0.36 to 2.20)	**1 fewer per 1'000** (from 4 fewer to 8 more)	⨁⨁⨁◯ Moderate[b,d]	CRITICAL
First hospitalisation in outpatients with influenza-like symptoms (follow-up: mean 8 days)								**Oseltamivir vs. Placebo**				

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious[e]	serious[q]	serious[b,d]	RCT industry funded*	1/202 (0.5%)	0/204 (0.0%)	no pooled effect Effect for single study: RR 3.03 (0.12 to 73.93)		⨁⨁◯◯ Low[b,d,e,q]	CRITICAL
First hospitalisation in outpatients without information about confirmed infection (follow-up: mean 22 days)								**Oseltamivir vs. Placebo**				
1	randomised trials	not serious	not serious[e]	serious[r]	serious[b,d]	RCT industry funded*	1/513 (0.2%)	0/309 (0.0%)	no pooled effect to less information to calculate effect for single study		⨁⨁◯◯ Low[b,d,e,r]	CRITICAL
First hospitalisation in outpatients with influenza-like symptoms (follow-up: mean 29 days)								**Oseltamivir vs. Baloxavir**				
1	randomised trials	not serious	not serious[e]	serious[s]	serious[b,d]	RCT industry funded*	0/58 (0.0%)	0/115 (0.0%)	No effect calculated because RCT reported zero events in both arms		⨁⨁◯◯ Low[b,d,e,s]	CRITICAL
First hospitalisation in outpatients with confirmed influenza (follow-up: mean 22 days)								**Oseltamivir vs. Baloxavir**				
1	randomised trials	not serious	not serious[e]	serious[t]	serious[b,d]	RCT industry funded*	4/389 (1.0%)	3/388 (0.8%)	no pooled effect Effect for single study: RR 1.28 (0.32 to 5.15)		⨁⨁◯◯ Low[b,d,e,t]	CRITICAL
First hospitalisation in outpatients without information about confirmed infection (follow-up: mean 22 days)								**Oseltamivir vs. Baloxavir**				
1	randomised trials	not serious	not serious[e]	serious[u]	serious[b,d]	RCT industry funded*	1/513 (0.2%)	0/610 (0.0%)	no pooled effect to less information to calculate effect for single study		⨁⨁◯◯ Low[b,d,e,u]	CRITICAL
First hospitalisation in outpatients with influenza-like symptoms (follow-up: range 10 days to 28 days)								**Oseltamivir vs. any non-antiviral treatment**				
2	randomised trials	serious[v]	not serious	serious[w]	serious[b,d]	1 RCT industry funded*	A pooled effect measure was not calculated because 1 RCT reported zero events in both groups; In 1 RCT with a population with influenza-like symptoms the risk was not significantly different: RR 0.98 (0.27 to 3.60).				⨁◯◯◯ Very low[b,d,v,w]	CRITICAL
First hospitalisation in outpatients with confirmed influenza (follow-up: mean 21 days)								**Oseltamivir vs. any non-antiviral treatment**				
1	randomised trials	not serious	not serious[e]	serious[x]	serious[b]	RCT industry funded*	2/27 (7.4%)	5/29 (17.2%)	no pooled effect Effect for single study: RR 0.49 (0.12 to 1.98)		⨁⨁◯◯ Low[b,e,x]	CRITICAL
First hospitalisation in outpatients without information about confirmed infection (follow-up: no information)								**Oseltamivir vs. any non-antiviral treatment**				

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study de-sign	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious[e]	serious[v]	serious[b]	RCT industry funded*	2/17 (11.8%)	7/24 (29.2%)	no pooled effect Effect for single study: RR 0.46 (0.13 to 1.69)		⨁⨁◯◯ Low[b,e,y]	CRITICAL
First hospitalisation in outpatients with confirmed influenza (follow-up: mean 22 days)								**Baloxavir vs. Placebo**				
2	randomised trials	not serious	not serious	serious[z]	serious[b,d]	all RCTs industry funded*	A pooled effect measure was not calculated because 1 RCT reported zero events in both groups; In the other RCT the risk was not significantly different: RR 0.63 (0.17 to 2.40) .				⨁⨁◯◯ Low[b,d,z]	CRITICAL

Abbreviations:
CI: confidence interval; RR: risk ratio
Notes:
a. Studies analysed specific population groups (hospitalised children and high-risk adolescent and adult outpatients) limiting generalisability to all influenza A or B patients.
b. The 95% CI is wide.
c. Studies analysed specific population groups (high-risk and not high-risk adolescents and adults, not high-risk children) limiting generalisability to all influenza A or B patients.
d. The event rate is very low or low and the sample size is not sufficiently large, the optimal information size is not met.
e. Not applicable because only one study was identified.
f. Study analysed specific population group (hospitalised adult) limiting generalisability to all influenza A or B patients.
g. Studies analysed specific population groups (high-risk and not high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
h. Studies analysed specific population groups (high-risk and not high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
i. Study analysed specific population group (not high-risk adults) limiting generalisability to all influenza A or B patients.
j. Study analysed specific population group (not high-risk children) limiting generalisability to all influenza A or B patients.
k. Study analysed specific population groups (high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
l. Raus 2015 was rated as having a high risk of bias for this outcome due to deviations from the intended interventions and missing outcome data.
m. Study analysed specific population groups (not high-risk patients) limiting generalisability to all influenza A or B patients.
n. Study analysed specific population groups (high risk patients) limiting generalisability to all influenza A or B patients.
o. Study analysed specific population groups (not high-risk adult outpatients) limiting generalisability to all influenza A or B patients.
p. Study analysed specific population groups (high risk adolescents and adults) limiting generalisability to all influenza A or B patients.
q. Study analysed specific population groups (high risk adolescents and adults) limiting generalisability to all influenza A or B patients.
r. Study analysed specific population groups (children) limiting generalisability to all influenza A or B patients.
s. Study analysed specific population groups (not high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
t. Study analysed specific population groups (high risk adolescents and adults) limiting generalisability to all influenza A or B patients.
u. Study analysed specific population groups (not high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
v. Raus 2015 and Butler 2020 were rated as having a high risk of bias for this outcome due to deviations from the intended interventions and missing outcome data.

w. Study analysed specific population groups (not high-risk patients) limiting generalisability to all influenza A or B patients.
x. Study analysed specific population groups (high-risk patients) limiting generalisability to all influenza A or B patients.
y. Study analysed specific population groups (adults) limiting generalisability to all influenza A or B patients.
z. Studies analysed specific population groups (not high-risk and high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
* Defined as studies sponsored by the industry

Table 50: Summary of findings table – PICO 1– Secondary outcomes and safety

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
Time to alleviation of symptoms (TTAS) in patients with confirmed influenza (follow-up: range 8 days to 28 days)						**Oseltamivir vs. Placebo**						
9	randomised trials	not serious	serious[a]	serious[b]	not serious	6 RCTs industry funded	1864	1920	-	median **23.7 hours fewer** (34.1 fewer to 13.4 fewer)	⨁⨁◯◯ Low[a,b]	CRITICAL
Time to alleviation of symptoms (TTAS) in patients with influenza-like symptoms (follow-up: range 8 days to 28 days)						**Oseltamivir vs. Placebo**						
2	randomised trials	not serious	not serious	serious[c]	not serious	2 RCTs industry funded	451	444	-	Median **19.9 hours fewer** (31.2 fewer to 8.6 fewer)	⨁⨁⨁◯ Moderate[c]	CRITICAL
Time to alleviation of symptoms (TTAS) in patients with confirmed influenza (follow-up: range 22 days to 29 days)						**Oseltamivir vs. Baloxavir**						
3	randomised trials	not serious	serious[d]	serious[e]	not serious	all RCTs industry funded	945	972	-	median **3.08 hours more** (3.93 fewer to 10.08 more)	⨁⨁◯◯ Low [d,e]	CRITICAL
Time to alleviation of symptoms (TTAS) - not measured						**Oseltamivir vs. any non-antiviral treatment**						
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Time to alleviation of symptoms (TTAS) in patients with confirmed influenza (follow-up: mean 22 days)						**Baloxavir vs. Placebo**						
3	randomised trials	not serious	not serious	serious[f]	not serious	all RCTs industry funded	940	715	-	median **26.39 hours fewer** (32.1 fewer to 20.68 fewer)	⨁⨁⨁◯ Moderate[f]	CRITICAL
Number of people with antibiotics use in patients with confirmed influenza (follow-up: range 12 days to 28 days)						**Oseltamivir vs. Placebo**						
6	randomised trials	not serious	not serious	serious[g]	not serious	4 RCTs industry funded	106/1041 (10.2%)	162/1061 (15.3%)	**RR 0.67** (0.54 to 0.84)	**50 fewer per 1'000** (from 70 fewer to 24 fewer)	⨁⨁⨁◯ Moderate[g]	CRITICAL
Number of people with antibiotics use in patients with confirmed influenza (follow-up: range 22 days to 29 days)						**Oseltamivir vs. Baloxavir**						
2	randomised trials	not serious	serious[h]	serious[i]	serious[i]	all RCTs industry funded	17/432 (3.9%)	17/468 (3.6%)	**RR 1.11** (0.57 to 2.17)	**4 more per 1'000** (from 16 fewer to 43 more)	⨁◯◯◯ Very low[h,i,j]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
Number of people with antibiotics use in per protocol population (follow-up: range 10 days to 28 days)						**Oseltamivir vs. any non-antiviral treatment**						
2	randomised trials	serious[k]	not serious	serious[l]	not serious	1 RCT industry funded	146/1752 (8.3%)	206/1732 (11.9%)	**RR 0.70** (0.58 to 0.86)	**36 fewer per 1'000** (from 50 fewer to 17 fewer)	⨁⨁◯◯ Low[k,l]	CRITICAL
Number of people with antibiotics use in patients with confirmed influenza (follow-up: mean 22 days)						**Baloxavir vs. Placebo**						
1	randomised trials	not serious	not serious[m]	serious[n]	serious[o]	RCT industry funded	13/388 (3.4%)	29/386 (7.5%)	no pooled effect Effect for single study: RR 0.45 (0.24 to 0.84)		⨁⨁◯◯ Low[m,n,o]	CRITICAL
Severe adverse events in patients with influenza-like symptoms (follow-up: range 8 days to 28 days)						**Oseltamivir vs. Placebo**						
4	randomised trials	not serious	not serious	serious[p]	serious[j,q]	2 RCTs industry funded	16/1311 (1.2%)	17/1302 (1.3%)	**RR 0.96** (0.46 to 2.02)	**1 fewer per 1'000** (from 7 fewer to 13 more)	⨁⨁◯◯ Low[j,p,q]	CRITICAL
Severe adverse events in patients with influenza-like symptoms (follow-up: range 22 days to 29 days)						**Oseltamivir vs. Baloxavir**						
2	randomised trials	not serious	not serious	serious[r]	serious[j,q]	all RCTs industry funded	A pooled effect measure was not calculated because 1 RCT reported zero events in both groups; In the other RCT the risk was not significantly different: RR 0.24 (0.01 to 4.94).				⨁⨁◯◯ Low[j,q,r]	CRITICAL
Severe adverse events in patients with confirmed influenza (follow-up: range 5 days to 22 days)						**Oseltamivir vs. Baloxavir**						
2	randomised trials	not serious	not serious	serious[s]	serious[j,q]	1 RCT industry funded	A pooled effect measure was not calculated because 1 RCT reported zero events in both groups; In the other RCT the risk was not significantly different: RR 5.06 (0.24 to 105.26).				⨁⨁◯◯ Low[j,q,s]	CRITICAL
Severe adverse events in patients with influenza-like symptoms (follow-up: mean 10 days)						**Oseltamivir vs. any non-antiviral treatment**						
1	randomised trials	not serious	not serious[m]	serious[t]	serious[j,q]	1 RCT industry funded	0/229 (0.0%)	0/291 (0.0%)	not estimable		⨁⨁◯◯ Low[j,m,q,t]	CRITICAL
Severe adverse events in patients with influenza-like symptoms (follow-up: mean 22 days)						**Baloxavir vs. Placebo**						
2	randomised trials	not serious	not serious	serious[u]	serious[j,q]	all RCTs industry funded	A pooled effect measure was not calculated because 1 RCT reported zero events in both groups; In the other RCT the risk was not significantly different: RR 2.54 (0.12 to 52.68).				⨁⨁◯◯ Low[j,q,u]	CRITICAL
Severe adverse events in patients with confirmed influenza (follow-up: mean 22 days)						**Baloxavir vs. Placebo**						

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious[m]	serious[v]	serious[i,q]	all RCTs industry funded	0/730 (0.0%)	2/727 (0.3%)	no pooled effect Effect for single study: RR 0.22 (0.01 to 4.14)		⨁⨁◯◯ Low[i,m,q,v]	CRITICAL
Adverse events in patients with influenza-like symptoms (follow-up: range 12 days to 28 days)						**Oseltamivir vs. Placebo**						
4	randomised trials	not serious	serious[w]	serious[x]	serious[i]	3 RCTs industry funded	215/1245 (17.3%)	186/1053 (17.7%)	**RR 1.12** (0.84 to 1.49)	**21 more per 1'000** (from 28 fewer to 87 more)	⨁◯◯◯ Very low[i,w,x]	IMPORTANT
Adverse events in patients with influenza-like symptoms (follow-up: range 22 days to 29 days)						**Oseltamivir vs. Baloxavir**						
2	randomised trials	not serious	not serious	serious[y]	serious[i]	all RCTs industry funded	48/571 (8.4%)	30/725 (4.1%)	**RR 2.00** (1.29 to 3.12)	**41 more per 1'000** (from 12 more to 88 more)	⨁⨁◯◯ Low[i,y]	IMPORTANT
Adverse events in patients with influenza-like symptoms (follow-up: range 10 days to 21 days)						**Oseltamivir vs. any non-antiviral treatment**						
2	randomised trials	serious[z]	not serious	serious[aa]	serious[i,q]	all RCTs industry funded	7/287 (2.4%)	4/291 (1.4%)	**RR 1.51** (0.48 to 4.74)	**7 more per 1'000** (from 7 fewer to 51 more)	⨁⨁◯◯ Very low[i,q,z,aa]	IMPORTANT
Adverse Events in patients with influenza-like symptoms (follow-up: mean 22 days)						**Baloxavir vs. Placebo**						
2	randomised trials	not serious	not serious	serious[ab]	serious[ac]	all RCTs industry funded	A pooled effect measure was not calculated because the two presented results reported on the same RCT. In both results the risk was not significantly different.				⨁⨁◯◯ Low[ab,ac]	IMPORTANT
Adverse Events in patients with confirmed influenza (follow-up: mean 22 days)						**Baloxavir vs. Placebo**						
1	randomised trials	not serious	not serious[m]	serious[ad]	serious[q]	all RCTs industry funded	41/730 (5.6%)	60/727 (8.3%)	no pooled effect Effect for single study: RR 0.68 (0.46 to 1.00)		⨁⨁◯◯ Low[m,q,ad]	IMPORTANT

Abbreviations:
CI: confidence interval
Notes:
a. Heterogeneity was high (I^2=78.4%) and remained unexplained.
b. Hospitalised patients are missing in the investigated studies limiting generalisability to all influenza A or B patients.

c. Studies analysed specific population groups (adults without risks) limiting generalisability to all influenza A or B patients.
d. The population of the 3 RCTs are not consistent: one assessed children, one high-risk adolescents and adults and one adolescents and adults without risks.
e. Studies analysed specific population groups (children and adolescents and adults with and without risks) limiting generalisability to all influenza A or B patients.
f. Studies analysed specific population groups (adolescents and adults with and without risks) limiting generalisability to all influenza A or B patients.
g. Studies analysed specific population groups (inpatient and outpatient children, adolescents and adults with and without risks) limiting generalisability to all influenza A or B patients.
h. The population of the 2 RCTs are not consistent: one assessed children without risks and one high-risk adolescents and adults.
i. Studies analysed specific population groups (children without risks, high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
j. The 95% CI is wide.
k. Raus 2015 and Butler 2020 were rated as having high risk of bias for this outcome due to deviations from the intended interventions and missing outcome data.
l. Studies analysed specific population groups (patients with influenza-like symptoms) limiting generalisability to all influenza A or B patients.
m. Not applicable because only one study was identified.
n. Study analysed specific population group (high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
o. The sample size is not sufficiently large, the optimal information size is not met.
p. Studies analysed specific population groups (children with asthma, children without comorbidities, hospitalised children, patients with all ages) limiting generalisability to all influenza A or B patients.
q. The event rate is very low or low and the sample size is not sufficiently large, the optimal information size is not met.
r. Studies analysed specific population groups (children without risks, not high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
s. Studies analysed specific population groups (not high-risk and high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
t. Study analysed specific population group (not high-risk patients) limiting generalisability to all influenza A or B patients.
u. Studies analysed specific population group (not high-risk adults and adolescents) limiting generalisability to all influenza A or B patients.
v. Studies analysed specific population groups (high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
w. Heterogeneity was high (I2=56.4%) and remained unexplained.
x. Studies analysed specific population groups (hospitalised children, children with asthma, not high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
y. Studies analysed specific population groups (not high-risk adolescents and adults, children) limiting generalisability to all influenza A or B patients.
z. Lin 2006 was rated as having a high risk of bias for this outcome due to the measurement of the outcome.
aa. Studies analysed specific population groups (high-risk patients, patients with influenza-like symptoms) limiting generalisability to all influenza A or B patients.
ab. Studies analysed specific population groups (high-risk and not high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.
ac. Assumed wide CI due to variation in effects.
ad. Study analysed specific population groups (not high-risk adolescents and adults) limiting generalisability to all influenza A or B patients.

Table 51: Summary of findings table – PICO 2 – Primary outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
Disease-specific and all-cause mortality (follow-up: range 8 days to 112 days)							**Oseltamivir vs. Placebo**					
3	randomised trials	not serious	not serious	serious[a]	serious[b,c]	all RCTs industry funded	3/568 (0.5%)	3/595 (0.5%)	**RR 1.13** (0.19 to 6.79)	**1 more per 1'000** (from 4 fewer to 29 more)	⨁⨁◯◯ Low[a,b,c]	CRITICAL
Disease-specific and all-cause mortality (follow-up: mean 10 days)							**Baloxavir vs. Placebo**					
1[a,b]	randomised trials	not serious	not serious[d]	serious[e]	serious[c]	RCT industry funded	0/374 (1.9%)	0/375 (13.6%)	not estimable		⨁⨁◯◯ Low[b,c,d,e]	CRITICAL
Laboratory-confirmed influenza (follow-up: range 8 days to 112 days)							**Oseltamivir vs. Placebo**					
5	randomised trials	not serious	serious[f]	serious[g]	not serious	all RCTs industry funded	106/1261 (8.4%)	173/1254 (13.8%)	**RR 0.66** (0.45 to 0.97)	**47 fewer per 1'000** (from 76 fewer to 4 fewer)	⨁⨁◯◯ Low[f,g]	CRITICAL
Laboratory-confirmed influenza (follow-up: mean 10 days)							**Baloxavir vs. Placebo**					
1[a,b]	randomised trials	not serious	not serious[d]	serious[h]	not serious	RCT industry funded	7/374 (1.9%)	51/375 (13.6%)	no pooled effect Effect for single study: RR 0.14 (0.06 to 0.30)		⨁⨁⨁◯ Moderate[d,h]	CRITICAL
Influenza confirmed with rapid diagnostic tests - not measured							**Oseltamivir vs. Placebo**					
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Influenza confirmed with rapid diagnostic tests - not measured							**Baloxavir vs. Placebo**					
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Influenza-associated complications (pneumonia, bronchitis, otitis media) (follow-up: mean 56 days)							**Oseltamivir vs. Placebo**					

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious[d]	serious[i]	serious[c]	publication bias strongly suspected[d] RCT industry funded	1/276 (0.4%)	7/272 (2.6%)	no pooled effect Effect for single study: RR 0.14 (0.02 to 1.14)		⨁◯◯◯ Very low[c,d,i]	CRITICAL
Influenza-associated complications (pneumonia, bronchitis, otitis media) (follow-up: mean 10 days)							**Baloxavir vs. Placebo**					
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Abbreviations:
CI: confidence interval; RR: risk ratio
Notes:
a. Studies analysed specific population groups (transplant recipients, elderly with a post-exposure administration, vaccinated frail older population) limiting generalisability to all persons receiving prophylactic treatment against influenza.
b. The 95% CI is wide.
c. The event rate is very low or low and the sample size is not sufficiently large, the optimal information size is not met.
d. Not applicable because only one study was identified.
e. Study analysed specific population group (not high-risk patients, post-exposure administration) limiting generalisability to all persons receiving prophylactic treatment against influenza.
f. Heterogeneity was high (I^2=74.4%) and remained unexplained.
g. Studies analysed specific population groups (adults without risk, influenza B, transplant recipients, vaccinated frail older population) limiting generalisability to all persons receiving prophylactic treatment against influenza.
h. Study analysed specific population group (not high-risk patients, post-exposure administration) limiting generalisability to all persons receiving prophylactic treatment against influenza.
i. Study analysed specific population group (vaccinated frail older population) limiting generalisability to all persons receiving prophylactic treatment against influenza.

Table 52: Summary of findings table – PICO 2 – Secondary outcomes and safety

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
Length of hospitalisation - not measured							**Oseltamivir vs. Placebo**					
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Length of hospitalisation - not measured							**Baloxavir vs. Placebo**					
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Severe adverse events (follow-up: range 25 days to 112 days)							**Oseltamivir vs. Placebo**					
4	randomised trials	not serious	serious[a]	serious[b]	serious[c]	3 RCTs industry funded	A pooled effect measure was not calculated because 3 RCT reported zero events in both groups; In the other RCT the risk was not significantly different: RR 0.78 (0.44 to 1.40).				⨁◯◯◯ Very low[a,b,c]	CRITICAL
Severe adverse events (follow-up: mean 10 days)							**Baloxavir vs. Placebo**					
1	randomised trials	not serious	not serious[d]	serious[e]	serious[c]	RCT industry funded	0/374 (0.0%)	0/375 (0.0%)	not estimable		⨁⨁◯◯ Low[c,d,e]	CRITICAL
Adverse events (follow-up: range 28 days to 112 days)							**Oseltamivir vs. Placebo**					
3	randomised trials	not serious	serious[f]	serious[g]	not serious	2 RCTs industry funded	133/386 (34.5%)	139/321 (43.3%)	**RR 0.96** (0.82 to 1.12)	**17 fewer per 1'000** (from 78 fewer to 52 more)	⨁⨁◯◯ Low[f,g]	IMPORTANT
Adverse events (follow-up: mean 10 days)							**Baloxavir vs. Placebo**					
1	randomised trials	not serious	not serious[d]	serious[e]	serious[c,h]	RCT industry funded	7/374 (1.9%)	6/375 (1.6%)	no pooled effect Effect for single study: RR 1.17 (0.40 to 3.45)		⨁⨁◯◯ Low[c,d,e,h]	IMPORTANT

Abbreviations:
CI: confidence interval; RR: risk ratio
Notes:
a. Inconsistent population including adults without risks and transplant recipients.

b. Studies analysed specific population groups (adults without risk, transplant recipients) limiting generalisability to all persons receiving prophylactic treatment against influenza.
c. The event rate is very low or low and the sample size is not sufficiently large, the optimal information size is not met.
d. Not applicable because only one study was identified.
e. Study analysed specific population group (not high-risk patients, post-exposure administration) limiting generalisability to all persons receiving prophylactic treatment against influenza.
f. Inconsistent population including adults with influenza B, transplant recipients and health workers.
g. Studies analysed specific population groups (adults with influenza B, transplant recipients and health workers) limiting generalisability to all persons receiving prophylactic treatment against influenza.
h. Assumed wide CI due to low event rate.

7.6 Ongoing, stopped or unpublished RCTs

Table 53 shows the results from RCTs that are published in trial registries but not in peer-reviewed journals. None of these RCTs that reported results compared oseltamivir with baloxavir. The findings indicate that oseltamivir reduces the time to symptom alleviation, shortens the duration of illness, and lowers the incidence of complications and adverse events. Compared to any non-antiviral treatment, oseltamivir also showed positive effects on time to recovery and serious adverse events. However, no differences were observed in non-serious adverse events or mortality. Similarly, baloxavir demonstrated statistically significant reductions in the time to symptom alleviation, ranging from 13.2 to 32.8 hours, depending on the timing of treatment initiation.

Table 53: Findings of protocols for PICO 1

Trial ID	Type of analysis	Population	Sample size	Median age (range) Sex (% women)	Outcome		
					Intervention	Comparator	Effect
Oseltamivir vs. Placebo							
CN-00311642 (Proceeding of an annual meeting by Hayden et al. 1998)[1]	In patients with confirmed influenza	Healthy adults	374	NR	**Time to alleviation of illness**		
					2.9 days	4.3 days	p<0.01
					Severity of illness and incidence of secondary complications were also significantly reduced and GS4104 recipients used less acetaminophen for symptom relief. (No concrete numerical results reported)		
NCT01980966	In patients with confirmed influenza	Healthy adults with no history of major medical conditions	40	I: 25 (20-43), C: 28 (20-43) I: 25%, C: 34%	**Treatment-emergent adverse events** Number of subjects Total number of adverse events		
					7 (N=8) 15 (N=8)	28 (N=32) 68 (N=32)	- -
NR (Congress paper by Zaug et al. 2001)	In patients with confirmed influenza	High-risk vaccinated patients (including the elderly and patients with pre-existing cardiac and/or pulmonary disease)	226	NR	**Median duration of illness**		
					153.8 h	196.3 h	-
					Incidence of influenza-related secondary respiratory complications		
					8 (N=64)	13 (N=76)	-
					Adverse events		
					46%	55%	-
Oseltamivir vs. Any non-antiviral treatment							
NCT01249833	NR	Adults	122	I: 37 (17-66), C: 32 (18-57) I: 49%, C: 52%	No relevant outcomes		
	NR				**Mean number of days to recovery**		

					5.71 (N=1533)	6.73 (N=1526)	-1.29 (95% CI -1.2 to -1.39)
					Serious adverse events (number of subjects affected)		
EUCTR2014-004471-23-SE		All ages and health states	3266	I: 36 (19) - mean (SD), C: 35 (19) - mean (SD) I: 56%, C: 55%	12 (N=1624)	17 (N=1635)	-
					Non-serious adverse events		
					0	0	-
					Deaths		
					0	0	-
Baloxavir vs. Placebo							
NR (Congress paper by Kawaguchi et al. 2018)	In patients with confirmed influenza	Healthy Adults/Adolescents	NR	NR	**Time to alleviation of symptoms (TTAS, median)** within 24h: within 72 h:		
					49.3 h (N = 238) 66.2 h (N = 217)	82.1 h (N = 120) 79.4 h (N = 110)	p < 0.0001 p = 0.0080

Abbreviations:
BID: twice a day, C: comparator, h: hours, I: intervention, NR: not reported, N: number of people, SD: standard deviation
Notes:
Unless otherwise specified, the dosage for all interventions is the standard.
Standard dose for oseltamivir: 30 mg twice daily for those weighting ≤15 kg, 45 mg for 15–23 kg, 60 mg for 23–40 kg, and 75 mg for >40 kg
Standard dose for baloxavir: 40 mg for 40-80 kg, 80 mg for ≥80 kg or 2 mg/kg for <20 kg in children
[1]Oseltamivir (75 or 150mg BID for 5 days)

8. Additional issues

8.1 Stockpiling Strategy in other countries

This chapter examines the strategies adopted by several countries—Denmark, France, England, Germany, the Netherlands, South Korea, and the USA. For a detailed overview, please refer to ***Table 60*** in the Appendix.

During the 2009/10 influenza pandemic caused by A(H1N1), all these countries maintained national stockpiles of Tamiflu® to cover approximately 20–30% of their populations. Analysis suggests that these stockpiles proved useful and effective in mitigating the impact of the pandemic. However, concerns about the high costs and effectiveness of Tamiflu® led to shifts in stockpiling strategies by 2023/2024.

More precisely, selected EU countries with social health insurance systems (France, Germany, the Netherlands), continue to maintain national antiviral stockpiles. Although detailed coverage information is unavailable, these stockpiles are likely reduced compared to previous levels. South Korea and the USA have also maintained strategic national influenza antiviral stockpiles.

In contrast, the two National Health Service (NHS)-based systems, Denmark and England, have abandoned national stockpiling. Denmark now relies on efficient medication distribution networks, requiring pharmaceutical companies to maintain their own stocks. Notably, Tamiflu® and Xofluza® are excluded from this policy. Instead, Denmark emphasises public health interventions, such as vaccination and awareness campaigns, to manage influenza outbreaks. England has shifted to a decentralised approach, with regional systems (formerly clinical commissioning groups (CCGs) and now integrated care systems (ICSs) since 2022) tasked with ensuring antiviral availability during flu seasons and outbreaks. NHS England has also commissioned specific pharmacies to stock antivirals, supported by courier arrangements for rapid distribution across the system.

Regarding Xofluza®, no information is available on any countries actively stockpiling this antiviral. However, there is a reference suggesting that South Korea might consider adding Xofluza® to its national stockpile. A rapid response report from Belgium highlights the potential benefit of stockpiling Xofluza® to facilitate RCTs during the onset of a new epidemic. Experts note that this recommendation could also apply to Tamiflu® (Oseltamivir).

9. Discussion

This report presents the clinical evidence on the efficacy and safety of oseltamivir and baloxavir for the treatment and prevention of influenza, based on a systematic literature review of published trials in peer-reviewed journals and in trial registries. The analyses compared oseltamivir with placebo, oseltamivir with any non-antiviral treatment, oseltamivir with baloxavir, and baloxavir with placebo across various outcomes. Thirty-four RCTs were identified and 6 unpublished trials reporting some results.

Summary findings PICO 1 from published RCTs

Mortality was rare across the included studies with no statistically significant differences observed between oseltamivir and placebo in patients with influenza-like symptoms (RR 3.00, 95% CI 0.31 to 28.82, low certainty). Meta-analyses could not be conducted for the other comparisons. However, narrative synthesis indicated no statistically significant differences between oseltamivir and baloxavir (low certainty), oseltamivir and any non-antiviral treatment (low certainty) and between baloxavir and placebo (low certainty).

For influenza-associated complications, oseltamivir was associated with statistically significantly fewer complications compared to placebo in patients with confirmed influenza (RR 0.60, 95% CI 0.47 to 0.78, moderate certainty). Meta-analyses could not be conducted for the other comparisons. Narrative synthesis revealed inconsistent results between oseltamivir and baloxavir (low certainty) oseltamivir and any non-antiviral treatment (very low to low certainty) and baloxavir and placebo (low certainty).

First hospitalisations were infrequent, with no statistically significant difference detected between oseltamivir and placebo in patients with confirmed influenza (RR 0.89, 95% CI 0.36 to 2.20, moderate certainty). Meta-analyses could not be conducted for the other comparisons. However, narrative synthesis indicated no differences between oseltamivir and baloxavir (low certainty), baloxavir and placebo (low certainty), or oseltamivir and any non-antiviral treatment (low certainty).

TTAS was statistically significantly shorter with oseltamivir and baloxavir compared to placebo (mean difference between oseltamivir and placebo in patients with confirmed influenza: -23.74 hours, 95% CI -34.14 to -13.35, low certainty and in patients with influenza- like symptoms: -19.89 hours, 95% CI -31.21 to -8.58, mean difference between baloxavir and placebo in patients with confirmed influenza: -26.39 hours, 95% CI -32.10 to -20.68, moderate certainty). No statistically significant differences were observed between baloxavir and oseltamivir in patients with confirmed influenza (mean difference: 3.08 hours, 95% CI -3.93 to 10.08, low certainty), while no study was identified analysing TTAS for oseltamivir compared to any non-antiviral treatment.

Meta-analyses for TTIIS could not be conducted. However, narrative synthesis indicated shorter TTIIS with oseltamivir compared to placebo and no difference with oseltamivir compared to baloxavir.

Time to resolution of fever was statistically significantly shorter with oseltamivir compared to placebo in patients with confirmed influenza but not in patients with influenza- like symptoms (mean difference: -20.50 hours, 95% CI -25.98 to -15.02 and -4.63 hours, 95% CI -11.67 to 2.41). Time to resolution of fever was statistically significantly longer with oseltamivir compared to baloxavir in patients with confirmed influenza (mean difference: 3.45 hours, 95% CI 0.32 to 6.58) and statistically significantly shorter with oseltamivir compared to any non-antiviral treatment in patients with confirmed influenza (mean difference: -19.77 hours, 95% CI -28.71 to -10.83). Meta-analyses for baloxavir compared to placebo could not be conducted.

Antibiotic use was statistically significantly lower with oseltamivir compared to placebo in patients with confirmed influenza (RR 0.67, 95% CI 0.54 to 0.84, moderate certainty) and any non-antiviral treatment in patients with influenza-like symptoms (RR 0.70, 95% CI 0.58 to 0.86, low certainty). No statistically significant differences in antibiotic use were found between oseltamivir and baloxavir in patients with confirmed influenza (RR 1.11, 95% CI 0.57 to 2.17, very low certainty). Meta-analyses for baloxavir compared to placebo could not be conducted.

Meta-analyses for length of hospitalisation could not be conducted. However, narrative synthesis revealed a marginal increase in hospital stays by one day for oseltamivir compared to any non-antiviral treatment.

The number of patients with re-consultation with a doctor was not statistically significantly different with oseltamivir compared to any non-antiviral treatment in patients with influenza-like symptoms (RR 1.03, 95% CI 0.81 to 1.30). Meta-analyses could not be conducted for the other comparisons.

Meta-analyses could not be conducted for the number of onward transmissions to household contacts. However, narrative synthesis revealed inconsistent results between oseltamivir and placebo and a lower number of onward transmission to household contacts with oseltamivir compared to any non-antiviral treatment.

Adverse events were not statistically significantly different between oseltamivir and placebo in patients with influenza-like symptom (RR 1.12, 95% CI 0.84 to 1.49, very low certainty) or any non-antiviral treatment in patients with influenza-like symptom (RR 1.51, 95% CI 0.48 to 4.74, very low certainty). Oseltamivir was associated with statistically significantly higher number of adverse events compared to baloxavir in patients with influenza-like symptoms (RR 2.00, 95% CI 1.29 to 3.12, low certainty). Meta-analyses could not be conducted for baloxavir versus placebo.

The number of people with severe adverse events were low across the included studies. No statistically significant differences in the occurrence of severe adverse events were observed between oseltamivir and placebo in patients with influenza -like symptoms (RR 0.96, 95% CI 0.46 to 2.02, low certainty). Meta-analyses could not be conducted for the other comparisons.

Summary findings PICO 2 from published RCTs

Mortality was rare across the included studies with no statistically significant differences observed between oseltamivir and placebo (RR 1.13, 95% CI 0.19 to 6.79, low certainty). Sensitivity analysis excluding the study with post-exposure administration did not change the result. Meta-analyses could not be conducted for the other comparisons. The number of individuals with laboratory-confirmed influenza was statistically significantly lower among participants who received oseltamivir as prevention compared to those who received placebo (RR 0.66, 95% CI 0.45 to 0.97, low certainty). Meta-analyses could not be conducted for the other comparisons.

None of the included studies assessed the effect on influenza confirmed with rapid diagnostic tests.

Meta-analyses for influenza-associated complications could not be conducted. However, narrative synthesis indicated that oseltamivir use was associated with a significant reduction in influenza-associated complication compared to placebo (very low certainty).

The incidence and length of hospitalisations were not reported in any of the included studies.

No statistically significant differences in adverse events were observed between oseltamivir and placebo (RR 0.96, 95% CI 0.82 to 1.12, low certainty). Meta-analyses could not be conducted for the other comparisons.

Meta-analyses could not be conducted for severe adverse events. However narrative synthesis revealed that severe adverse events were rare across the included studies and no significant differences in the occurrence of severe adverse events were detected between oseltamivir or baloxavir and placebo (very low and low certainty).

Evidence on resistance

Due to the high mutation and replication rates of the influenza virus, there is a risk that some patients may develop mutations rendering the virus less susceptible to antiviral drugs. For instance, specific mutations can alter the shape of the binding sites targeted by NAIs (such as oseltamivir) or CEN inhibitors (such as baloxavir). These changes can prevent the drugs from effectively binding to the virus, resulting in either reduced susceptibility (less effective treatment) or full antiviral resistance (complete treatment failure).[103,104] Variants typically emerge due to alterations in the neuraminidase and polymerase acidic proteins, which can drive resistance of oseltamivir or baloxavir.[105]

The rates of resistance vary based on the antiviral drug, virus type and subtype, and the affected population subgroup.[106,107] High-risk groups, such as immunocompromised individuals and children, are more prone to developing resistance. For example, in Switzerland, the number of reported cases of oseltamivir resistance is very low and mainly observed in hospitalised patients.[108]

From the included studies, 3 RCTs investigated oseltamivir resistance, revealing mixed results.[72,80,82] In particular, no emergence of drug-resistant variants of influenza B was detected by testing last-day isolates in neuraminidase inhibition assays, while of the 124 seasonal influenza A H1N1 viruses tested, all were resistant to oseltamivir at enrolment.[80,82] In Heinonen et al. 2010[72] 3 of a total of 31 (9.7%) subtype A/H1N1 viruses isolated were resistant to oseltamivir. No RCTs reported resistance data for baloxavir.

Findings from observational studies indicate that resistance is more frequent in paediatric patients (1–5 years old) compared to older age groups and it does not significantly impact symptom resolution, despite a delayed viral clearance.[109,110] An observational study has also showed a higher rate of baloxavir-resistant variants (25% of patients) compared to oseltamivir-resistant variants (19% of patients) with prolonged viral shedding by 3 days.[109] A Japanese study, on the other hand, found higher viral detection rates with oseltamivir compared to baloxavir but no oseltamivir-resistant mutations post-treatment and no statistically significant differences in clinical symptoms between the two drugs, underscoring baloxavir's efficacy against A(H3N2) and suggesting that post-treatment resistance emergence has minimal clinical impact.

Evidence gaps

For influenza prevention, no studies comparing oseltamivir with baloxavir are available, and only one study has compared baloxavir with placebo.

Results from unpublished trials

The results of the unpublished trials align with those of the published trials, although the effect sizes for both efficacy and safety favouring oseltamivir are generally larger in the unpublished trials compared to the published ones. However, this is based on only a few unpublished trials, as the majority did not report any results.

Comparison with other Systematic Reviews

The findings in this document align with and expand on results from several systematic reviews and meta-analyses.

For oseltamivir, this analysis is consistent with a systematic review and meta-analysis by Hanula et al. 2024, which concluded, that oseltamivir was not associated with a reduced risk of first hospitalisation.[44] Furthermore, it corroborates the results of an umbrella review by Doll et al. 2017, which found that oseltamivir reduces the duration of symptoms and complications compared to placebo, though questions about its efficacy in reducing hospitalisations remained.[111] Similarly, the HTA by Heneghan et al. 2016 emphasised oseltamivir's role in reducing time to symptom alleviation but raised concerns about limited evidence for reducing mortality.[112] Additionally, Jefferson et al. 2014 in The Cochrane Review highlighted oseltamivir's efficacy in reducing complications and symptom duration, though it raised concerns about potential publication bias.[38] The inclusion of trials not published in peer-reviewed journals in this synthesis reveals that 9 out of 20 unpublished trials were completed. Notably, the reported effect sizes in these unpublished trials tend to be higher than those in published trials. Moreover, the WHO clinical practice guidelines for influenza 2024 issued 1) a strong recommendation against the use of oseltamivir for patients with non-severe influenza, 2) a conditional recommendation for the use of oseltamivir for patients with severe influenza, and 3) a conditional recommendation for the use of oseltamivir for asymptomatic persons at extremely high risk for hospitalisation if they were to develop seasonal influenza (prevention).[28] In this analysis, there were no included study that only analysed patients with severe influenza, and subgroup analysis with non-severe and severe influenza was not possible.

Regarding baloxavir, the results are consistent with the systematic review by Kuo et al. 2021, which demonstrated baloxavir's effectiveness in symptom alleviation and its generally favourable safety profile.[39] Another systematic review reported similar efficacy between oseltamivir and baloxavir but highlighted fewer adverse events with baloxavir.[40] The current report confirms these findings, but adds that there are no significant differences in the occurrence of severe adverse events between oseltamivir and baloxavir (low certainty). The 2024 WHO clinical practice guidelines for influenza made 1) a conditional recommendation for the use of baloxavir for patients with non-severe influenza and at high risk for progression to severe disease, 2) a conditional recommendation against the use of baloxavir for patients with non-severe influenza at low risk of progression to severe disease and 3) a conditional recommendation for the use of baloxavir for asymptomatic persons at extremely high risk for hospitalisation if they were to develop seasonal influenza (prevention).[28] The studies included in this analysis did not assess the risk of progression to severe disease. Therefore, no conclusions could be drawn regarding the effectiveness of the interventions in preventing severe disease progression.

Additionally, two recent systematic reviews explored the comparative effectiveness of antivirals, reinforcing that both oseltamivir and baloxavir shorten symptom duration compared to placebo, though baloxavir’s single-dose regimen offers a practical advantage.[113,114]

Stockpiling

The Centers for Disease Control and Prevention (CDC) issued Emergency Use Instructions on July 19, 2024, outlining the emergency use of oseltamivir for the prevention and treatment of illnesses caused by pandemic influenza A viruses or novel influenza A viruses with pandemic potential.[115] Antiviral stockpiling remains a cornerstone of pandemic preparedness, with oseltamivir playing a pivotal role. During the 2009/10 H1N1 pandemic, stockpiles significantly mitigated societal and economic impacts.[3] By 2024, countries like France, Germany, and the USA maintained scaled-down antiviral reserves, while others, such as Denmark, adopted decentralised stockpiling strategies with efficient distribution networks.

Baloxavir, though not widely stockpiled, is under consideration in South Korea and Belgium for its shorter treatment duration and good safety profile, potentially complementing oseltamivir in future reserves. This report underscores the ongoing importance of both oseltamivir and baloxavir in influenza management, emphasising the need to address resistance patterns.

Strengths and Limitations

This evidence synthesis has several strengths. It systematically addresses the specified research questions and provides an in-depth evaluation of the identified literature. By comprehensively comparing oseltamivir, baloxavir, placebo, and any non-antiviral treatment, it offers a holistic overview of the current evidence base. The inclusion of the most recent studies and the conduction of meta-analyses enhance the robustness of the findings. Additionally, the inclusion and analysis of unpublished data provide a more complete picture, reducing publication bias and enhancing the reliability of the conclusions.

Nevertheless, this evidence synthesis is subject to also some limitations. The use of ITT-analysis for pooling results, chosen to reflect real-world scenarios in pandemic situations, meant that some available data could not contribute to the meta-analysis. Similarly, study results with zero events in both arms were excluded due to computational limitations, potentially omitting relevant data. Outcomes such as mortality were potentially underreported, as the short follow-up periods in RCTs limited their measurement. While observational studies could have provided insights into such outcomes, these were not considered due to inherent methodological limitations, such as the lack of randomisation and blinding.

10. Conclusions

This report provides an extensive review of the efficacy and safety of oseltamivir and baloxavir in treating and preventing influenza, based on published and unpublished trials. Both drugs showed effectiveness in the treatment of influenza, with oseltamivir linked to fewer influenza-associated complications (moderate certainty) compared to placebo, while baloxavir had fewer adverse events compared to oseltamivir (low certainty). However, treatment with oseltamivir or baloxavir did not

statistically significantly improve mortality (low certainty) or hospitalisations (oseltamivir: moderate certainty, baloxavir: low certainty). In addition, there were no statistically significant differences between the two treatments in terms of mortality rates (low certainty) or severe adverse events (low certainty). In terms of prevention, both oseltamivir and baloxavir were found to significantly reduce laboratory-confirmed influenza compared to placebo (oseltamivir: low certainty, baloxavir: moderate certainty), while no statistically significant differences were reported for oseltamivir or baloxavir compared to placebo (low certainty) with respect to mortality. Adverse events and severe adverse events were rare across the included studies and no significant differences were detected between oseltamivir or baloxavir and placebo (oseltamivir: low certainty for adverse events and very low certainty for severe adverse events, baloxavir: low certainty).

Although oseltamivir and baloxavir do not seem to differ statistically significantly in most outcomes, baloxavir offers certain advantages, such that it is easier to administer, requiring only a single dose, which may improve adherence.

Based on the available evidence, the generalisation of oseltamivir and baloxavir use to special populations, such as high-risk individuals or pregnant women, remains unclear.

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12. Appendices

12.1 Search strategies

Medline (Ovid)

Population	Influenza, Human/ OR alphainfluenzavirus/ OR exp Influenza A virus/ OR betainfluenzavirus/ or influenza b virus/ OR (influenza* OR flu OR flu-like).ti,ab,kf.
Intervention	oseltamivir/ OR baloxavir.nm. OR Neuraminidase/ai OR Endonucleases/ai OR (oseltamivir OR oseltamavir OR Tamiflu).ti,ab,kf. OR (baloxavir OR Xofluza).ti,ab,kf. OR ((neuraminidase OR sialidase OR esterase OR endonuclease) adj2 inhibitor*).ti,ab,kf.
Comparator	No search string
Outcomes	No search string
Limits	*Limit to humans* not (animals not humans).sh.
	Limit to Randomized Controlled Trials[1] (exp randomized controlled trial/ OR controlled clinical trial.pt. OR randomized.ab. OR randomised.ab. OR placebo.ab. OR drug therapy.fs. OR randomly.ab. OR trial.ab. OR groups.ab.) NOT ((((random* ADJ sampl* ADJ8 ("cross section*" OR questionnaire* OR survey or surveys OR database or databases)).ti,ab.) NOT (comparative study/ OR "randomized controlled".ti,ab. OR "randomised controlled".ti,ab. OR "randomly assigned".ti,ab.)) OR (Cross-Sectional Studies/ NOT (exp randomized controlled trial/ OR "randomized controlled".ti,ab. OR "randomised controlled".ti,ab. OR "control group".ti,ab. OR "control groups".ti,ab.)) OR ("case control*".ti,ab. AND random*.ti,ab. NOT ("randomized controlled".ti,ab. OR "randomised controlled".ti,ab.)) OR ("systematic review".ti. NOT (trial.ti. OR study.ti.)) OR (nonrandom*.ti,ab. NOT random*.ti,ab.) OR "random field*".ti,ab. OR (("random cluster" ADJ4 sampl*).ti,ab.) OR (review.ab. AND review.pt. NOT trial.ti.) OR ("we searched".ab. AND (review.ti. OR review.pt.)) OR "update review".ab. OR ((databases ADJ5 searched).ab.) OR (rat.ti. OR rats.ti. OR mouse.ti. OR mice.ti. OR swine.ti. OR porcine.ti. OR murine.ti. OR sheep.ti. OR lambs.ti. OR pigs.ti. OR piglets.ti. OR rabbit.ti. OR rabbits.ti. OR cat.ti. OR cats.ti. OR dog.ti. OR dogs.ti. OR cattle.ti. OR bovine.ti. OR monkey.ti. OR monkeys.ti. OR trout.ti. OR marmoset*.ti.))
	Limit to Clinical Studies (broad)

	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt. OR (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt. OR Multicenter Study.pt. OR Clinical Studies as Topic/ OR exp Clinical Trials as Topic/ or Clinical Trial Protocols as Topic/ or Multicenter Studies as Topic/ OR Random Allocation/ OR Double-Blind Method/ OR Single-Blind Method/ OR Placebos/ OR Control Groups/ OR Cross-Over Studies/ OR (random* or sham or placebo*).ti,ab,hw,kf. OR ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. OR ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. OR (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf. OR (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf. OR (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf. OR (phase adj6 (study or studies or trial*)).ti,ab,hw,kf. OR ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf. OR ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf. OR allocated.ti,ab,hw. OR ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. OR ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. OR (pragmatic study or pragmatic studies).ti,ab,hw,kf. OR ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. OR ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. OR trial.ti,kf.

Notes:
[1]The MEDLINE filter from the technical supplement was modified by translating sections of the Embase filter for MEDLINE (Ovid) with the intent to minimize the number of non-controlled studies and systematic reviews retrieved with the MEDLINE search strategy.

Embase (Elsevier)

Population	'influenza'/de OR 'influenza a'/exp OR 'influenza b'/exp OR 'seasonal influenza'/exp OR 'pandemic influenza'/exp OR 'influenza virus'/de OR 'influenzavirus a'/exp OR 'influenzavirus b'/exp OR (influenza* OR flu OR flu-like):ti,ab,kw
Intervention	'oseltamivir'/exp OR 'baloxavir'/exp OR 'baloxavir marboxil'/exp OR 'sialidase inhibitor'/de OR 'esterase inhibitor'/de OR (oseltamivir OR oseltamavir OR Tamiflu):ti,ab,kw OR (baloxavir OR Xofluza):ti,ab,kw OR ((neuraminidase OR sialidase OR esterase OR endonuclease) NEAR/2 inhibitor*):ti,ab,kw
Comparator	No search string
Outcomes	No search string
Limits	*Limit to humans* NOT (('animal'/de OR 'animal experiment'/exp OR 'nonhuman'/de) NOT ('human'/exp OR 'human experiment'/de))
	Limit to Randomized Controlled Trials 'randomized controlled trial'/exp OR 'controlled clinical trial'/de OR random*:ti,ab,tt or 'randomization'/de or 'intermethod comparison'/de OR placebo:ti,ab,tt OR (compare or compared or comparison):ti,tt OR ((evaluated or evaluate or evaluating or assessed or assess) AND (compare or compared or comparing or comparison)):ab OR (open NEXT/1 label):ti,ab,tt OR ((double or single or doubly or singly) NEAR/1 (blind or blinded or blindly)):ti,ab,tt OR 'double blind procedure'/de OR (parallel NEXT/1 group*):ti,ab,tt OR (crossover or "cross over"):ti,ab,tt OR ((assign* or match or matched or allocation) NEAR/6 (alternate or group or groups or intervention or interventions or patient or patients or subject or subjects or participant or participants)):ti,ab,tt OR (assigned or allocated):ti,ab,tt OR (controlled NEAR/8 (study or design or trial)):ti,ab,tt OR (volunteer or volunteers):ti,ab,tt OR 'human experiment'/de OR trial:ti,tt NOT ((((random* NEXT/1 sampl* NEAR/8 ("cross section*" OR questionnaire* OR survey or surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR "randomized controlled":ti,ab,tt OR "randomised controlled":ti,ab,tt OR "randomly assigned":ti,ab,tt)) OR ('cross-sectional study'/de NOT ('randomized controlled trial'/exp OR 'controlled clinical trial'/de OR 'controlled study'/de OR "randomized controlled":ti,ab,tt OR "randomised controlled":ti,ab,tt OR "control group":ti,ab,tt OR "control groups":ti,ab,tt)) OR ("case control*":ti,ab,tt AND random*:ti,ab,tt NOT ("randomized controlled":ti,ab,tt OR "randomised controlled":ti,ab,tt)) OR ("systematic review":ti,tt NOT (trial:ti,tt OR study:ti,tt)) OR

	(nonrandom*:ti,ab,tt NOT random*:ti,ab,tt) OR "random field*":ti,ab,tt OR (("random cluster" NEAR/4 sampl*):ti,ab,tt) OR (review:ab AND "review":it NOT trial:ti,tt) OR ("we searched":ab AND (review:ti,tt OR "review":it)) OR "update review":ab OR ((databases NEAR/5 searched):ab) OR ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND ‘animal experiment’/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de)))
	Limit to Clinical Studies (broad) 'clinical study'/exp OR 'clinical trial (topic)'/exp OR 'clinical trial protocol'/exp OR 'randomization'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'placebo'/exp OR 'control group'/exp OR 'crossover procedure'/exp OR (random* or sham or placebo*):ti,ab,kw OR ((singl* or doubl*) NEAR/1 (blind* or dumm* or mask*)):ti,ab,kw OR ((tripl* or trebl*) NEAR/1 (blind* or dumm* or mask*)):ti,ab,kw OR (control* NEAR/3 (study or studies or trial* or group*)):ti,ab,kw OR (Nonrandom* or "non random*" or non-random* or quasi-random* or quasirandom*):ti,ab,kw OR (phase NEAR/6 (study or studies or trial*)):ti,ab,kw OR ((crossover or cross-over) NEAR/3 (study or studies or trial*)):ti,ab,kw OR ((multicent* or "multi-cent*") NEAR/3 (study or studies or trial*)):ti,ab,kw OR allocated:ti,ab OR (("open label" or "open-label") NEAR/5 (study or studies or trial*)):ti,ab,kw OR ((equivalence or superiority or non-inferiority or noninferiority) NEAR/3 (study or studies or trial*)):ti,ab,kw OR (pragmatic study or pragmatic studies):ti,ab,kw OR ((pragmatic or practical) NEAR/3 trial*):ti,ab,kw OR ((quasiexperimental or quasi-experimental) NEAR/3 (study or studies or trial*)):ti,ab,kw OR trial:ti,kw

Cochrane Central Register of Controlled Trials (Cochrane Library via Wiley)

Population	(influenza* OR flu OR flu-like):ti,ab,kw
Intervention	(oseltamivir OR oseltamavir OR Tamiflu):ti,ab,kw OR (baloxavir OR Xofluza):ti,ab,kw OR ((neuraminidase OR sialidase OR esterase OR endonuclease) NEAR/2 inhibitor*):ti,ab,kw
Comparator	No search string
Outcomes	No search string
Limits	No limits applied as database is restricted to clinical studies in humans

Web of Science Core Collection

Population	TS=(influenza* OR flu OR flu-like)
Intervention	TS=(oseltamivir OR oseltamavir OR Tamiflu) OR TS=(baloxavir OR Xofluza) OR TS=((neuraminidase OR sialidase OR esterase OR endonuclease) NEAR/2 inhibitor*)
Comparator	No search string
Outcomes	No search string
Limits	*Limit to Randomized Controlled Trials* (TS=(random* OR rtc OR crossover* OR "cross over" OR factorial* OR placebo* OR volunteer*) OR TS=((singl* OR doubl* OR trebl* OR tripl*) NEAR/25 (blind* OR mask)) OR TS=(clin* NEAR/25 trial*) OR TS=((controlled OR multicenter) NEAR/3 (study OR studies)) OR TI=(trial*)) AND Review Article (Exclude – Document Types)

Clinicaltrials.gov

Population	Flu OR Influenza, Human OR Influenza-like Illness
Intervention	oseltamivir OR Tamiflu OR baloxavir OR Xofluza
Comparator	No search string
Outcomes	No search string
Limits	*Study Type* Limit to interventional studies using native filter

WHO International Clinical Trials Registry Platform Search Portal

Population	*Advanced search, in field "Condition"* (influenza* OR flu OR flu-like)
Intervention	*Advanced search, in field "Intervention"* (oseltamivir OR Tamiflu OR baloxavir OR Xofluza)
Comparator	No search string
Outcomes	No search string
Limits	No limits applied as registry consists of clinical studies in humans. Limit for interventional studies is not available.

12.2 Results

12.2.1 Risk of bias

Table 54: Risk of bias of included studies for PICO 1 using the intention-to-treat analysis - Mortality, Influenza-associated complications, Hospitalisation, TTAS

Outcome	Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
PICO 1									
Disease-specific and all-cause mortality	Dawood 2016	Oseltamivir	Placebo	+	+	!	+	+	!
	Ison 2020	Oseltamivir	Baloxavir	+	+	!	+	+	!
	Ison 2020	Oseltamivir	Placebo	+	+	!	+	+	!
	Johnston 2005	Oseltamivir	Placebo	!	+	!	+	!	!
Influenza-associated complications	Ison 2020	Oseltamivir	Placebo	+	+	!	+	+	!
	Li 2004	Oseltamivir	Placebo	+	+	!	+	!	!
	Treanor 2000	Oseltamivir	Placebo	+	+	+	+	!	!
	Whitley 2001	Oseltamivir	Placebo	+	+	+	!	!	!
	Nicholson 2000	Oseltamivir	Placebo	+	+	!	+	!	!
First hospitalisation due to influenza symptoms	Dharan 2011	Oseltamivir	Placebo	!	-	!	+	!	-
	Ison 2020	Oseltamivir	Placebo	+	+	!	+	+	!
	Johnston 2005	Oseltamivir	Placebo	!	+	!	+	!	!
	Whitley 2001	Oseltamivir	Placebo	+	+	+	+	!	!
	Fry 2014	Oseltamivir	Placebo	+	+	+	+	!	!
Time to alleviation of influenza symptoms (TTAS)	Baker 2020	Oseltamivir	Baloxavir	!	!	+	+	+	!
	Beigel 2020	Oseltamivir	Placebo	+	+	+	+	+	+
	Dharan 2011	Oseltamivir	Placebo	!	-	!	+	!	-
	Hayden 2018	Oseltamivir	Baloxavir	+	+	+	+	+	+
	Heinonen 2010	Oseltamivir	Placebo	!	+	+	+	!	!
	Ison 2020	Oseltamivir	Baloxavir	+	+	!	+	+	!
	Ison 2020	Baloxavir	Placebo	+	+	!	+	+	!
	Ison 2020	Oseltamivir	Placebo	+	+	!	+	+	!
	Whitley 2001	Oseltamivir	Placebo	+	+	+	!	!	!
	Fry 2014	Oseltamivir	Placebo	+	+	+	+	!	!
	Nicholson 2000	Oseltamivir	Placebo	+	+	!	!	!	!
	Treanor 2000	Oseltamivir	Placebo	+	+	+	+	!	!
	Johnston 2005	Oseltamivir	Placebo	!	!	!	!	!	!
	Nicholson 2000	Oseltamivir	Placebo	+	+	!	!	!	!
	Treanor 2000	Oseltamivir	Placebo	+	+	+	+	!	!
	Hayden 2018 Phase 2	Baloxavir	Placebo	+	+	+	+	+	+
	Hayden 2018 Phase 3	Baloxavir	Placebo	+	+	+	+	+	+

Domains
D1: Randomisation process
D2: Deviations from the intended interventions
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result

Judgment
+ Low risk
! Some concerns
- High risk

Table 55: Risk of bias of included studies for PICO 1 using the intention-to-treat analysis – Time to resolution of fever, Antibiotic use

Outcome	Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
PICO 1									
Time to resolutin of fever	Qiu 2024	Oseltamivir	Baloxavir	+	+	+	+	!	!
	Baker 2020	Oseltamivir	Baloxavir	!	!	+	+	+	!
	Heinonen 2010	Oseltamivir	Placebo	!	+	+	+	+	!
	Ison 2020	Oseltamivir	Baloxavir	+	+	!	+	+	!
	Ison 2020	Oseltamivir	Placebo	+	+	!	+	+	!
	Lin 2006	Oseltamivir	Routine treatment	+	!	+	!	!	!
	Sato 2005 Influenza A	Oseltamivir	No antiviral agent	!	!	+	-	!	-
	Sato 2005 Influenza B	Oseltamivir	No antiviral agent	!	!	+	-	!	-
	Treanor 2000	Oseltamivir	Placebo	+	+	+	+	!	!
	Whitley 2001	Oseltamivir	Placebo	+	+	+	!	!	!
	Fry 2014	Oseltamivir	Placebo	+	+	+	+	+	+
	Li 2004	Oseltamivir	Placebo	+	+	!	+	!	!
	Nicholson 2000	Oseltamivir	Placebo	+	+	!	+	!	!
	Martin 2001	Oseltamivir	Placebo	!	+	-	+	!	-
	Li 2004	Oseltamivir	Placebo	+	+	+	+	!	!
	Nicholson 2000	Oseltamivir	Placebo	+	+	!	+	!	!
Number of people with antibiotics use	Baker 2020	Oseltamivir	Baloxavir	!	!	+	+	+	!
	Dawood 2016	Oseltamivir	Placebo	+	+	+	+	!	!
	Ison 2020	Oseltamivir	Baloxavir	+	+	!	+	+	!
	Ison 2020	Oseltamivir	Placebo	+	+	!	+	+	!
	Li 2004	Oseltamivir	Placebo	+	+	!	+	!	!
	Treanor 2000	Oseltamivir	Placebo	+	+	+	+	!	!
	Whitley 2001	Oseltamivir	Placebo	+	+	+	!	!	!
	Nicholson 2000	Oseltamivir	Placebo	+	+	!	+	!	!

Domains
D1: Randomisation process
D2: Deviations from the intended interventions
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result

Judgment
+ Low risk
! Some concerns
- High risk

Table 56: Risk of bias of included studies for PICO 1 using the intention-to-treat analysis – Severe adverse events, Adverse events

Outcome	Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
PICO 1									
Severe adverse events	Dawood 2016	Oseltamivir	Placebo	+	!	+	+	!	!
	Heinonen 2010	Oseltamivir	Placebo	!	+	+	+	!	!
	Johnston 2005	Oseltamivir	Placebo	!	!	!	!	!	!
	Fry 2014	Oseltamivir	Placebo	+	+	+	+	!	!
Adverse events	Baker 2020	Oseltamivir	Baloxavir	!	!	+	+	+	!
	Dawood 2016	Oseltamivir	Placebo	+	!	+	+	!	!
	Hayden 2018	Oseltamivir	Baloxavir	+	+	+	+	+	+
	Hayden 2018	Oseltamivir	Placebo	+	+	+	+	+	+
	Johnston 2005	Oseltamivir	Placebo	!	!	!	!	!	!
	Li 2004	Oseltamivir	Placebo	+	+	+	+	!	!
	Lin 2006	Oseltamivir	Routine treatment	+	!	+	-	!	-
	Raus 2015	Oseltamivir	Echinaforce Hotdrink	+	+	+	+	!	!

Domains
D1: Randomisation process
D2: Deviations from the intended interventions
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result

Judgment
+ Low risk
! Some concerns
- High risk

Table 57: Risk of bias of included studies for PICO 2 using the intention-to-treat analysis – Mortality, Laboratory-confirmed influenza, Severe adverse events, Adverse events

Outcome	Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
PICO 2									
Disease-specific and all-cause mortality	Ison 2012	Oseltamivir	Placebo	!	+	+	+	!	!
	Peters 2001	Oseltamivir	Placebo	!	+	+	+	!	!
	van der Sande 2014	Oseltamivir	Placebo	!	+	+	+	!	!
Laboratory-confirmed influenza	Anekthananon 2013	Oseltamivir	Placebo	+	+	!	+	!	!
	Hayden 1999	Oseltamivir	Placebo	+	+	+	+	!	!
	Ison 2012	Oseltamivir	Placebo	!	+	+	+	+	!
	Peters 2001	Oseltamivir	Placebo	!	+	+	+	!	!
	Welliver 2001	Oseltamivir	Placebo	!	+	+	+	!	!
	Hayden 2000	Oseltamivir	Placebo	!	+	+	+	!	!
Severe adverse events	Hayden 2000	Oseltamivir	Placebo	!	!	+	!	!	!
	Hayden 2000	Oseltamivir	Placebo	!	!	+	!	!	!
Adverse events	Anekthananon 2013	Oseltamivir	Placebo	+	+	+	+	!	!
	Hayden 2000	Oseltamivir	Placebo	!	!	+	!	!	!
	Ison 2012	Oseltamivir	Placebo	!	!	+	!	!	!

Domains
D1: Randomisation process
D2: Deviations from the intended interventions
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result

Judgment
+ Low risk
! Some concerns
- High risk

Table 58: Risk of bias of included studies for PICO 1 using the per-protocol analysis – Re-consultation with a doctor, Antibiotic use

Outcome	Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
PICO 1									
Re-consultations with a doctor	Butler 2020	Oseltamivir	Usual primary care	+	-	-	+	+	-
	Raus 2015	Oseltamivir	Echinaforce Hotdrink	+	-	-	+	+	-
Number of people with antibiotics use	Butler 2020	Oseltamivir	Usual primary care	+	-	-	!	+	-
	Raus 2015	Oseltamivir	Echinaforce Hotdrink	+	-	-	+	+	-

Domains
D1: Randomisation process
D2: Deviations from the intended interventions
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result

Judgment
+ Low risk
! Some concerns
- High risk

12.2.2 Overview of evidence and synthesis method

Table 59: Overview of evidence and synthesis method

Outcomes	Oseltamivir vs. Placebo	Oseltamivir vs. Baloxavir	Oseltamivir vs. Any non-antiviral treatment	Baloxavir vs. Placebo
PICO 1				
Efficacy:				
Primary Outcomes				
Disease-specific and all-cause mortality	MA & SWiM	SWiM	SWiM	SWiM
Number of people with influenza-associated complications	MA & SWiM	SWiM	SWiM	SWiM
First hospitalisation due to influenza symptoms	MA & SWiM	SWiM	SWiM	SWiM
Secondary Outcomes				
Time to alleviation of influenza symptoms (TTAS)	MA & SWiM	MA	-	MA & SWiM
Time to improvement of influenza symptoms (TTIIS)	SWiM	SWiM	-	SWiM
Time to resolution of fever	MA & SWiM	MA	MA & SWiM	SWiM
Number of people with antibiotic use	MA & SWiM	MA	MA & SWiM	SWiM
Length of hospitalisation	-	-	SWiM	-
Number of patients with re-consultations with a doctor	-	-	MA	-
Number of onward transmissions to household contacts	SWiM	-	SWiM	-
Safety:				
Adverse events	MA & SWiM	MA & SWiM	MA & SWiM	SWiM
Severe adverse events	MA & SWiM	SWiM	SWiM	SWiM
Toxicities	-	-	-	-
PICO 2				
Efficacy:				
Primary Outcomes				

Disease-specific and all-cause mortality	MA	-	-	SWiM
Number of people with laboratory-confirmed influenza	MA	-	-	SWiM
Influenza confirmed with rapid diagnostic tests	-	-	-	-
Number of people with influenza-associated complications	SWiM	-	-	-
First hospitalisation due to influenza symptoms	-	-	-	-
Secondary Outcomes				
Length of hospitalization	-	-	-	-
Safety:				
Adverse events	MA & SWiM	-	-	SWiM
Severe adverse events	SWiM	-	-	SWiM
Toxicities	-	-	-	-

12.2.3 Meta analysis PICO 1 efficacy

Figure 32: Meta-analysis showing mortalitys of oseltamivir versus placebo treatment in patients with influenza-like symptoms using continuity correction of 0.1

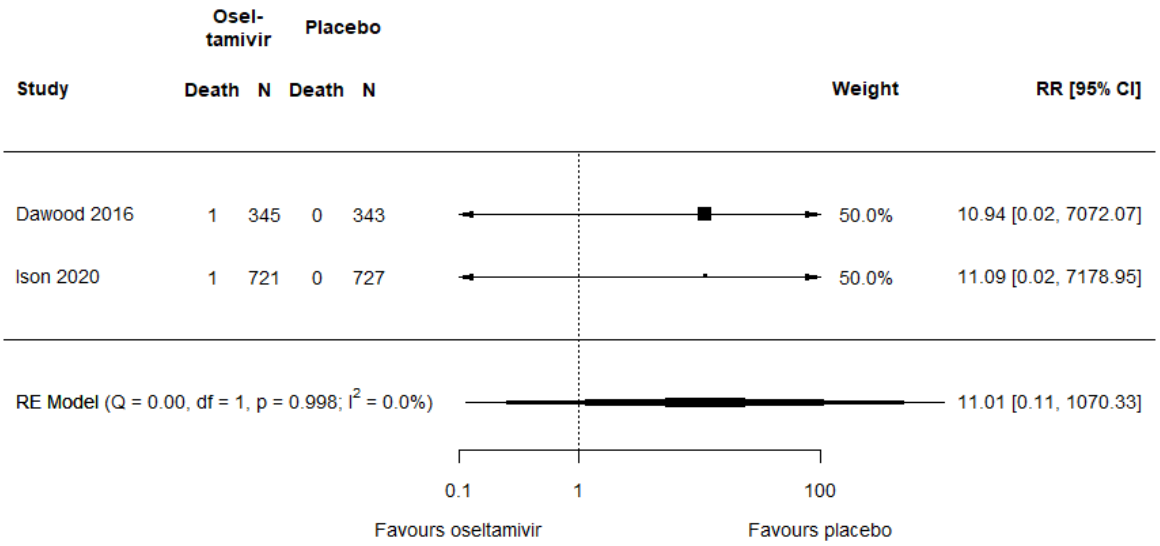
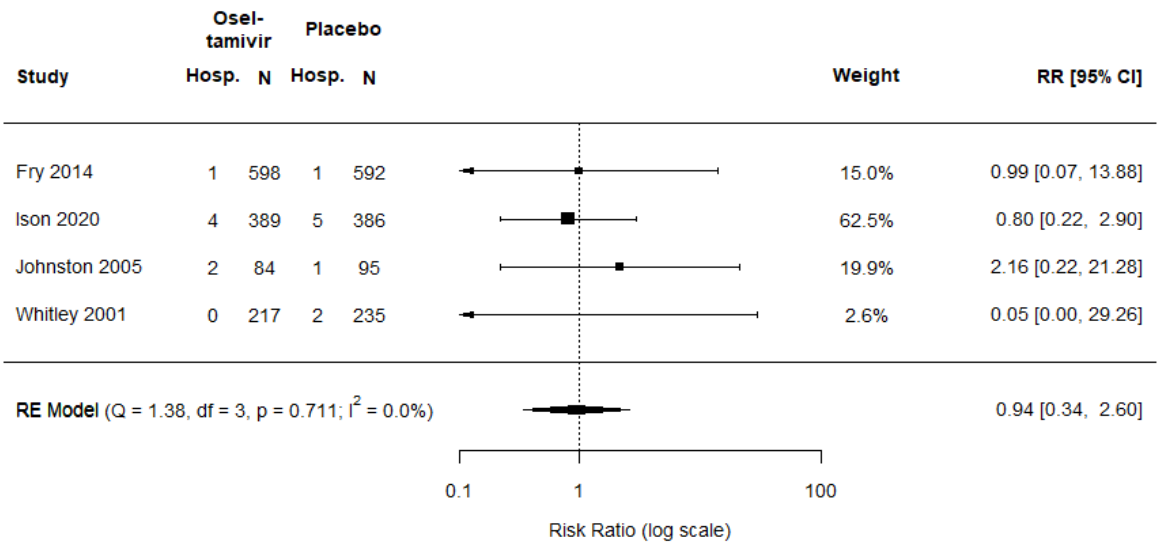
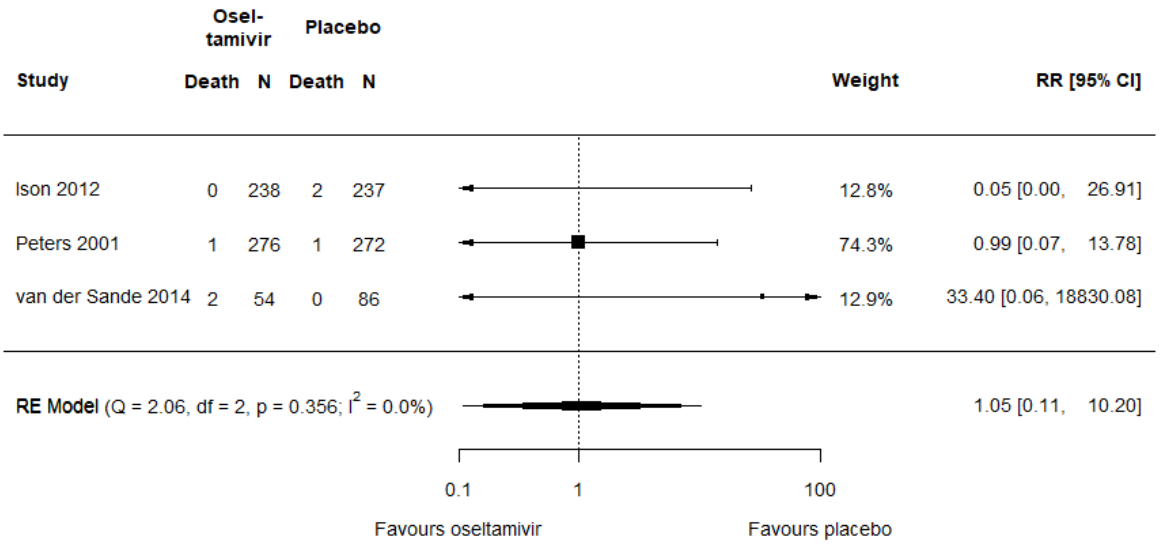


Figure 33: Meta-analysis showing hospitalisation of oseltamivir versus placebo treatment in patients with confirmed influenza using continuity correction of 0.1



12.2.4 Meta analysis PICO 2 efficacy

Figure 34: Meta-analysis showing mortalityof oseltamivir versus placebo in patients with influenza-like symptoms using continuity correction of 0.1



12.2.5 Meta analysis PICO 1 safety

Figure 35: Meta-analysis showing severe adverse events of oseltamivir versus placebo treatment in patients with influenza-like symptoms using continuity correction of 0.1

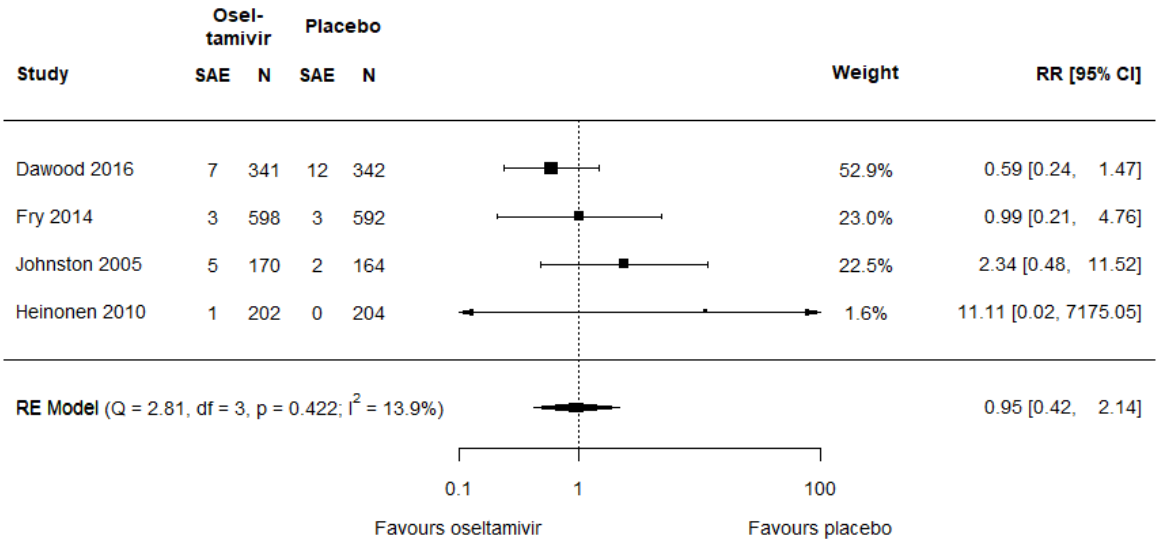
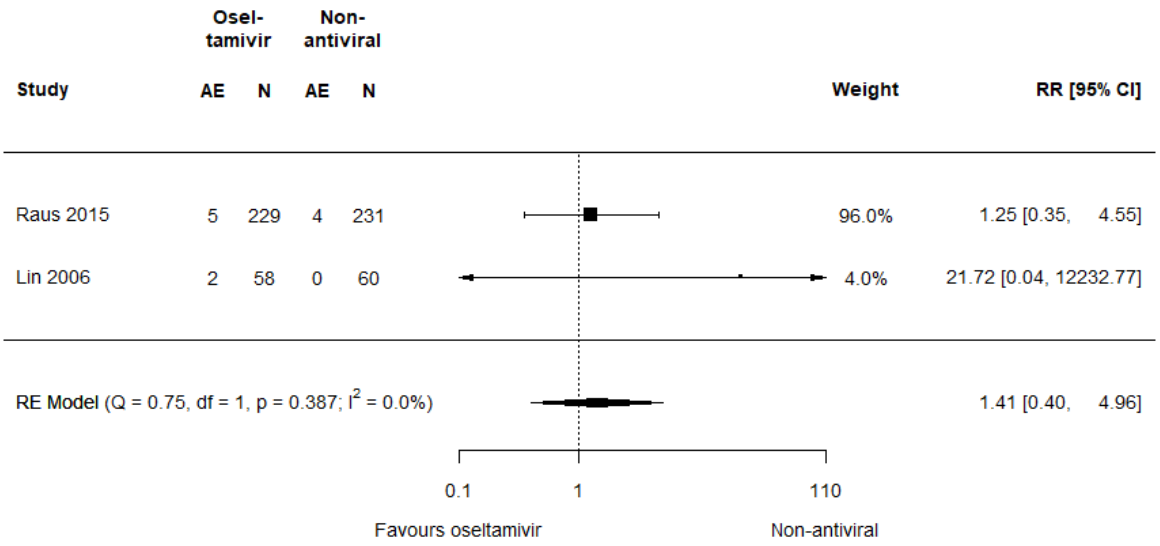
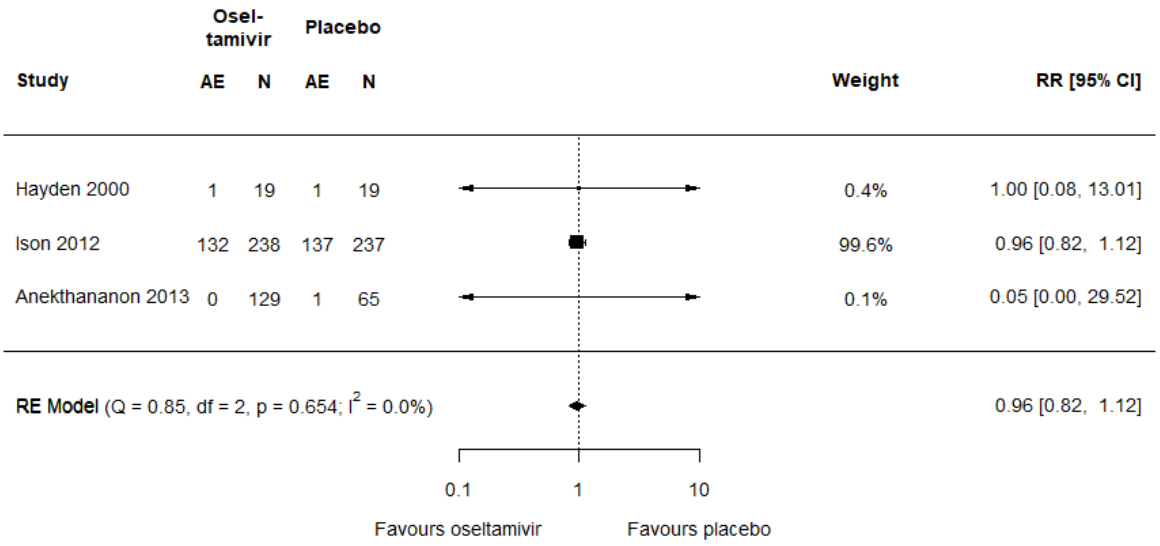


Figure 36: Meta-analysis showing adverse events of oseltamivir versus non-antiviral treatment in patients with influenza-like symptoms using continuity correction of 0.1



12.2.6 Meta analysis PICO 2 safety

Figure 37: Meta-analysis showing adverse events of oseltamivir versus placebo in patients with influenza-like symptoms



12.2.7 Stockpiling strategies in other countries

Table 60: Stockpiling strategies

Country	National stockpiling strategy	Influenza pandemic: Other national measures / strategy	Tamiflu® national stock in anticipation or response to influenza pandemic such as 2009/10 Grippevirus A(H1N1) - Schweinegrippe	Tamiflu® national stock 2024 (or most recent year)	Xofluza® national stock 2024 (or most recent year)	Rationale for change of strategy	links
Belgium	(not investigated)	(not investigated)	(not investigated)	(not investigated)	NO (for treatment) YES (for research) Based on the framework for a systematic and comprehensive assessment of stockpiling needs, the current state of the evidence, and the need for data on critical clinical outcomes, the Task Force Therapeutics Viral Diseases considers that **stockpiling baloxavir for the treatment of influenza is not the preferred option**. However, the need to **generate new evidence can justify stockpiling sufficient quantities of baloxavir to start a RCT at the onset of a new epidemic**. Therefore, the Task Force recommends purchasing sufficient quantities of baloxavir to initiate or contribute to randomised controlled trials at the onset of an influenza pandemic. **The same recommendation can apply to oseltamivir**		https://kce.fgov.be/sites/default/files/2024-10/R3_01_Advice_TFTx_Baloxavir.pdf

Denmark	On 4 June 2024, the Danish Parliament adopted the Danish Act on Stockpiling of Critical Medicines, which commits **companies** placing critical medicines on the Danish market to **maintain a security stock** of the concerned medicines. It will soon be mandatory for companies behind the most critical medicines **to maintain stocks to cover initially six weeks' consumption** and to **report stocks regularly** to the Danish Medicines Agency. An initial 350 critical medicines will be comprised by the stockpiling obligation; Oseltamivir and baloxavir Marboxil are **not** part of this policy (https://www.retsinformation.dk/eli/lta/2024/870)	The Danish healthcare system relies on efficient distribution networks for medications and emphasises public health interventions, such as **vaccination** and **awareness campaigns**, to mitigate influenza outbreaks	YES Denmark stockpiled Tamiflu®, but predominantly in bulk powder form for reconstitution into oral suspension, rather than as capsules, in order to reduce price and prolong shell-life. In total, Denmark purchased sufficient Tamiflu® powder to cover 6% of the population prophylactically, or 19% for treatment of infection. Lower in comparison to other Scandinavian countries: Norway (30%) and Finland (25%)	NO Currently, there is no specific indication that Denmark actively stockpiles Tamiflu® (oseltamivir) as part of its public health preparedness in 2023 or 2024. Denmark has a strong public health framework that includes influenza vaccination and medication distribution through pharmacies and hospitals. While European trends indicate a general preparedness for influenza and antiviral drug accessibility, including Tamiflu®, detailed policies specific to Denmark's stockpiling efforts have not been highlighted in recent sources.	no information (probably NO)	probably limited evidence on effectiveness	https://pmc.ncbi.nlm.nih.gov/articles/PMC6166586/pdf/fdx101.pdf https://laegemiddelstyrelsen.dk/en/news/2024/new-regulations-on-stockpiling-of-critical-medicines-effective-on-july-1-2024/

England	As of 2024, NHS England does not appear to maintain a specific, centralised stockpile of Tamiflu® (oseltamivir) for general use but ensures that systems are in place for antiviral access during flu outbreaks. According to NHS guidelines, Tamiflu® is recommended and made available through prescriptions when flu activity is high and in defined circumstances, particularly for at-risk groups such as older adults and those with chronic health conditions. **Regional systems are tasked with ensuring availability** during flu seasons and outbreaks	YES Between 2006-07 and 2012-13, the Department spent £560 million on antiviral medicines for use in an influenza pandemic - £424 million on Tamiflu®. Just under 40 million units of Tamiflu® were purchased	NO (no national stock but rather decentralised stockholding pharmacies) Influenza Season 2024/25: Use Of Antiviral Medicines in England. Prescribers working in primary care may now prescribe, and community pharmacists may now supply antiviral medicines (oseltamivir and zanamivir) for the prevention and treatment of influenza at NHS expense. Service expectations for system commissioners on requirements previously outlined in 2017 and restated for clinical commissioning groups (CCGs) Example CCG Morecambe Bay: Agreement to stock antivirals (oseltamivir) for the treatment and prevention of influenza for Care Home Residents. NHS England has commissioned a number of pharmacies to hold stocks of antivirals for supply against FP10s with courier arrangements to transport medicines to care home(s) if needed. Each of the pharmacies has been commissioned to deliver this service across the whole NHS England. These stockholding pharmacies can be accessed if the usual local pharmacy cannot supply the required antivirals within the required timeline.	NO There is currently no recommended treatment option by the National Institute for Health and Care Excellence (NICE) for reducing the transmission of influenza. NICE recommends oseltamivir and zanamivir for the post-exposure prevention of influenza.	https://publications.parliament.uk/pa/cm201314/cmselect/cmpubacc/295/295.pdf https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=104185 https://www.england.nhs.uk/long-read/services-for-the-provision-of-antiviral-drugs-for-the-treatment-and-post-exposure-prophylaxis-of-influenza-like-illness-ili-in-at-risk-patients-including-care-home-residents/ https://www.io.nihr.ac.uk/wp-content/uploads/2024/06/27430-Baloxavir-Marboxil-for-Influenza-V1.0-JUN2024-NON-CONF.pdf https://cplsc.communitypharmacy.org.uk/wp-content/uploads/sites/141/2023/08/Pharmacy-agreement-to-stock-antivirals-MBCCG-2021_22.pdf https://sefton.communitypharmacy.org.uk/resources/sv/tamiflu-stockholding-2020-24/ https://database.inahta.org/article/19495

France	In France, a strategic stockpile of healthcare products has been set up by the government to deal with exceptional health situations. This stockpile is managed by the **Établissement de Préparation et de Réponse aux Urgences Sanitaires (EPRUS) on behalf of the Ministry of Health**. The Établissement de Préparation et de Réponse aux Urgences Sanitaires (EPRUS) was a French health security agency and a public administrative body under the authority of the French Ministry of Health, **created in 2007 and dissolved in 2016**. When it was dissolved in May 2016, its remit was merged with that of other bodies within the National Public Health Agency	The HCSP underscores the importance of complying with hygiene measures during a patient's treatment. It also highlights the importance of vaccinating target groups deemed at risk against seasonal influenza, according to the immunisation schedule	YES In the report on the accounts and management of the Établissement de Préparation et de Réponse aux Urgences Sanitaires since its creation, dated September 2010, it is stated that the antiviral reserve of the strategic stockpile comprised 33 million treatments [Jégou, 2009], including 7 million treatments of oseltamivir in capsule form, 17 million treatments of oseltamivir in powder form (17 tonnes), etc. [Jégou, 2009]. Based on the 2010 French population of over 65 million [Pla and Beaumel, 2011], this stock provided coverage for just over 50% of the population; however, one report states that 15 million of these treatments were for curative treatment, while the remainder were for preventive use, providing curative coverage for around 25% of the population [Jégou, 2009].	YES (probably even for whole EU) There is no reason to change the recommendation on stockpile sizing. stockpile size: this should be sufficient to treat (curative and preventive) 30% of the French population (paediatric and adult forms). In 2017, WHO downgraded oseltamivir (neuraminidase inhibitor antiviral treatment) in the list of essential medicines from a "core" drug to one that is "complementary" and deemed less cost effective. In light of recent data from studies, summaries and meta-analyses on the efficacy and tolerance of oseltamivir, the French Haut Conseil de la santé publique (HCSP, High Council for Public Health) previous recommendations – which were already highly targeted – remain unchanged. The operational interface with the European Commission for the use of rescEU stocks is managed by the civil protection staff of the Directorate-General for Civil Protection and Crisis Management (DGSCGC). The stocks built up and maintained by France under the supervision of the Directorate General for Health (DGS) include health products (antidotes, medicines, vaccines, medical devices), medical and non-medical equipment (in particular protective equipment and equipment for environmental detection of CBRN risks). Some of the stocks are packaged in operational trunks containing different products for immediate use by the emergency services. Located in France, they can be mobilised 24 hours a day.	no information There is no publicly available information indicating that France maintains a national stockpile of Xofluza®.	https://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=ad1192932.pdf https://database.inahta.org/article/19495 https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=709 https://www.bing.com/ck/a?!&&p=75ab4e67ab1ba7f83a4a57c3ed40d626d8db639b6d56f0bab7ee743c6515c308JmltdHM9MTczNDA0ODAwMA&ptn=3&ver=2&hsh=4&fclid=17a5d1dd-a789-6f95-02a1-c553a6306e81&psq=r%c3%a9serve+strategique+d%e2%80%99antiviraux+contre+l%e2%80%99influenza+france+oseltamivir&u=a1aHR0cHM6Ly93d3cuc2FudGVwdWJsaXF1ZWZyYW5jZS5mci9tYWxhZGllcy1ldC10cmF1bWF0aXNtZXMvbWFsY-WRpZXMtZXQtaW5mZWN0aW9ucy1yZXNwaXJhdG9pcmVzL2dyaXBwZS9kb2N1bWV-u-dHMvYXZpcy9hdmlzLWQtZXhwZXJ0cy1yZWxhdGlmcy1hLWxhLXN0cmF0ZWdpZS1kZS1jb25zdGl0dXRpb24tZC11bi1zdG9jay1kZS1jb250cmUtbWVzdXJlcy1tZWRpY2FsZXMtZmFjZS1hLXVuZS1wYW5kZW1pZS1ncmlwcGFsZQ&ntb=1 https://www.interieur.gouv.fr/Le-ministere/Securite-civile/Nos-missions/La-promotion-de-la-securite-civile-a-l-etranger/La-contribution-de-la-France-aux-stocks-europeens-face-aux-risques-NRBC-et-pandemiques

Germany	In Germany, the **Federal Ministry of Health** manages the antiviral stockpile	YES As part of the H1N1 pandemic in 2009, the BMG procured and stored a federal reserve of antiviral drugs and stored them. The stored oseltamivir powder was procured to supply the population with a total of population with a total of 7.5 million therapy units. The federal reserve supplements the stockpiling of antiviral drugs for the German population in all federal states. To the knowledge of the Federal Government, the federal states have antiviral drugs for at least 20 per cent of the German population by 2009 as part of pandemic planning. The federal states have not only stockpiled the finished drug Tamiflu®, but also the active ingredient oseltamivir.	YES In 2009, when swine flu caused a worldwide stir, and in 2013, according to the Federal Ministry of Health, the antiviral finished medicinal product Tamiflu® and the active ingredient oseltamivir were procured and stored. 'The stocks of antiviral medicines of the federal states stored by the Bundeswehr were completely destroyed because they had exceeded their shelf life,' writes the BMG. Only 'a stock of oseltamivir is now being stored for the federal government'. No details are given on the quantity. Of the eight state health ministries surveyed, only the one in North Rhine-Westphalia commented on the question of drug stocks: It says it is stockpiling the active substance oseltamivir phosphate for around 26 per cent of its population. According to the Federal Ministry of Health, the federal government currently has around 7,500 kg of oseltamivir powder in stock.	NO With its novel mechanism of action and single oral dose, Xofluza® was considered an innovation in the field of influenza prevention and treatment. However, the G-BA only partially recognised this in the early benefit assessment. Roche is now (Oct 2021) withdrawing baloxavir from the German market as a consequence	probably limited evidence on effectiveness	https://dserver.bundestag.de/btd/17/132/1713202.pdf https://www.aerztezeitung.de/Politik/Vorbereitung-auf-Vogelgrippe-H5N1-Impfstoff-Vertraege-sind-schon-geschlossen-452700.html

Netherlands	The national stockpile is managed by the Dutch government, specifically the **Center for Infectious Disease Control (Centrum Infectieziektebestrijding, CIb)**. The CIb was responsible for recommendations regarding the distribution and strategic use of antiviral drugs to minimise the pandemic's impact on the population and the healthcare system	YES Summary of the Report Gezondheitsrat: The Netherlands had a national stockpile of Tamiflu® (Oseltamivir) in 2009. As part of preparations for a possible influenza pandemic, the Dutch government had procured approximately five million courses of neuraminidase inhibitors (including Oseltamivir and Zanamivir) since 2005 5 Million courses on a population of 16.5 Mio (2009) => 30%	YES. National Institute for Public Health and the Environment's (RIVM) current policy (last update Feb 2023): The **prevention** policy (oseltamivir) should be determined - preferably in consultation with the LCI - 'tailor-made' and 'in moderation'. he RIVM has a national stock of antiviral agents that can be used for prevention in the event of outbreaks of avian influenza on a poultry farm. Municipal health services can use this after consultation with the LCI and the NVWA . This stock is the property of the NVWA and is not intended for other indications. In most cases, a human infection with an animal influenza virus is 'self-limiting'. **Treatment** of human infections with animal influenza is in principle only indicated for highly pathogenic animal influenza known to humans to stop further spread and prevent reassortment during outbreaks. Oseltamivir stops virus (re)production within a few hours when the virus is sensitive to Oseltamivir. Treatment with oseltamivir should start within 48 hours. If no oseltamivir has been given and serious complications occur later, it is advisable to start oseltamivir anyway (due to persistent virus replication).	no information (probably NO) In addition to the treatment of uncomplicated influenza, baloxavir is also registered for the prevention of influenza after exposure in persons aged 1 year and older. This concerns a single dose that should be taken as soon as possible within 48 hours after close contact with someone known or suspected to have influenza. In the Netherlands, no advice has yet been established for baloxavir regarding its place in influenza **prevention.** **Treatment**: Because influenza is usually a harmless condition that heals by itself in previously healthy individuals, it generally does not require treatment (Van Essen 2009). A fever and pain reducing agent can be used to relieve the symptoms. Nasal drops can also relieve the symptoms. Antiviral agents: Antiviral therapy may be considered in patients at high risk of complications who have proven or suspected influenza, such as nursing home residents and immunocompromised individuals.	probably limited evidence on effectiveness	https://www.gezondheidsraad.nl/binaries/gezondheidsraad/documenten/adviezen/2015/12/8/antivirale-middelen-bij-grieppandemie/briefadvies_antivirale_middelen_bij_een_grieppandemie_201530_0.pdf https://lci.rivm.nl/richtlijnen/influenza-van-dierlijke-oorsprong https://lci.rivm.nl/richtlijnen/influenza

South Korea	To prepare for a novel influenza pandemic, the **Korea Center for Disease Control and Prevention (KCDC)** has a management plan for national stockpiles of antiviral drugs and personal protective equipment.	Although vaccines and antiviral agents can be used in the control of influenza, so far, they have not yielded very satisfactory results [2,3]. Therefore, a well-organised **surveillance system** is necessary to monitor and respond effectively to influenza epidemics. Regarding infectious diseases outbreaks and the risk of pandemics, Korea, as a global economic hub, is exposed to virus or pathogens in a similar manner to most OECD countries.	YES At the beginning of the pandemic (i.e. e 2009 H1N1 pandemic), the stockpile of antiviral drugs managed by KCDC was for 2.5 million patients. During the pandemic, an additional antiviral drugs for 13.7 million patients were purchased.(Kim et al. 2022)	YES Since then, the KCDC has continued to maintain a national influenza antiviral stockpile (Kim et al. 2022) 2013: South Korea Won't Extend Stockpiled Tamiflu® Expiration Dates: MFDS rejects Korea Centers for Disease Control and Prevention bid to retain expiring Tamiflu® stockpile. South Korea would need to replace expiring supplies to maintain same levels of stockpile.	no information (probably YES) Moreover, a new antiviral drug with a different mode of action—cap-dependent endonuclease inhibitor (CENI), also known as baloxavir marboxil—has been approved as an alternative to neuraminidase inhibitors (NAIs). It is necessary to adjust the antiviral stockpile to reflect improved intervention measures and a new drug.(Kim et al. 2022)		https://www.sciencedirect.com/science/article/pii/S1876034122001320?via%3Dihub https://insights.citeline.com/SC084546/South-Korea-Wont-Extend-Stockpiled-Tamiflu-Expiration-Dates/ https://pmc.ncbi.nlm.nih.gov/articles/PMC6609753/ https://www.oecd.org/content/dam/oecd/en/publications/reports/2020/03/oecd-reviews-of-public-health-korea_335bc8ac/be2b7063-en.pdf
USA	**Strategic National Stockpile (SNS)**, which is managed by the **Centers for Disease Control and Prevention (CDC).** The National Pharmaceutical Stockpile was created in 1999 to ensure the nation's readiness against potential agents of bioterrorism like botulism, anthrax, smallpox, plague, viral hemorrhagic fevers, and tularemia. The mission was to assemble large quantities of essential medical supplies that could be delivered to states and communities during the emergency within 12 hours of the federal decision to use the stockpile. The national antiviral-drug procurement strategy was based on the 2005 Department of Health and Human Services (DHHS) pandemic influenza plan.The plan recommended treatment (rather than prevention) as the primary use of available antiviral drugs		YES US government has added oseltamivir to its strategic national stockpile. 40 millions regimens (HHS Antiviral Subsidy Vendor Contract between 2006-2009)	YES Dez 2022: The U.S. Department of Health and Human Services is increasing the country's stockpile of an antiviral medication used to treat influenza Jurisdictions that have exhausted their own stockpiled supplies of Tamiflu® may request supplemental Tamiflu® 75mg from the Strategic National Stockpile (SNS)	no information (probably NO)	no change of strategy	https://aspr.hhs.gov/SNS/Pages/default.aspx https://pubmed.ncbi.nlm.nih.gov/19707215/ https://database.inahta.org/article/19495