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Clinical Evidence Synthesis Protocol

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

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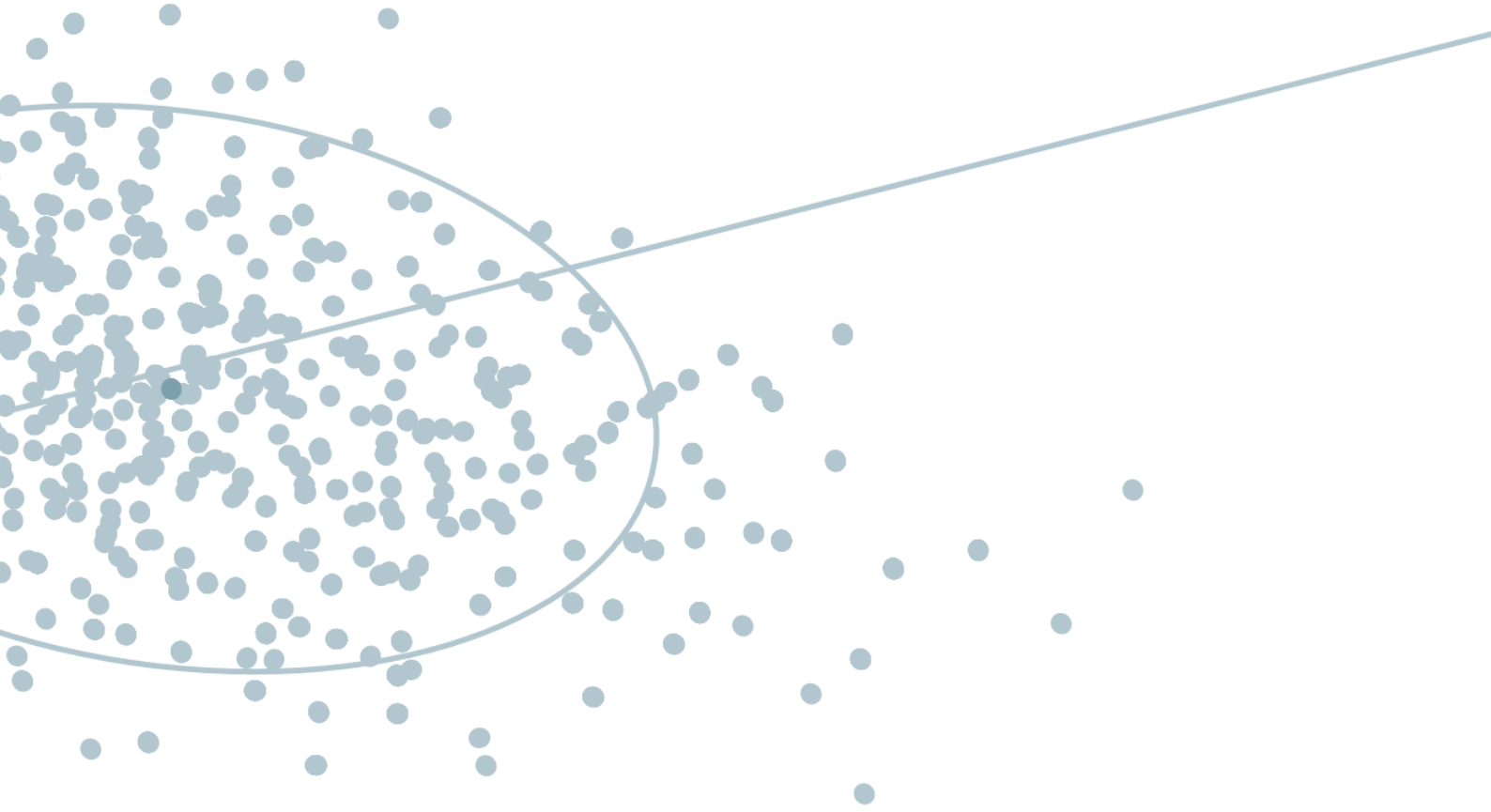

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Title	Oseltamivir and baloxavir marboxil to treat or prevent influenza A and B
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Conflict of Interest:

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

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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 (Xofluza®) are approved for treatment and prophylaxis 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 marboxil. To inform these strategic stockpiling decisions, a clinical evidence synthesis regarding the efficacy and safety of oseltamivir and baloxavir marboxil is of interest.

Objective: This protocol defines the population, intervention, comparator and outcomes (PICO), as well as the key research questions and describes the methodology to conduct a systematic literature search, and extract, analyse and synthesise the data in the report.

Research questions: 1) Are oseltamivir (Tamiflu®) and baloxavir marboxil (Xofluza®) efficacious and safe compared to each other, placebo or any non-antiviral treatment in patients with influenza A or B or influenza A-, B-like symptoms? 2) Are oseltamivir (Tamiflu®) and baloxavir marboxil (Xofluza®) efficacious and safe compared to each other, placebo or any non-antiviral treatment in persons receiving prophylactic treatment against influenza (e.g., healthcare personnel or persons at risk)?

Methods: A systematic literature search in Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Medline and Web of Science databases will be conducted. Eligible studies are randomised controlled trials (RCTs) that compare oseltamivir and baloxavir marboxil to each other, placebo or any non-antiviral treatment and assess relevant outcomes such as mortality, influenza-associated symptoms or complications and hospitalisation. In addition, RCTs registered with clinicaltrials.gov and the WHO International Clinical Trials Registry Platform will be searched, and their completion status will be checked. The number of completed but unpublished trials will also be examined to account for publication bias. If relevant outcomes such as mortality, influenza-associated symptoms or complications and hospitalisation is not covered by RCTs, an additional systematic literature search for observational studies may be conducted. If possible, meta-analyses will be performed to estimate pooled effect estimates. In order to explore possible heterogeneity among pooled effect estimates, subgroup and sensitivity analyses will be performed. Outcomes which cannot be summarized with pooled estimates will be analysed narratively by using the Synthesis Without Meta-analysis (SWiM) guideline. If possible, a network meta-analysis will be conducted to increase precision in the estimations of efficacy and safety and to estimate a rank order for the 2 investigated drugs. If network meta-analyses are not feasible, the comparators will be limited to influenza treatments approved for use in Switzerland. Although approved in Switzerland, zanamivir is not included because its

production has been discontinued worldwide. The methodological quality of included RCTs will be critically appraised according to the Cochrane Risk of Bias tool for randomized trials (RoB 2). In case observational studies will be considered, their methodological quality will be appraised according to the Cochrane Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool. The certainty of evidence for relevant outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for pairwise meta-analyses and the Confidence in Network Meta-Analysis (CINeMA) tool for network meta-analysis.

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Abbreviations and acronyms

CINeMA	Confidence in Network Meta-Analysis
ELSO	Ethical, Legal, Social and Organizational
FOPH	Federal Office of Public health
CENTRAL	Cochrane Central Register of Controlled Trials
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HTA	Health Technology Assessment
NAIs	Neuraminidase inhibitors
PA	Acidic protein
PCR	Polymerase chain reaction
PICO	Population, Intervention, Comparator, Outcome
PRISMA	Preferred Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
REML	Restricted Maximum Likelihood
RNA	Ribonucleic acid
RoB	Risk of Bias
RoB 2	Risk of Bias 2 tool
ROBINS-I	Cochrane Risk of Bias in Non-randomised Studies of Interventions
ROB-ME	Risk Of Bias due to Missing Evidence in a meta-analysis
ROB-MEN	Risk Of Bias due to Missing Evidence in Network meta-analysis
SWiM	Synthesis Without Meta-analysis
TTAS	Time to alleviation of symptoms
WHO	World health organisation

Objective of the protocol

Based on a preliminary screening of the literature the objective of the protocol is to formulate the key questions, to define the population, intervention, comparator, outcomes (PICO) and describe the methodology to conduct a systematic literature search, extract, analyse and synthesise the data in the report on the topic. Key questions are defined, addressing the domain clinical efficacy/effectiveness and safety.

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.[4] To inform this strategic stockpiling decision for future influenza pandemics, the Section Emerging Infectious Diseases and International Cooperation of the FOPH has commissioned a clinical evidence synthesis on the efficacy and safety of oseltamivir (Tamiflu ®) and baloxavir marboxil (Xofluza®).[4]

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 flu 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 generalized pain and gastrointestinal symptoms.[5,6] The symptoms generally appear 1-4 days after exposure.[6] 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 industrialized countries, most influenza-related deaths occur in individuals aged 65 and older.[1]

Seasonal influenza are annual flu epidemics.[7] 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.[8] An influenza pandemic is a worldwide spread of a new influenza virus that significantly differs from the currently and recently circulating seasonal influenza viruses.[7] Switzerland has experienced four pandemics in the past century: 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), and 2009 (H1N1pdm09).[4] 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.

2.2 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 categorized 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]

2.3 Surveillance and diagnosis

In Switzerland, influenza seasons are monitored by the Sentinella surveillance system and the laboratory tests employed to confirm the diagnosis of influenza within this framework are Hemagglutination inhibition and Polymerase chain reaction (PCR) tests.[10] However, seasonal influenza is usually diagnosed based on symptoms and patients are rarely tested with laboratory diagnostics.[5]

2.4 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.[11–13] However, influenza viruses undergo frequent genetic changes, particularly through antigenic drift and shift.[14,15] 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]

2.5 Treatments

Several measures can help ease influenza symptoms. Hydration is crucial to replace water lost due to fever. Antipyretics like ibuprofen or acetaminophen can reduce fever, prevent additional water loss, and relieve muscle pain and chills, but they do not affect the duration of the illness. Neuraminidase inhibitors (NAIs) oseltamivir (Tamiflu®), zanamivir (Relenza®, Dectova®), and peramivir (Alpivab®, Rapivab®) as well as the cap-dependent endonuclease inhibitor baloxavir marboxil (Xofluza®) are antiviral treatments for influenza A and B.[6]

2.6 Burden of influenza

The impact of influenza on public health is significant, leading to widespread morbidity and mortality during peak seasons.[16] Influenza epidemics can lead to substantial productivity losses due to absenteeism by workers and students, 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 hospitalizations, and several hundred deaths per year.[17] 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.[18] Almost 80% of these costs were attributable to hospitalizations.[18] 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.[5] 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.[5] Only 0.05% of the suspected cases received antiviral treatment and 11.8% had been vaccinated against the flu during the last season.[5]

3. Technology

The neuraminidase inhibitors (NAIs) oseltamivir (Tamiflu®) and zanamivir (Relenza®, Dectova®), are antiviral medications used for the prevention and treatment of influenza A and B. These drugs work by blocking the function of the neuraminidase enzyme, which is essential for the release of new viral particles from infected cells.[19,20] In contrast, cap-dependent endonuclease inhibitors, such as baloxavir marboxil (Xofluza®), represent a newer class of antiviral agents targeting the polymerase acidic protein (PA) of the influenza virus. This mechanism interferes with viral RNA transcription, preventing the virus from replicating effectively.[19]

In Switzerland, the antivirals oseltamivir (Tamiflu®), baloxavir marboxil (Xofluza®) and zanamivir (Relenza®) are approved for treatment and prophylaxis of influenza A and B. The approval of these antivirals differs in Switzerland with respect to the indicated age groups, the treatment duration, the administration routes and the dosing.[6] Tamiflu® is approved for treatment and prophylaxis in adults and children over one year of age. Xofluza® is approved for treatment of uncomplicated influenza in patients symptomatic for up to 48 hours, including children 1 year and older and healthy adults, as well as adolescents 12 years and older and adults at high risk for influenza-related complications. For prophylaxis Xofluza® is approved in adults and children over one year of age. Relenza® is approved for treatment in adults and children over 7 years old and for prophylaxis in adults and children over 12 years old.[21–23] Relenza® is contraindicated in patients with severe milk protein allergy, and not recommended for people with underlying respiratory disease like asthma and COPD.[19] Currently, none of them is on the list of pharmaceutical specialties ("Spezialitätenliste") reimbursed by the mandatory health insurance in Switzerland. However, case-by-case remuneration is possible, and they may be reimbursed during a pandemic.[4]

Zanamivir (Relenza®) is not considered as an intervention in the present study as its production has been discontinued worldwide, and peramivir (Alpivab®, Rapivab®) is not considered as it is not approved in Switzerland.

The M2 inhibitors amandine (Symmetrel®) and rimantadine (Flumadine®) are not recommended due to high levels of resistance among influenza A viruses while the NAIs laninamivir (Inavir®) is only approved in Japan for the treatment of influenza, and the viral RNA-dependent RNA polymerase inhibitor favipiravir (Avigan®) is only approved in Japan and China.[19,24,25]

Tamiflu® and Xofluza® are available in the form of capsules and as a powder, whereas Relenza® is available as oral inhalation.[21,23,23] For Tamiflu®, the dosage for treatment for adults and children over 12 years is 1 capsule (75mg) twice daily for 5 days. In case of an influenza wave, the recommended oral dose for prophylaxis of influenza after close contact with an influenza-infected person or for persons at risk is 1 capsule (75mg) daily for 10 days for adults and 12-year-old children and older. For children ≤ 12 years old the dose depends on body weight, in both cases.[21] For Relenza®, the dosage for treatment is 2 oral inhalations twice daily (=20 mg/day) for 5 days. In prophylaxis, it is 10mg/day for 10 days and can be pro-longed up to 28 days.[22] For Xofluza®, the dosage is 1 single oral dose of 40 mg or 80 mg capsule or suspension powder, according to body weight.[23]

Antiviral treatment should be taken as early as possible after the onset of symptoms.[6] However, according to guidelines from the World Health Organisation (WHO)[26] and the Swiss Society for Infectious Diseases[27], antiviral drugs should be used sparingly. Preventive use is recommended for exposed healthcare workers and therapeutic use is advised for at-risk individuals and hospitalised patients.[3] Widespread use of antiviral drugs should be avoided to prevent the development of resistant strains.[3] Of note, yearly vaccination is the best method for preventing and mitigating influenza's impact. However, the efficacy can vary by influenza type and subtype.[5] In specific cases, antiviral drugs for pre- or post-exposure prevention can aid in outbreak control in certain populations.[28]

Although approved in Switzerland, zanamivir is not included because its production has been discontinued worldwide.

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 marboxil (Xofluza®)
C:	Baloxavir marboxil (Xofluza®) Placebo Any non-antiviral treatment	Oseltamivir (Tamiflu®) Placebo Any non-antiviral treatment
O:	**Efficacy** Primary Outcomes • Disease-specific and all-cause mortality • Influenza-associated symptoms or complications such as fever, headache, pneumonia, bronchitis, otitis media • Hospitalisation due to influenza symptoms Secondary Outcomes • Time to alleviation of influenza symptoms (TTAS) • Change of antibiotics use during clinical course • Length of hospitalisation • Number of patients with re-consultations with a doctor • Number of onward transmissions to household contacts **Safety:** • Adverse drug reactions • Toxicities	

Table 2 PICO 2: Post-exposure prophylaxis

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

4.1 Population

The 2 populations of interest are persons with influenza A or B or influenza A-, B-like symptoms (PICO 1) and persons receiving prophylactic treatment against influenza (PICO 2). Population subgroups, such as children, the elderly, and people at risk, will be analysed, if possible, based on the information extracted from the included studies (see ***Chapter 6.3.2***).

4.2 Intervention

The 2 interventions of interest are oseltamivir (Tamiflu®) and baloxavir marboxil (Xofluza®), considering any dose. Antiviral combination therapies with the drugs of interest are not considered, as they do not seem to provide additional clinical benefits over monotherapy for the primary outcomes investigated in the studies and there is limited clinical evidence on their safety.[29–36]

4.3 Comparator

These 2 drugs will be compared to each other, placebo and any non-antiviral treatment.

4.4 Outcomes

Outcomes PICO 1

The outcomes that will be considered for patients with influenza A or B or influenza A-, B-like symptoms are the following.

Efficacy:

Primary Outcomes

- Disease-specific and all-cause mortality
- Influenza-associated symptoms or complications such as fever, headache, pneumonia, bronchitis, otitis media
- Hospitalisation due to influenza symptoms

Secondary Outcomes

- Time to alleviation of the influenza symptoms (TTAS)
- Change of antibiotics use during clinical course
- Length of hospitalisation
- Number of patients with re-consultations with a doctor
- Number of onward transmissions to household contacts

Safety:

- Adverse drug reactions
- Toxicities

More outcomes may be considered based on the reported results of the included studies, such as resistance defined as occurrence of drug-resistant mutants. As the rate of mutation and replication of the influenza virus is high, there is a chance that some patients will develop a mutation that is not susceptible to some antiviral drugs. For example, certain mutations change the shape of the binding site of NAIs such that these can no longer attach to exert their effect. Due to this mechanism, the virus can become resistant to one or another type of NAI. The rates of resistance can vary depending on the drug that is used, the virus type and subtype, as well as the population subgroup affected.[37] In Switzerland, the reported number of cases with oseltamivir resistance is very low and refers to hospitalized patients.[38] Populations at risk such as immunocompromised individuals and children are more likely to develop resistance. In case, resistance is not observed in the included studies, this issue will be addressed under “Additional Issues” in the report with a targeted search.[37]

Outcomes PICO 2

The outcomes that will be considered for persons receiving prophylactic treatment against influenza (e.g. healthcare personnel or persons at risk) are the following.

Efficacy:

Primary Outcomes

- Laboratory-confirmed influenza
- Influenza confirmed with rapid diagnostic tests
- Influenza-associated symptoms or complications such as fever, headache, pneumonia, bronchitis, otitis media

Secondary Outcomes

- Length of hospitalisation

Safety:

- Adverse drug reactions
- Toxicities

5. Research questions

5.1 Research questions

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

1. Are oseltamivir and baloxavir marboxil efficacious compared to each other, placebo or any non-antiviral treatment in patients with influenza A or B?
2. Are oseltamivir and baloxavir marboxil safe compared to each other, placebo or any non-antiviral treatment in patients with influenza A or B?
3. Are oseltamivir and baloxavir marboxil efficacious compared to each other, placebo or any non-antiviral treatment in persons receiving prophylactic treatment against influenza?
4. Are oseltamivir and baloxavir marboxil 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 marboxil. Costs, cost-effectiveness, budget impact as well as ethical, legal, social and organizational (ELSO) issues will not be addressed.

6. Methodology

The systematic literature review and meta-analysis related to the clinical efficacy and safety is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[39–41] The methodology consists of a stepwise approach. A systematic literature review of randomised controlled trials (RCTs) will be conducted. If relevant outcomes such as mortality, influenza-associated symptoms or complications and hospitalisation is not covered by RCTs, conducting an additional systematic search for observational studies will be considered.

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 will be conducted in the following databases: Cochrane Library, Embase, Medline, Web of Science, clinicaltrials.gov and WHO International Clinical Trials Registry. The search strategy focuses on the population and intervention components of PICO, while comparators or outcomes are not specified to avoid undue narrowing of the search results. Search limits are applied to include only RCTs on humans. The limits for including observational studies, which will be applied if a second systematic review is conducted, are also shown. No restrictions are 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.[42–53] The detailed search strategy in each database is outlined in ***Appendix 9.1***. To identify additional issues, the international HTA database (INAHTA) and websites of prominent HTA agencies will also be searched. All studies will be imported to Covidence for study selection and data extraction.[54]

6.2 Study selection

The inclusion and exclusion criteria were defined according to the PICO framework and are shown in ***Table 3***. All outcomes will be considered if they are within the domains outlined in the PICO (***Chapter 4***). In addition to the PICO, other antiviral medications are included as a comparator, since they may provide valuable information for a potential network meta-analysis, allowing for indirect comparisons. The country and the setting are not restricted. The study design for the primary systematic literature review is restricted to RCTs. In case a second systematic review is deemed necessary, observational studies will also be included. Studies are 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 must be English, French, German, or Italian. If relevant additional criteria emerge during study selection, this will be documented in the report.

Table 3 Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	Human	Animal
Intervention	• Oseltamivir • Baloxavir marboxil	Any other intervention or combination therapy
Comparator	• Oseltamivir • Baloxavir marboxil • Other antiviral medications, such as zanamivir or peramivir • Placebo • Any non-antiviral treatment	Any other comparator or combination therapy
Outcomes	Efficacy and safety outcomes mentioned in ***Chapter 4***	• No efficacy or safety outcomes • Outcomes only on pharmacokinetics or pharmacodynamics
Study design	RCT[1]	Not RCT
Language	English, French, German or Italian	Not English, French, German or Italian
Country	No restrictions	—
Setting	No restrictions	—
Publication status	Published full text or the essential data could be obtained	Not published full text or the essential data could not be obtained

Abbreviation: RCT: Randomized Controlled Trial

[1]This refers to the primary systematic literature review. If a second will be conducted observational studies will also be included.

In a first step, the studies will be title-and-abstract-screened by 2 reviewers independently according to the inclusion and exclusion criteria. In a second step, 2 reviewers will independently review full texts of studies retained from the first step. Disagreements will be resolved by consensus and if consensus cannot be reached, a third reviewer will be consulted. To increase consistency between reviewers, prior training sessions will be held. A PRISMA flow diagram will be created to illustrate the study selection results and will also include the primary reasons for exclusion.

6.3 Data extraction, analysis and synthesis

6.3.1 Data extraction

Relevant data from the included studies will be extracted by a single reviewer into the Covidence platform[54], which will be pilot-tested with selected studies retained after full-text screening. A second reviewer will perform data checking against the original publication. Disagreements will be resolved by consensus and if consensus cannot be reached, a third reviewer will be consulted. To increase consistency between reviewers, prior training sessions will be held. The Covidence data extraction form will include:

- Study characteristics (country, setting, study period, length of follow-up and source of funding)
- Population (e.g., age and sex structure, diagnosis definition, disease(s), sample size, comorbidities, 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., frequency, intensity and duration of disease, TTAS, risk of mortality and hospitalisation, prolongation of hospitalization, drug-related adverse events, time the outcome was assessed, transmission to household contacts)
- Information relevant to assess the quality of studies (i.e., information to perform the Risk of Bias (RoB), Grading of Recommendations Assessment, Development and Evaluation (GRADE), Confidence in Network Meta-Analysis (CINeMA). The quality assessment itself will be performed outside of Covidence.)
- Additional comments (study limitations or issues which are not identifiable from other extracted data)

Details of ongoing, stopped or unpublished RCTs found in clinical trial registries will be 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

6.3.2 Data analysis and synthesis

The included studies will be presented in a table including information on the study characteristics and relevant outcomes, grouped by relevant patient subpopulations. Risk of bias figures and a CINeMA or GRADE summary table will also be provided (see ***Chapter 6.3.3***).

In a first step, and where possible, separate pairwise meta-analyses will be performed for each PICO to pool the estimates of outcomes with sufficient data from the included studies and the highest relevance for the patients. These are outcomes that are most frequently reported by RCTs and are judged as critical outcomes to quantitatively summarize the estimated efficacy and safety in the included studies. When possible, forest plots will be presented. Meta-analyses will be conducted using the *metafor* command in R.[55]

Continuous data will be pooled using weighted mean differences. Binary data will be pooled using risk ratios as the effect measure.[56] Uncertainty will be expressed using 95% confidence intervals. Furthermore, the prediction interval will be assessed to consider heterogeneity.

If possible, a network meta-analysis will be conducted in a second step to increase precision in the estimations by incorporating direct and indirect evidence and to estimate a rank order of efficacy and safety for the 2 analysed drugs. The *metan* command in R will be used.[57] To conduct a network meta-analysis, it must be ensured that there are no differences between studies in treatment effect modifiers (e.g., age, dose, timing of drug administration, comorbidities) and that the transitivity assumption is likely to hold.[58,59] Transitivity will be evaluated by comparing the distribution of effect modifiers across the different comparisons and by conducting subgroup analyses based on the identified effect modifiers.[58,60] Global and local tests for inconsistency will be conducted and the range of values included in confidence intervals of the incoherence factors will be interpreted.[59] Heterogeneity within direct comparisons and across the network using a random-effects model will be assessed. Tau square will be estimated by the Restricted Maximum Likelihood (REML) method using the *metafor* command in R. Sensitivity analyses to assess the robustness of the findings will be conducted. Studies with extreme values of effect modifiers or those contributing to inconsistencies will be excluded to assess the change of the overall results. An expert statistician will be involved to support the process of the network meta-analysis. The network meta-analysis will be reported according to the PRISMA Extension Statement for reporting systematic reviews incorporating network meta-analyses of health care interventions.[40,41]

If network meta-analyses are not feasible, the comparator will be limited to influenza treatments approved for use in Switzerland. Although approved in Switzerlandzanamivir will not be considered because its production has been discontinued worldwide.If meta-analyses are not feasible, the evidence will be described narratively using the Synthesis Without Meta-analysis (SWiM) guideline.[61]

Subgroup analyses and meta-regression analyses will be performed if deemed appropriate to identify possible effect modifiers. The following subgroup analyses will be considered:

- Age groups (children, adolescents, adults, >65 years)
- High-risk groups (e.g., immunocompetent, immunosuppressed, pregnant women, people with a chronic Illness)
- Virus type
- Mutation
- Type of diagnosis (e.g., influenza symptoms, laboratory-confirmed diagnosis)
- Timing of drug administration (e.g., within 48 hours, post-48 hours of symptoms)
- Exposure (e.g. prophylaxis before and after exposure)
- Dosage

- Frequency of administration
- Setting (e.g., community, inpatient, long-term care, nursing home)

6.3.3 Assessment of quality of evidence

The methodological quality of included RCTs will be critically appraised according to the Cochrane Risk of Bias 2 tool for randomized trials (RoB 2).[62,63] In case observational studies will be considered, they will be appraised according to the Cochrane Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool.[64] If a study adequately addresses the specific risk of bias domain (e.g. adequate generation of random sequence for randomisation), it will be judged as “low risk of bias” in this domain. Description of an inadequate method will be judged as “high risk of bias” and, if incomplete information is given, as “unclear risk of bias”. The assessment will be performed in duplicate and inconsistencies will be solved by consensus. Where consensus cannot be found, a third reviewer will be consulted.

Bias due to missing evidence will be assessed using the Risk of Bias due to Missing Evidence tool in a meta-analysis (ROB-ME) or in a network meta-analysis (ROB-MEN).[65,66] The effect of small sample sizes will be estimated using Egger’s test and funnel plots.[39,67–69]

To obtain an overall rating of confidence in the estimated effects, the GRADE approach will be applied and the confidence in the meta-analysis results will be rated in duplicate.[70] The GRADE evidence table will be derived using the online tool.[71] Inconsistencies will be solved by consensus. Where consensus cannot be found, a third reviewer will be consulted. If a network meta-analysis will also be conducted, the CINeMA approach will be applied instead of GRADE.[72] The online software at cinema.ispm.unibe.ch will be used to generate the contribution matrix and rate the confidence in the results of the network meta-analysis.[73]

7. Summary and Outlook

7.1 Summary

To inform pandemic stockpiling decisions, a clinical evidence synthesis evaluating the efficacy and safety of oseltamivir (Tamiflu®) and baloxavir marboxil (Xofluza®) compared to each other, placebo or any non-antiviral treatment in patients with influenza A or B, influenza A-, B-like symptoms or persons receiving prophylactic treatment against influenza will be conducted.

The methodology consists of a systematic literature review of RCTs. If relevant information is not covered by RCTs, an additional systematic search for observational studies may be conducted. The searches will be conducted in 6 data sources and studies will be selected based on predefined inclusion and exclusion criteria. The methodological quality of the included studies will be critically appraised, and the relevant information will be extracted. The certainty of the evidence for relevant outcomes will be assessed with GRADE or CINeMA. Pairwise meta-analysis will be performed and,

if possible, a network meta-analysis will be added. Meta-regressions, subgroup and sensitivity analyses will also be performed where possible.

One of the primary challenges in synthesizing clinical evidence in this field is the volume of available data, including ongoing, discontinued, or unpublished RCTs, which are crucial for addressing potential publication bias.[43] However, the number of trials directly comparing oseltamivir with baloxavir marboxil is unclear, necessitating a broader definition of the comparator group should a network meta-analysis be feasible. Another challenge arises from the high heterogeneity across studies, particularly in terms of patient populations and assessed outcomes. This heterogeneity is compounded by inconsistent definitions of outcomes and variations in the units used to report them, making meta-analyses and subgroup analyses particularly difficult. Lastly, while high-risk individuals and the elderly are the most relevant populations, the majority of studies seem to primarily focus on otherwise healthy adults, which could limit the generalizability of findings to more vulnerable groups.

7.2 Outlook

The protocol is followed by the production of a report. The objective of the report is to generate a focused assessment of various aspects of the health technology in question. The applied analytic methods, their execution and the results are described. The analytical process is comparative, systematic, and transparent. The external review group that was consulted during the protocol phase is consulted again during the report phase. Subsequently, the report draft is presented to the stakeholders for consultation. Communication with the reviewers and the stakeholders is coordinated by the FOPH.

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9. Appendix

9.1 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.

[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 Protocols, Reviews and 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.