# Influenza Therapeutics: Evaluating the Benefits and Harms of Oseltamivir and Corticosteroids

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**Abstract**

***Background:*** Influenza infections result in a heavy burden of disease with every seasonal epidemic, and to a greater extent, during any pandemic. Fortunately, several therapeutics are available to help mitigate severe clinical outcomes. Oseltamivir (Tamiflu®) is the predominant antiviral prescribed by many healthcare providers and is recommended in several treatment guidelines. Yet, the supporting evidence is largely observational, with studies showing conflicting results, and most suffering from considerable bias. One other therapeutic for hospitalized patients gaining popularity is systemic corticosteroids. Having recently been shown to reduce mortality in severe COVID-19 cases, it is possible a similar effect could be observed with influenza. However, the existing influenza literature consists solely of limited observational data that is subject to substantial confounding by indication and conflicting results.

***Objectives:*** The primary goal of my thesis was to produce a robust body of evidence on oseltamivir, (for both outpatients and hospitalized individuals), as well as corticosteroids, (only for inpatients), with respect to two important clinical outcomes: hospitalization and inpatient mortality. I also aimed to highlight any knowledge gaps in the published literature. As such, I first intended to conduct a systematic review and meta-analysis on the risk of hospitalization for outpatients treated with oseltamivir. Second, I then aimed to review the evidence on the effect of oseltamivir and corticosteroids on inpatient mortality. Finally, based on those findings, my third objective was to design an inpatient study that addressed any gaps I identified.

***Methods and Results:*** *Objective #1 - Oseltamivir to Prevent Hospitalization in Outpatients*. I performed a systematic review and meta-analysis that included 15 randomized controlled trials (RCTs) (N=6295 patients). Overall, oseltamivir did not reduce the risk of hospitalization compared to placebo [risk ratio (RR): 0.77 (95% confidence interval (CI): 0.47 to 1.27)] even amongst high-risk individuals (RR: 0.90, 95% CI: 0.37 to 2.17). *Objective #2 - Oseltamivir and Corticosteroids to Prevent Mortality in Hospitalized Patients*. I conducted a rapid review and meta-analysis involving 32 studies (N=5774 patients). Oseltamivir had a lower in-hospital [pooled proportion (PP): 6.9% (95% CI: 3.2 to 13.9%) and 30-day mortality (PP: 3.1%, 95% CI: 1.6 to 6.0%) than corticosteroids, (in-hospital PP: 41.9%, 95% CI: 32.9 to 51.5%, 30-day PP: N/A), but had non-significant effects versus standard of care (in-hospital RR: 0.71, 95% CI: 0.34

to 1.47, 30-day RR: 0.45, 95% CI: 0.04 to 5.72). However, no definitive conclusions could be made due to the limited number of steroid studies (4) and the absence of placebo-controlled RCTs for either treatment. *Objective #3 - Designing a Trial to Assess the Safety & Efficacy of Oseltamivir and Dexamethasone*. Based on the gaps identified by the prior review, I designed an adequately powered, placebo-controlled RCT protocol that will evaluate the efficacies of oseltamivir and dexamethasone against inpatient mortality.

***Discussion:*** With the conclusion of my research, I achieved each of my objectives and subsequently contributed to advancing the field of influenza therapeutics. My first systematic review demonstrated that oseltamivir provides no meaningful benefit against hospitalization with the most extensive and up-to-date estimate. Similarly, my review on the efficacy of oseltamivir and corticosteroids on inpatient mortality was, to my knowledge, the first attempt to synthesize the literature. Through this process I discovered the urgent unmet need for an inpatient RCT to evaluate these treatments. As a result, I also designed the first placebo-controlled trial adequately powered on mortality with respect to either drug. Altogether, the outpatient evidence base I created via my systematic review may cause treatment guidelines to change, which in turn will enhance the therapeutic strategies of healthcare providers and improve patient care. Furthermore, the eventual results of my inpatient RCT may change practice as well by establishing the benefits and/or harms of both treatments across different inpatient populations.

**Résumé**

***Contexte:*** Les infections grippales entraînent une lourde charge de morbidité lors de chaque épidémie saisonnière et, dans une plus large mesure, lors de toute pandémie. Heureusement, plusieurs médicaments sont disponibles pour aider à atténuer les résultats cliniques graves. L'oséltamivir (Tamiflu®) est l'antiviral prédominant prescrit par de nombreux prestataires de soins de santé et est recommandé dans plusieurs directives de traitement. Pourtant, les preuves à l'appui sont largement basées sur des études observationnelles qui montrent des résultats contradictoires et dont la plupart souffrent d'un biais considérable. Les corticostéroïdes systémiques sont une autre thérapie pour les patients hospitalisés qui gagnent en popularité. Comme il a été récemment démontré qu'ils réduisaient la mortalité dans les cas graves de COVID-19, il est possible qu'un effet semblable puisse être observé pour la grippe. Cependant, les écrits scientifiques sur la grippe comprennent uniquement des données d'observation limitées, qui sont également sujettes à une confusion importante par indication et à des résultats contradictoires.

***Objectifs :*** L'objectif principal de ma thèse était de produire un ensemble de preuves solides sur l'oséltamivir (pour les patients ambulatoires et les personnes hospitalisées), ainsi que sur les corticostéroïdes (uniquement pour les patients hospitalisés), en ce qui concerne deux résultats cliniques importants : l'hospitalisation et la mortalité des patients hospitalisés. J'ai également cherché à mettre en évidence toute lacune dans les connaissances de la littérature publiée. Ainsi, j'ai d'abord eu l'intention de mener une revue systématique et une méta-analyse sur le risque d'hospitalisation des patients externes traités à l'oséltamivir. Ensuite, j'ai voulu examiner les preuves de l'effet de l'oséltamivir et des corticostéroïdes sur la mortalité des patients hospitalisés. Enfin, sur la base de ces résultats, mon troisième objectif était de concevoir une étude sur les patients hospitalisés afin de combler les lacunes que j'avais identifiées.

***Méthodes et résultats:*** Objectif 1 - L'oséltamivir pour prévenir l'hospitalisation chez les patients externes. J'ai effectué un examen systématique et une méta-analyse comprenant 15 essais contrôlés randomisés (ECR) (N=6295 patients). Dans l'ensemble, l'oséltamivir n'a pas réduit le risque d'hospitalisation par rapport au placebo [rapport de risque (RR) : 0,77 (intervalle de confiance (IC) de 95 % : 0,47 à 1,27)], même chez les personnes à haut risque (RR : 0,90, IC de

95 % : 0,37 à 2,17). Objectif n° 2 - Oséltamivir et corticostéroïdes pour prévenir la mortalité chez les patients hospitalisés. J'ai effectué un examen systématique informel et une méta-analyse portant sur 32 études (N=5774 patients). L'oséltamivir avait un taux de mortalité à l'hôpital (proportion groupée (PP) : 6,9% (IC 95% : 3,2 à 13,9%) et à 30 jours (PP : 3,1%, IC 95% : 1,6 à 6,0%) inférieur à celui des corticostéroïdes (PP à l'hôpital : 41. 9 %, IC 95 % : 32,9 à 51,5 %, PP à 30 jours : N/A), mais avaient des effets non significatifs par rapport aux soins standard (RR à l'hôpital : 0,71, IC 95 % : 0,34 à 1,47, RR à 30 jours : 0,45, IC 95 % : 0,04 à 5,72). Toutefois, aucune conclusion définitive n'a pu être tirée en raison du nombre limité d'études sur les stéroïdes (4) et de l'absence d'ECR contrôlés par placebo pour l'un ou l'autre des traitements. Objectif n° 3 - Concevoir un essai pour évaluer l'innocuité et l'efficacité de l'oséltamivir et de la dexaméthasone. Sur la base des lacunes identifiées par l'examen préalable, j'ai conçu un protocole d'ECR adéquatement alimenté et contrôlé par placebo qui évaluera les avantages de l'oséltamivir et de la dexaméthasone contre la mortalité des patients hospitalisés.

***Discussion :*** Avec la conclusion de ma recherche, j'ai atteint chacun de mes objectifs et j'ai ensuite contribué à faire avancer le domaine de la thérapeutique de la grippe. Ma première revue systématique a montré que l'oséltamivir n'apporte aucun bénéfice significatif contre l'hospitalisation avec l'estimation la plus extensive et la plus récente. De même, mon examen de l'efficacité de l'oséltamivir et des corticostéroïdes sur la mortalité des patients hospitalisés a été, à ma connaissance, la première tentative de synthèse de la littérature. Ce processus m'a permis de découvrir le besoin urgent et non satisfait d'un ECR sur les patients hospitalisés pour évaluer l'efficacité réelle de ces traitements. En conséquence, j'ai également conçu le premier essai contrôlé par placebo ayant une puissance adéquate sur la mortalité pour l'un ou l'autre des médicaments. Dans l'ensemble, la base de données probantes sur les patients externes que j'ai créée par le biais de mon examen systématique pourrait faire évoluer les directives de traitement, ce qui, à son tour, renforcerait les stratégies thérapeutiques des prestataires de soins de santé et améliorerait les soins aux patients. En outre, les résultats éventuels de mon ECR sur les patients hospitalisés pourraient également modifier la pratique, car l'étude établira les avantages et/ou les inconvénients des deux traitements pour différents groupes de patients hospitalisés à risque.

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**Author Contributions**

Regarding the overall thesis, my contributions were drafting and revising the main manuscript, conducting the search, screening, data extraction and analyses for the literature review incorporated in chapter three, and conducting adequate research to write the informative and referenced introduction and discussion. Dr. Emily G. McDonald and Dr. Todd C. Lee both reviewed the overall document and provided guidance regarding structuring of the manuscript.

**Manuscript 1:** Dr. Lee, Dr. McDonald and I conceptualized the systematic review and meta-analysis. Émilie-Bortolussi-Courval and I identified and selected the studies, collected the data, and assessed the certainty of evidence and risk of bias. I analyzed and synthesized the data independently. Émilie-Bortolussi-Courval, Dr. Arielle Mendel, Dr. Brian Ward, Dr. Lee and Dr. McDonald all provided advice for the manuscript. I drafted the manuscript with input from Emile-Bortolussi-Courval, Dr. Lee, and Dr. McDonald. All authors helped review and edit the manuscript and approved the submitted version.

**Manuscript 2:** Dr. Lee, Dr. McDonald and I conceptualized the protocol. I drafted the primary version of the manuscript. All three individuals helped review and edit the protocol as well as approved the final version.

**Abbreviations**

95% CI = 95% confidence interval

ARDS = acute respiratory distress syndrome

AMMI = Association of Medical Microbiologists and Infectious Diseases

CDC = Centers for Disease Control and Prevention

COVID-19 = coronavirus disease of 2019

ICU = intensive care unit

OR = odds ratio

PP = pooled proportion

RCT = randomized controlled trial

RR = risk ratio

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## Chapter 1. Introduction

*Influenza Background*

Influenza viruses (commonly referred to as 'the flu'), are segmented, negative sense, single-stranded RNA viruses belonging to the *Orthomyxoviridae* family.[1] Composed of 4 types (A, B, C and D), influenza strains are categorized according to their core proteins, with type A strains being further subtyped based on their major surface glycoproteins: hemagglutinin and neuraminidase.[2] Yet, types A and B are the only strains with clinical importance given their causative role in the seasonal epidemics (A and B) and pandemics (A) that occur.[3]

After being first reported in 1510, influenza became an important public health issue in the modern era after the 1918 global pandemic.[4] Prompted by the pandemic's tragically high morbidity, the virus has become a predominant healthcare concern with billions of influenza infections subsequently recorded. Detected in all regions of the world, the disease particularly affects those considered most at risk, including pregnant individuals, those with comorbidities, people over the age of 65, and children less than 5 years old.[5] Most patients present with one or more of the following symptoms: fever, cough, muscle aches and pains, headache, chills, loss of appetite, fatigue, sore throat, runny or stuffy nose, diarrhea, nausea, or vomiting.[6] However, infections typically self-resolve in 5-7 days with supportive care.[7]

*Health and Economic Impact*

In total, it is estimated influenza annually infects 1 billion individuals worldwide, and causes an estimated 9-41 million illnesses in the United States.[8,9] While many individuals recover without difficulty, a substantial proportion of those infected require urgent care visits or hospitalization. In fact, roughly 12,200 Canadians get admitted for influenza-related illnesses every year.[8] Once again, although most patients fully recuperate, a substantial mortality still exists, evidenced by the approximately 3500 deaths in Canada annually associated with influenza.[8] Not only does the significant disease burden lead to massive loss of life and impairment, but it also negatively influences economic output as well. For instance, direct expenses like emergency department visits and hospitalizations cost the United States healthcare system $3.2 billion in 2015.[10]

Meanwhile, indirect costs stemming from lost earnings due to death or short term work absences were associated with another estimated $8.0 billion in losses.[10]

Startlingly, each of these calculations pertain only to seasonal influenza epidemics. Pandemics, such as the one most recently experienced in 2009 (the H1N1 pandemic), increases these amounts exponentially. Unfortunately, institutions around the globe are currently expected to have difficulty handling any additional burden following the near collapse of healthcare systems and economic recessions due to the COVID-19 pandemic. With a globally projected 62 million deaths and $500 billion in annual losses should the emergence of a 1918-like influenza virus occur, having the right tools, which includes safe and effective therapeutics, in place could substantially mitigate any impact.[11,12] Thus, effective treatments to deal with seasonal influenza and any future pandemic are of extreme importance to healthcare providers, public health experts, policy makers, and most importantly, patients.

*Treatments Overview*

As of now, four main categories of influenza therapeutics exist. The first and oldest class is adamantane antivirals (amantadine and rimantadine), which disrupt the viral wall to prevent viral replication.[13,14] Once a common choice of treatment, the drugs are now rarely recommended due to high circulating levels of viral resistance.[14] The second and more current option, neuraminidase inhibitor antivirals, are regularly prescribed both to treat symptoms and reduce the risk of complications. Approved by a majority of national regulatory agencies, oseltamivir (Tamiflu®), zanamivir (Relenza®) and peramivir (Rapivab®) have become the primary treatments in most markets. Other antivirals with different mechanisms of action like baloxivir (Xofluza®) and favipiravir (Avigan®) do exist, but are not widely used within North America. A third category of treatment includes monoclonal antibodies. Still progressing through trial stages, experimental candidates have been observed to safely reduce viral loads and potentially yield better clinical outcomes (i.e. mortality and hospitalization) as seen in COVID-19 patients.[15,16] Despite their promise, issues based on their substantial cost, complexity of administration, and lack of robustness to viral variants need to be resolved before they could become a practical future option.[17,18] Finally, the fourth, yet potentially most understudied option in severe disease, are anti-inflammatory medications like systemic corticosteroids. After demonstrating an ability

to reduce in-hospital complications and inpatient mortality in several COVID-19 studies, corticosteroids have been re-envisioned as a potential influenza treatment.[19,20]

Of the available treatment options which may have the largest global impact, systemic corticosteroids and oseltamivir stand out as the optimal choices due to their relatively low price, excellent safety profiles, oral formulations, and worldwide availability. As a result, these two treatments were the focus of the research contained in my thesis and I will examine them in further detail in the subsequent paragraphs.

*Select Treatments*

*Oseltamivir*

First created in 1996 and brought to market by Roche Pharmaceuticals, oseltamivir (Tamiflu®) has risen to become the predominant influenza antiviral in all clinical settings. Proven to reduce the proportion of symptomatic influenza, time to first alleviation of symptoms, and respiratory complications in high-risk patients, oseltamivir provides both prophylactic and therapeutic benefits.[21,22] Consequently, the drug is available in over 100 countries and has 2.5-3 million courses annually prescribed in the United States.[23,24] Costing an average of $70-80 USD for a routine 5-day course, Roche earned $537 million from oseltamivir in 2017, and grossed an additional $9 billion in sales from agreements to supply doses for the pandemic stockpiles of 95 countries.[25,26]

One driving factor behind oseltamivir's significant uptake may be a result of its inclusion in community treatment guidelines authored by the Association of Medical Microbiologists and Infectious Diseases (AMMI) and the Centers for Disease Control and Prevention (CDC).[27,28] Their assertion that oseltamivir reduces symptom duration and probably decreases both the risk of hospitalization and mortality has likely led many healthcare providers to prescribe oseltamivir as a first line therapy. However, some experts have recently questioned the validity of the underlying evidence and have raised some uncertainty on whether widespread use of oseltamivir is warranted. Most notably, the 2014 study by Jefferson et al. claimed the initial series of oseltamivir trials funded by Roche as part of the drug's clinical development suffered from a high risk of selective reporting bias, ghost authorship (e.g. redacted names and no claims of

authorship), and poor methodology (e.g. missing statistical analysis plans and randomization codes).[29] In fact, based on the evidence uncovered, Roche was then served with a 1.5 billion dollar lawsuit alleging they made false claims about oseltamivir's efficacy in their sale of 50 million courses to the United States.[30] Considering oseltamivir continues to remain a favored influenza medication and the one to which new drugs are compared, I first set out to reexamine the evidence to conclusively determine if the efficacy data objectively supports its usage.

*Corticosteroids*

Corticosteroids are a class of synthetic adrenal steroid hormones that reduce inflammation by repressing multiple pro-inflammatory genes, generally through signal transduction by their steroid receptors.[31] Consequently, within a clinical context, corticosteroids are commonly used to treat autoimmune conditions, chronic and acute exacerbations of some inflammatory lung diseases such as asthma and chronic obstructive pulmonary disease, and as replacement therapy for adrenal insufficiency.[32] More recently, they have begun to be utilized as treatments for several severe pulmonary inflammatory conditions due to their efficacy in decreasing inpatient mortality. For instance, compared to non-active comparator controls, corticosteroids reduced all-cause 30-day mortality in patients with community-acquired pneumonia [odds ratio (OR): 0.63, 95% CI: 0.42-0.95], early acute respiratory distress syndrome (ARDS) (OR: 0.61, 95% CI: 0.44-0.85), and COVID-19 infections (OR: 0.66, 95% CI: 0.53-0.82).[33-35]

Acknowledging the similar pathologies between these conditions and severe influenza infections, it is possible that corticosteroids could provide benefit to the sickest influenza patients. However, with respect to influenza, steroids have primarily been given to select patients rather than as a routine treatment for all severe cases. This hesitancy stems from deep-rooted debate as to whether steroids yield benefit or harm. Conflicting evidence suggests they could either improve lung inflammation and decrease mortality, or delay viral clearance and increase mortality instead.[36,37] In fact, the earliest guidelines for COVID-19 recommended against steroids on the basis of observational studies in severe influenza. However, once randomized controlled trials were conducted, it was discovered that steroids decreased all-cause mortality in COVID-19.[35] As a result, I proposed to employ part of my thesis to determine whether the mortality benefit of

corticosteroids might also translate to influenza. If so, steroids could become an important treatment strategy in providing optimal care to hospitalized patients.

*Problems with the Existing Literature*

Unfortunately, much of the literature pertaining to the usage of oseltamivir and corticosteroids for influenza patients is insufficient due to two key problems. First, previous studies have reached conflicting conclusions regarding the effect of oseltamivir on hospitalization as well as the efficacy it and steroids have against inpatient mortality. While systematic reviews normally resolve this problem by synthesizing the literature, none have been conducted on oseltamivir or corticosteroids (without antiviral co-treatment) versus inpatient mortality. In addition, although some reviews have examined the effect of oseltamivir on hospitalization, these too suffer from conflicting conclusions and do not provide definitive estimates. Second, there is also a lack of high quality randomized controlled trials for oseltamivir and corticosteroids with respect to inpatient mortality. Not one RCT exists that evaluates corticosteroids and only 8 investigate oseltamivir, none of which utilize placebo as a control. Of those 8, one study incorporates standard of care as a comparator, but only includes 74 patients confirmed to have influenza and reports a total of 2 deaths, significantly limiting the power of any estimate.[38]

Yet, the COVID-19 pandemic has demonstrated that we are capable of generating robust evidence on the benefits of therapeutics and that the prevention of outpatient hospitalization and/or inpatient mortality are realistic research and therapeutic goals. Considering that hospitalization and mortality are also considered key targets in the effort to reduce influenza's disease burden, properly conducted placebo controlled RCTs are needed. In their absence, rigorously executed systematic reviews and meta-analyses could provide some much needed evidence for or against certain treatments. For that reason, my thesis addresses 1) the existing evidence base for corticosteroids and oseltamivir for the treatment of influenza, and 2) serves as the foundation for a proposed RCT, which I have designed.

*Thesis Objectives*

Altogether, given the insufficient and inadequate evidence on oseltamivir and corticosteroids plus the uninformed prescribing behaviors subsequently caused, the goal of my thesis was to

produce conclusive studies that help identify optimal influenza treatment strategies. More specifically, I sought to determine whether the clinical efficacy of oseltamivir justifies its prevalent usage for both outpatients and hospitalized individuals, as well as to establish if corticosteroids could serve as a more effective successor in select inpatient populations. These findings would not only advance the academic field, but have immense real-world implications considering the health and economic ramifications of influenza.

Therefore, my thesis research had three specific objectives. With respect to my first manuscript, I sought to determine whether oseltamivir reduces the risk of hospitalization as an outpatient treatment by synthesizing the respective literature in a systematic review and meta-analysis. Second, I planned to conduct another, yet rapid, review on the efficacies of oseltamivir and corticosteroids against inpatient mortality to discover any gaps or issues within the existing literature. Finally, based on my findings, I then aimed to design a study that addressed these problems in the form of my second manuscript.

## Chapter 2. Oseltamivir to prevent hospitalization in outpatients with influenza: a systematic review and meta-analysis

### Preamble to Manuscript One

My research began by conducting a systematic review and meta-analysis on all placebo-controlled randomized trials of influenza-infected outpatients treated with oseltamivir. The aim was to report the relative risk of hospitalization and adverse events to better inform the prescription behaviors of healthcare providers and the creation of treatment guidelines by policy makers. This would be accomplished by reviewing and synthesizing a literature base currently comprised of conflicting conclusions at both the study and review level.

Three systematic reviews (published in 2003, 2014, and 2015), have previously addressed the impact of oseltamivir on the risk of hospitalization but are subject to several limitations.[29,39,40] All three relied solely on studies from the controversial Roche oseltamivir trial programme and none included the multiple large, independent RCTs that were conducted after 2014. In addition, the first and third reviews which provided more optimistic conclusions had funding connections to Roche which could be a source of bias. Thus, I believed an updated systematic review and meta-analysis, independent from any industry sponsor, was needed to address these major limitations and conclusively determine whether oseltamivir is likely to have a clinically significant effect on the risk of hospitalization in outpatients with influenza.

Wanting to present this manuscript as the final analysis needed regarding the efficacy of oseltamivir, I sought to generate incontrovertible evidence by applying the highest scientific standards and methodology. Therefore, RCTs were specifically chosen as an inclusion criteria in order to generate pooled estimates that included only the highest quality of evidence. Since observational studies suffer from substantial risks of biases, they were excluded to prevent my findings from being constrained by those limitations.[41] In particular, RCTs minimize the distortion of effect sizes by avoiding 1) immortal time bias where the receipt of drugs in observational datasets is associated with a period of time where those patients could not be admitted to hospital, 2) residual confounding where observational datasets are not granular enough to account for comorbidity or demographic differences, and 3) confounding by indication

where differences in how the patient appeared to the physician could impact the decision to prescribe the drug. Similarly, the review was also restricted to populations over the age of 12 with confirmed influenza to minimize uncertainty based on heterogeneous populations or other possible respiratory infections.

The systematic review and meta-analysis was submitted to the Journal of the American Medical Association (JAMA): Internal Medicine on July 15, 2022, resubmitted with revisions on December 1, 2022, and is now currently under final review. The protocol was also registered before any searches or analyses began on PROSPERO, the international prospective register of systematic reviews (CRD42022299030).[42] This was done to ensure transparency of my results by providing a prespecified protocol for comparison and to communicate my intention so that no duplicate reviews were conducted before mine was publicized.

**Title Page**

# Oseltamivir to prevent hospitalization in outpatients with influenza: a systematic review and meta-analysis

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**Key Points**

**Question:** Does the administration of oseltamivir to adult and adolescent outpatients with confirmed influenza reduce the risk of first hospitalization?

**Findings:** In this systematic review and meta-analysis of randomized controlled trials, oseltamivir did not reduce the risk of first hospitalization compared to placebo or standard-of-care. Results were similar in a subgroup of patients considered at high-risk of hospitalization; however, the confidence intervals were wide.

**Meaning:** An adequately powered trial in a suitably high risk population is needed to determine who might benefit from early treatment with oseltamivir to prevent hospitalization.

**Abstract**

**Importance:** Despite widespread use, summary evidence from prior meta-analyses has contradictory conclusions regarding whether oseltamivir decreases the risk of hospitalization when given to outpatients. Several large investigator-initiated randomized controlled trials have not yet been meta-analyzed.

**Objective:** To determine the efficacy and safety of oseltamivir in preventing hospitalization among influenza-infected adult and adolescent outpatients

**Data Sources:** PubMed, Ovid Medline, Embase, Europe PMC, Web of Science, Cochrane CENTRAL, clinicaltrials.gov and trialsearch.who.int were searched from inception to January 4, 2022.

**Study Selection:** Included studies were randomized controlled trials comparing oseltamivir versus placebo or non-active controls in outpatients with confirmed influenza infection.

**Data Extraction:** PRISMA guidelines were followed. Two independent reviewers extracted data and assessed risk of bias using the Cochrane Risk of Bias Tool 2.0. Each effect size was pooled using a restricted maximum-likelihood random effects model. Quality of evidence was graded using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.

**Main Outcome Measures:** Hospitalization was pooled as risk ratio (RR) and risk difference (RD) estimates with 95% confidence intervals (CIs).

**Results:** Of 2352 studies identified, 15 were included. The intention-to-treat infected (ITTi) population was comprised of 6295 individuals, with 54.7% prescribed oseltamivir. Across study populations, 54.5% were female and the mean age was 44.1. Overall, oseltamivir did not reduce the risk of hospitalization within the ITTi population [RR: 0.77 (95% CI: 0.47 to 1.27), RD: -0.14% (95% CI: -0.32% to 0.16%)]. Oseltamivir also did not reduce hospitalization in older populations (mean age ≥65: RR: 0.99, 95% CI: 0.19 to 5.13) or in patients considered at greater

risk of hospitalization (RR: 0.90, 95% CI: 0.37 to 2.17). Within the safety population, oseltamivir increased nausea (RR: 1.43 95% CI: 1.13 to 1.82) and vomiting (RR: 1.83, 95% CI: 1.28 to 2.63), but not serious adverse events (RR: 0.71. 95% CI: 0.46 to 1.08).

**Conclusions and Relevance:** Among influenza-infected outpatients, oseltamivir did not reduce the risk of hospitalization but significantly increased gastrointestinal adverse events. To justify continued use, future trials should aim to identify specific high-risk population(s) that may benefit.

**Introduction:**

Prior to COVID-19, influenza was one of the most clinically burdensome respiratory viruses.[1] The U.S. Centers for Disease Control and Prevention estimated 29 million cases, 380,000 hospitalizations, and 28,000 deaths from influenza in the United States during the 2018-2019 season.[2] While COVID-19 led to a temporary reduction in infections, influenza is now expected to have a resurgence.[3] Novel strains or a rise in a relatively less immune population could trigger an influenza pandemic resembling the crises experienced in 1968 or 2009.[4] As such, the availability of safe and effective treatments is critical to avoid overwhelming healthcare systems and to reduce morbidity and mortality. Indeed, a breakthrough in the COVID-19 pandemic occurred when randomized controlled treatment trials demonstrated reductions in hospitalization and death.[5] In contrast, despite the significant threat that influenza poses, there are no evidence-based outpatient treatments proven to prevent the progression to hospitalization.

Oseltamivir (Tamiflu) is an antiviral that is commonly prescribed to accelerate recovery and prevent complications. Detailing by key opinion leaders, guideline panels, and the manufacturer has even led to stockpiling of the drug as part of national pandemic responses.[6] Yet, despite guideline recommendations,[7,8] and millions of doses prescribed, it is unclear whether oseltamivir reduces severe complications requiring hospitalization. Three prior systematic reviews (one independent and two supported by the manufacturer) have arrived at different conclusions.[9-11] Since these publications, several large randomized controlled trials (RCTs) have been completed and have yet to be meta-analyzed.[12-15] We therefore sought to clarify whether oseltamivir is a high value medical treatment (achieving optimal results for patients balanced with an efficient use of resources).[16] To do so, we conducted a systematic review and meta-analysis of RCTs of oseltamivir for the prevention of first hospitalization in adolescent and adult outpatients (effectiveness) and of treatment-associated adverse events (safety).

**Methods:**

The protocol was prospectively registered on PROSPERO (CRD42022299030).[17] Findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18]

*Search Methods*

We searched PubMed, Ovid Medline, Embase, Europe PMC, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL), as well as clinicaltrials.gov and trialsearch.who.int (**Supplemental Table 1**) from inception to January 4, 2022. The central search strategy consisted of MeSH terms and keywords corresponding to the subjects of influenza, randomized controlled trials, and oseltamivir. This was then adapted to meet each database- or registry-specific terminology. Bibliographies of included articles and relevant systematic reviews were hand searched. Unpublished Roche-sponsored clinical study reports (CSRs) were obtained from the British Medical Journal's open database for oseltamivir.[19] No language restrictions, filters, or limits were applied.

*Selection Criteria*

Published and unpublished RCTs were included in this review. Observational studies were excluded. Each included trial compared oseltamivir at the recommended oral dosage of 75 mg twice daily for 5 days versus a non-active control equivalent (placebo or standard of care) and reported the outcome of hospitalization. Only the first hospitalization was considered, readmissions were not counted. Study populations included outpatients 12 years of age and older diagnosed with natural influenza infections based on clinical history and laboratory evidence. Most often this was by viral culture or PCR; however, in Roche sponsored-studies, infection could also be established by a 4-fold rise in antibody titers at day 30.

*Study Selection and Extraction*

Search results were imported to EndNote version 9.3.3 (EndNote, United States) and duplicates were removed. Unique studies were uploaded to Rayyan and two reviewers (RH & ÉBC) independently screened all titles and abstracts and removed clearly irrelevant results, selected eligible studies from full text review, and recorded reasons for exclusion. The same reviewers then independently extracted the data from included studies using a pre-established data extraction table in Microsoft Excel. Disagreements were resolved by consensus with a third reviewer (TCL).

*Outcomes and Data Items*

Extracted study characteristics included the year, number of participants, method of confirming influenza, follow-up duration, and study sponsor. Relevant participant demographics were extracted (e.g., race/ethnicity, sex, influenza A or B). Missing study demographics were assumed to be unavailable.

The primary efficacy outcome was the number of first all-cause hospitalizations per treatment arm in the intention-to-treat infected (ITTi) population; individuals confirmed to have influenza according to the study definition. Hospitalization was defined as the first admission to a hospital or healthcare center during the treatment or follow-up period, for any cause and any duration. Emergency room visits with direct discharge home were excluded. When this was not specifically reported in the ITTi population, we made up to 8 email data requests to the senior and/or corresponding author. The British Medical Journal database contains unpublished Roche CSRs.[19] Within these we identified hospitalized patients from the serious adverse event narratives and cross-referenced their participant identification numbers to the study's diagnostic results to confirm their case positivity.

The primary safety outcome was the rate of any adverse event, regardless of grade, and included nausea, vomiting, diarrhea, cardiac, psychiatric, neurologic, and a composite of any gastrointestinal symptom (e.g., nausea, diarrhea, gastritis etc.) Non-industry studies either had thresholds for reporting neurological side effects or did not report these at all; Roche CSRs recorded neurological side effects (severe and non-severe), but excluded headache and fatigue if these occurred during the five days of treatment and were accompanied by one or more additional typical symptoms of influenza (e.g., myalgias). In addition, total serious adverse events (as defined by the studies) were analyzed separately whenever possible (based on reporting). Adverse events were measured within the safety population; all randomized patients who received at least one treatment dose.

*Risk of Bias*

The risk of bias for each study was assessed by two independent reviewers (RH & ÉBC) using the Cochrane risk of bias tool 2.0.[20] Disagreements were settled by consensus and assessments were rendered by robvis.[21]

*Statistical Analyses*

Under the Cochrane handbook's assumption that some heterogeneity is inevitable, a restricted maximum-likelihood (REML) random effects model was utilized for the meta-analyses using the meta command in Stata version 17.0 (StataCorp, USA).[22] Hospitalization was summarized as a risk ratio (RR) with 95% confidence intervals (95% CI). A continuity correction of 0.5 was used for cells with zero events. Using the *metaprop_one* module, we estimated the control event rate using a generalized linear mixed model (GLMM) to pool the control event rate across studies. We multiplied the pooled control event rate by (1-risk ratio) and its 95% CIs to estimate the absolute risk difference (RD) with 95% CIs. Common adverse event types were meta-analyzed using a REML random effects model and were reported on the RR and RD scales and if statistically significant, the number-needed-to-harm (NNH) was reported.[22] Statistical heterogeneity was examined with the $I^2$ test whereby a value greater than 50% was considered significant heterogeneity.[23]

Several secondary analyses were conducted for the outcome of hospitalization on the RR scale. First, to explore potential causes of heterogeneity, pre-specified subgroup analyses were performed based on each study's: mean population age (≥ 65 years vs. < 65 years); the method of confirming influenza (PCR, viral culture, or rapid antigen); population risk level [high-risk (defined as populations with a mean age ≥ 65 **or** comprised solely of patients with high-risk factors like chronic illnesses) vs not]; and trial sponsor (Roche vs other). A subgroup analysis was also conducted based on study quality with studies grouped as either low or at greater than low risk of bias. Finally, for hospitalization, we performed a remove-one meta-analysis to ensure no singular study significantly influenced the pooled estimate and a cumulative meta-analysis to investigate change in efficacy over time.

Finally, since Roche studies confirmed influenza infections via viral culture as well as a fourfold or greater increase in antibody titer, and given prior studies have found oseltamivir reduces the odds of a four-fold antibody rise by almost 20%, we conducted a post-hoc analysis using the ITT populations from Roche-sponsored studies for our primary and secondary efficacy outcomes.[24]

To assess for publication bias we visually inspected a funnel plot and performed an Egger test for asymmetry.[23] A p-value threshold of <0.1 was selected as an indicator of significant publication bias.[25]

*Certainty of Evidence*

Two independent reviewers evaluated the certainty of the evidence for the outcome of hospitalization using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework.[26]

**Results**

*Search Results*

The initial database and registry searches yielded 2352 unique studies (**Figure 1**). Following title and abstract screening, 2269 were excluded. From 83 full-text reviews, 76 were subsequently excluded, leaving 7 included.[12-15, 27-29] Hand searching of bibliographies resulted in the inclusion of 8 additional unpublished clinical study reports from Roche Pharmaceuticals for a total of N=15 studies in the final meta-analysis.[30-37]

*Risk of Bias*

Of the 15 studies assessed, 9 (60%) were considered at low risk of bias, 5 (33.3%) had some concerns, and 1 (6.7%) was considered high risk (**Supplemental Figure 1**).

*Study and Population Characteristics*

The ITTi population comprised 6295 individuals, 3443 of whom were assigned to oseltamivir (54.7%). Overall trial demographics are included in **Table 1** based on the total study populations. Participants were 70.2 % Caucasian, 20.8% Asian, 54.5% female; and 60.4% were infected with influenza A. At the study-level, 9/15 (60%) trials were sponsored by Roche and were conducted between 1998 and 2006. Across studies, the control rate of hospitalization was low (0.6%).

*Efficacy Outcome*

Overall, oseltamivir did not reduce the risk of first hospitalization in the ITTi population [RR 0.77 (95% CI: 0.47 to 1.27, $I^2$ = 0%); RD -0.14% (95% CI: -0.32% to 0.16%); **Figure 2**]

*Subgroup Analyses*

Risk of hospitalization differed substantially between the industry and non-industry sponsored studies [RR: 0.50 (95% CI: 0.25 to 0.97) vs. RR: 1.32 (95% CI: 0.63 to 2.75), respectively; **Supplemental Figure 2A**)]. Industry sponsored studies were also more likely to use viral culture and/or serologic confirmation as opposed to modern molecular diagnostics (**Supplemental Figure 2B)**. Oseltamivir did not reduce hospitalization in older populations [mean age ≥65; RR: 0.99 (95% CI: 0.19 to 5.13) vs. mean age <65; RR: 0.72 (95% CI: 0.39 to 1.34); **Supplemental Figure 2C**]. Likewise, there was no observed reduction in the subgroup stratified according to patient risk [high-risk; RR: 0.90 (95% CI: 0.37 to 2.17) vs. low-risk; RR: 0.63 (95% CI: 0.32 to 1.24); **Supplemental Figure 2D**]. Subgroup analysis dichotomized by study quality (high vs. low risk of bias) also did not impact the findings [high risk of bias; RR of 0.78 (95% CI: 0.36 to 1.71) vs. low risk of bias; RR of 0.76 (95% CI: 0.39 to 1.48) (**Supplemental Figure 2E**)].

*Sensitivity Analyses*

A remove-one analysis found Butler (2020) and WV1819 + WV15876 + WV15978 (2000) had a greater influence on the overall effect size (**Supplemental Figure 3**). Cumulatively, estimated efficacy decreased over time, particularly when non-industry studies began to dominate the literature. (**Supplemental Figure 4**). A post-hoc analysis restricted to placebo-controlled trials found no difference in the efficacy of oseltamivir [RR: 0.66 (95% CI: 0.38 to 1.13)].

The sensitivity analysis using the ITT populations for Roche-sponsored studies shifted the overall effect size towards the null [RR: 0.85 (95% CI: 0.55 to 1.30)] (**Supplemental Figure 5)**. Similarly, when analyzed as a subgroup, Roche sponsored studies also shifted closer to the null [RR: 0.68 (95% CI: 0.41 to 1.15)]. Additional subgroup analyses revealed no appreciable changes in the point estimates (**Supplemental Figures 6A-E**).

*Safety Outcomes*

**Table 2** summarizes the risk of key adverse events. Patients prescribed oseltamivir experienced significantly more nausea [RR: 1.43 (95% CI: 1.13 to 1.82)], vomiting [RR: 1.83 (95% CI: 1.28 to 2.63)], and a composite of gastrointestinal symptoms [RR: 1.21 (95% CI: 1.02-1.45)]. There

was a reduced risk of diarrhea [RR: 0.76 (95% CI: 0.57 to 1.00)]. The risk of neurological disorders [RR: 1.15 (95% CI: 0.91 to 1.45)] was not statistically higher in the oseltamivir group. Oseltamivir did not increase serious adverse events compared to controls [RR: 0.71 (95% CI: 0.46 to 1.08)].

*Publication Bias*

Visual inspection of the funnel plot revealed asymmetry **(Supplemental Figure 7**); however, the Egger test was not statistically significant (p= 0.66).

*GRADE Certainty of Evidence*

We concluded with moderate certainty evidence that oseltamivir had little to no effect on hospitalization. While all included studies were RCTs directly evaluating oseltamivir, there was imprecision in the estimates due to wide variability between study results, not all studies were placebo controlled, and some studies were at risk of bias. Although our analysis stratified by risk of bias produced similar estimates, these aforementioned factors decreased our certainty from strong to moderate.

**Discussion**

Our systematic review and meta-analysis of oseltamivir for the outpatient treatment of laboratory-confirmed influenza included approximately 3400 more patients than prior analyses.[9,11] Despite this, oseltamivir did not significantly reduce hospitalization in general or in prespecified high-risk subgroups. Interestingly, the subgroup analysis limited to industry sponsored studies did suggest a reduced risk of hospitalization in the ITTi population. One possible explanation is that due to the time period, the associated use of viral culture by the older industry studies may have caused a number of true infections to be missed. Compared to the PCR method used in modern trials, viral culture has a weaker sensitivity in detecting milder cases with lower viral loads and/or residual non-viable virus. As a result, healthier patients who would have likely suppressed the overall hospitalization rate given their negligible risk for the outcome may have been excluded despite being technically infected. Another possibility includes Roche's allowance of a four-fold rise in antibody responses to confirm infection. There is evidence that oseltamivir may reduce seroconversion and therefore patients hospitalized with

negative serology in the oseltamivir arm may have been misclassified as non-infected.[24] A final explanation could be the lower prevalence of oseltamivir resistance during the time the industry studies were conducted. Since then, a greater than 10-fold rise in resistance has been observed (0.32% in the early 2000s to 3.56% between 2008 and 2013) which may have negatively influenced the efficacy of oseltamivir to a larger extent in the more recent trials.[38,39] Nonetheless, many of these industry trials only came to light after a legal challenge, and it is reasonable to look at the evidence in total. It was also somewhat reassuring that there was no increase in severe adverse events observed despite oseltamivir being strongly associated with an increased risk of gastrointestinal side effects (nausea and vomiting).

Based on our analyses, it appeared unlikely that administration of oseltamivir to a general outpatient population had a meaningful impact on serious influenza-related outcomes culminating in hospitalization. That said, it should be noted that the rate of hospitalization was exceedingly low, with a control event rate of 0.6% (95% CI: 0.14% to 1.07%). For oseltamivir to continue to be part of a viable influenza response, with respect to preventing severe complications, future studies should focus on identifying the groups of higher risk participants, with laboratory-confirmed influenza, who may derive benefit. Conducting an adequately powered trial would require a large sample size; however, given millions have received oseltamivir, such a trial doesn't seem unreasonable. As examples, we modeled two possible scenarios. First, if the risk of hospitalization is very low (e.g., a ~1% rate as observed in the general population)[40], a study of 30,716 participants would be required to demonstrate a 30% relative risk reduction with 80% power and 2-sided alpha of 0.05. By comparison, to conduct a trial focused on patients at greater risk of hospitalization, (e.g., the 2% event rate amongst this population in our analysis), 15,232 participants would be required. To succeed at recruitment, such trials would need to either take place during an epidemic or pandemic year, or over several years of seasonal influenza. Though the required sample size is large, it is potentially achievable; PANORAMIC (Platform Adaptive trial of NOvel antiviRals for eArly treatMent of covid-19 In the Community) recruited 25,783 participants to early outpatient COVID-19 treatments between the 8 December 2021 and 27 April 2022.[41]

Our meta-analysis has several limitations. First, we analyzed CSRs together with published and non-industry trials; these differed in the timeframe over which they took place, the mechanism for diagnosing infection, and the granularity of the data included. Second, the mean age of the patients was young (mid-40s) and the rate of hospitalization was low. This might have limited the power to detect an effect, but also implies that any missed effect would have a very high number needed to treat. We also chose *a priori* to analyze first hospitalization, whereas others have included readmissions.[24]This difference, and the inclusion of the newer trials, should be factored in when comparing our results with prior analyses. Similarly, we excluded patients assigned to high dose oseltamivir as this is not the approved dosing and therefore is less clinically relevant. Third, although our search methodology was robust, there is always the possibility that some studies, particularly unpublished, were missed. Fourth, we did not study symptomatic improvement or transmission rates, which, along with the associated outcome of return to work, could be important during a pandemic. Although there has been no evidence of a reduction in transmission, prior studies have reported small improvements in symptom duration (16.8-25.2 hours).[9,11] Whether this decrease is meaningful when compared with drug costs, an increase in non-severe adverse events, and the opportunity cost of missing out on the discovery of more effective therapies, remains a topic of study for healthcare economists and discussion on an individual patient basis. Finally, we excluded observational data from our analysis. While observational data can contribute larger numbers of patients, and the data can be more affordable and faster to access, it is also subject to substantial biases (e.g., immortal time bias, confounding by indication, residual confounding) which make it unsuitable for evaluating drug efficacy even with the most robust statistical methods.[42]

To our knowledge, this is the first systematic review and meta-analysis focusing on oseltamivir specifically for the reduction of all-cause hospitalization, an important outcome to prevent overwhelming healthcare systems. Given many of the side effects of oseltamivir can overlap with symptoms of influenza, we thought it important to study all-cause hospitalization, rather than influenza-related hospitalizations, which would overlook complications related to drug side-effects. This is particularly relevant for older high-risk adults where seemingly mild gastrointestinal side effects might still increase the risk of hospitalization through anorexia and dehydration.

**Conclusions**

Based on the available RCT data, there is a lack of convincing evidence that oseltamivir reduces serious complications in outpatients with influenza, though its use is associated with an increase in non-severe gastrointestinal adverse events. This meta-analysis provides important data for healthcare providers, patients, and policy makers to contextualize the evidence and inform guidelines. Future research should focus on the conduct of an adequately powered placebo-controlled trial in a suitably high-risk population.

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**Conflict of Interest:** All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Author Contributions:** RH, TCL and EGM conceptualized the review. RH and ÉBC identified and selected the studies,collected the data, and assessed the certainty of evidence and risk of bias. RH analyzed and synthesized the data. ÉBC, AM, BW, TCL and EGM provided advice for the manuscript. RH, ÉBC, TCL and EGM drafted the manuscript. All authors helped review and edit the manuscript as well as approve the final version. RH is the guarantor. The corresponding author attests that all listed authors fulfill the ICMJE authorship criteria and that no others meeting the criteria have been omitted.

**Transparency Statement:** I, Ryan Hanula, affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

**Data Sharing:** Data sharing is available upon request.

**References**


1. Macias AE, McElhaney JE, Chaves SS, et al. The disease burden of influenza beyond respiratory illness. *Vaccine*. 2021/03/15/ 2021;39:A6-A14. doi:https://doi.org/10.1016/j.vaccine.2020.09.048
2. Estimated Flu-Related Illnesses, Medical visits, Hospitalizations, and Deaths in the United States — 2018–2019 Flu Season (Centre for Disease Control and Prevention) (2020).
3. Wijesundara DK, Williams C, Sun W, Furuya AM, Furuya Y. Fear of Influenza Resurgence amid COVID-19 Pandemic: Need for Effective Flu Vaccine Still Exists. *Vaccines*. 2021;9(10):1198. doi:10.3390/vaccines9101198
4. Saunders-Hastings P, Krewski D. Reviewing the History of Pandemic Influenza: Understanding Patterns of Emergence and Transmission. *Pathogens*. 2016;5(4):66. doi:10.3390/pathogens5040066
5. Lee TC, Morris AM, Grover SA, Murthy S, McDonald EG. Outpatient Therapies for COVID-19: How Do We Choose? *Open Forum Infectious Diseases*. 2022;9(3)doi:10.1093/ofid/ofac008
6. Kelland K. Stockpiles of Roche Tamiflu drug are waste of money, review finds. *Reuters*. April 10, 2014. https://www.reuters.com/article/us-roche-hldg-novartis-search-idUSBREA390EJ20140410
7. Ontario) OAfHPaPPH. *Antiviral Medications for Seasonal Influenza: Information for Health Care Providers* 2019:12. *Public Health Ontario*.
8. Gupta YK, Meenu M, Mohan P. The Tamiflu fiasco and lessons learnt. *Indian J Pharmacol*. Jan-Feb 2015;47(1):11-6. doi:10.4103/0253-7613.150308
9. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ*. 2014;348(apr09 2):g2545-g2545. doi:10.1136/bmj.g2545
10. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of Oseltamivir Treatment on Influenza-Related Lower Respiratory Tract Complications and Hospitalizations. *Archives of Internal Medicine*. 2003;163(14):1667. doi:10.1001/archinte.163.14.1667
11. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *The Lancet*. 2015/05/02/ 2015;385(9979):1729-1737. doi:https://doi.org/10.1016/S0140-6736(14)62449-1
12. Beigel JH, Manosuthi W, Beeler J, et al. Effect of Oral Oseltamivir on Virological Outcomes in Low-risk Adults With Influenza: A Randomized Clinical Trial. *Clinical Infectious Diseases*. 2020;70(11):2317-2324. doi:10.1093/cid/ciz634
13. Butler CC, van der Velden AW, Bongard E, et al. Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised

controlled trial. *The Lancet*. 2020/01/04/ 2020;395(10217):42-52. doi:https://doi.org/10.1016/S0140-6736(19)32982-4
14. Ison MG, Portsmouth S, Yoshida Y, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. *The Lancet Infectious Diseases*. 2020;20(10):1204-1214. doi:10.1016/s1473-3099(20)30004-9
15. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. *New England Journal of Medicine*. 2018;379(10):913-923. doi:10.1056/nejmoa1716197
16. Razmaria AA. High-Value Care. *JAMA*. 2015;314(22):2462. doi:10.1001/jama.2015.16990
17. Hanula R, Lee TC, McDonald EG. Oseltamivir and the rate of hospitalizations for influenza-infected outpatients: a systematic review and meta-analysis of randomized controlled trials. *PROSPERO*. 2022;CRD42022299030
18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *International Journal of Surgery*. 2021/04/01/ 2021;88:105906. doi:https://doi.org/10.1016/j.ijsu.2021.105906
19. Jefferson T, Jones M, Doshi P, et al. Data from: Data from: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. 2014. doi:https://doi.org/10.5061/dryad.77471
20. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
21. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods*. 2020;doi:10.1002/jrsm.1411
22. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. John Wiley & Sons; 2019.
23. West SL, Gartlehner G, Mansfield AJ, et al. Comparative Effectiveness Review Methods: Clinical Heterogeneity. Agency for Healthcare Research and Quality (US), Rockville (MD); 2010.
24. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database Syst Rev*. Apr 10 2014;2014(4):Cd008965. doi:10.1002/14651858.CD008965.pub4
25. Hayashino Y, Noguchi Y, Fukui T. Systematic evaluation and comparison of statistical tests for publication bias. *J Epidemiol*. Nov 2005;15(6):235-43. doi:10.2188/jea.15.235
26. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.ad
27. Fry AM, Goswami D, Nahar K, et al. Efficacy of oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration and virus shedding in an

urban setting in Bangladesh: a randomised placebo-controlled trial. *The Lancet Infectious Diseases*. 2014;14(2):109-118. doi:10.1016/s1473-3099(13)70267-6
28. Lin J-T, Yu X-Z, Cui D-J, et al. A multicentre, randomized, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population. *Current Medical Research and Opinion*. 2006;22(1):75-82. doi:10.1185/030079906x80297
29. Roberts G, Chen S, Yates P, et al. Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Clinical Effect of Danirixin in Adults With Acute, Uncomplicated Influenza. *Open Forum Infectious Diseases*. 2019;6(4)doi:10.1093/ofid/ofz072
30. McGarty T. *Final Clinical Study Report - Protocol M76001: A randomized, double-blind, placebo-controlled, multicenter study of efficacy based on the time to treatment of influenza infection with the nuraminidase inhibitor Ro 64-0796 (also known as GS 4104)*. Clinical Study Report. 2000:9809. *Final Clinical Study Report - Protocol M76001*. 2000.
31. Dorkings J. *Final Clinical Study Report – Protocol WV15670: A double-blind, randomized, placebo controlled study of oral Ro 64-0796 (also known as GS 4104) in the treatment of influenza infection*. 1998:4010. *Final Clinical Study Report - Protocol WV15670*.
32. Dorkings J. *Clinical Study Report - Protocol GS 97-803 (WV15671): A double-blind, randomized, placebo controlled study of GS 4104 (Ro 64-0796) in the treatment of influenza infection*. 1999:3648. *Clinical Study Report - Protocol GS 97-803*.
33. Grosse M. *Clinical Study Report – Protocol WV15707: A double-blind, stratified, randomized, placebo controlled study of Ro 64-0796 (GS4104) in the treatment of influenza infection in elderly adults*. 1999:929. *Clinical Study Report - Protocol WV15707*.
34. McCarvil M. *Final Clinical Study Report (Protocols WV15812 and WV15872) – A double-blind, stratified, randomised, placebo controlled study of Ro 64-0796 (also known as GS4104) in the treatment of influenza in chronically ill adults*. 2000:3355.
35. Pharmaceuticals R. *Final Clinical Study Report – Protocols WV15819, WV15876 and WV15978. A double- blind, randomized, stratified, placebo-controlled study of Ro 64-0796 (also known as GS4104) in the treatment of influenza infection in elderly patients*. 2000:4363. *Final Clinical Study Report – Protocols WV15819, WV15876 and WV15978*.
36. Pharmaceuticals R. *Clinical Study Report – Protocol WV16277. A double-blind, randomized, stratified, placebo-controlled study of oseltamivir in the treatment of influenza infection in patients*. 2003:4310. *Clinical Study Report – Protocol WV16277*.
37. Dorkings J. *Clinical Study Report / Protocol WV15730: a double-blind, stratified, randomized, placebo controlled study of Ro 64-0796 (GS4104) in the treatment of influenza infection in adults*. 1999:1325. *Clinical Study Report / Protocol WV15730*.

38. Aoki FY, Boivin G, Roberts N. Influenza Virus Susceptibility and Resistance to Oseltamivir. *Antiviral Therapy*. 2007;12(4_part_2):603-616. doi:10.1177/135965350701200s04.1
39. Lina B, Boucher C, Osterhaus A, et al. Five years of monitoring for the emergence of oseltamivir resistance in patients with influenza A infections in the Influenza Resistance Information Study. https://doi.org/10.1111/irv.12534. *Influenza and Other Respiratory Viruses*. 2018/03/01 2018;12(2):267-278. doi:https://doi.org/10.1111/irv.12534
40. Near AM, Tse J, Young-Xu Y, Hong DK, Reyes CM. Burden of influenza hospitalization among high-risk groups in the United States. *BMC Health Serv Res*. 2022/09/28 2022;22(1):1209. doi:10.1186/s12913-022-08586-y
41. Butler C, Hobbs, R.F.D, Gbinigie O, et al. Molnupiravir Plus Usual Care Versus Usual Care Alone as Early Treatment for Adults with COVID-19 at Increased Risk of Adverse Outcomes (PANORAMIC): Preliminary Analysis from the United Kingdom Randomised, Controlled Open-Label, Platform Adaptive Trial (October 4, 2022). Available at SSRN: https://ssrn.com/abstract=4237902 or http://dx.doi.org/10.2139/ssrn.4237902
42. Albuquerque AM, Eckert I, Tramujas L, et al. Effect of tocilizumab, sarilumab, and baricitinib on mortality among patients hospitalized for COVID-19 treated with corticosteroids: a systematic review and meta-analysis. *Clin Microbiol Infect*. Jul 19 2022;doi:10.1016/j.cmi.2022.07.008

## Figures and Tables

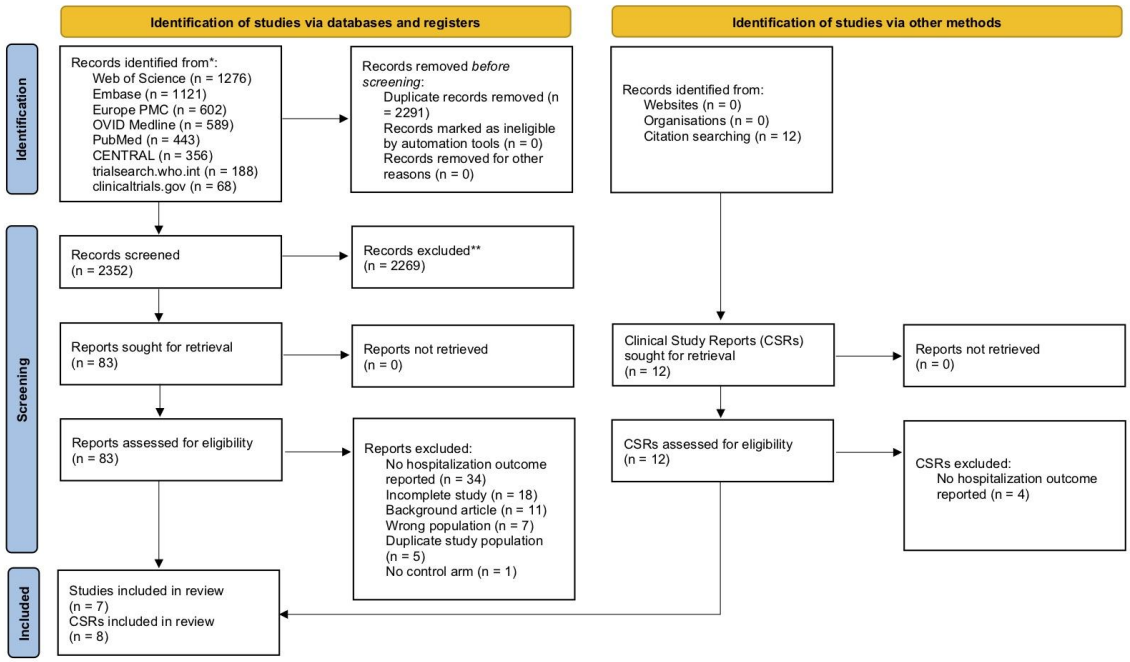


**Figure 1.** PRISMA 2020 Flow Diagram. For a systematic review which included searches of databases, registers, and other sources. All records identified via other methods were clinical study reports provided by Roche to the British Medical Journal.

**Table 1.** Study design and population characteristics.

| Trial (Year) | ITTi Population N (Control - Oseltamivir) | Comparator | Duration of Follow - Up | Method to Confirm Influenza Infection | Sponsor | Male N (%) | Mean Age | Mean Weight / BMI | Ethnicities N (%) | Influenza Type A N (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Beigel (2020) [12] | 279 - 277 | Placebo | 28 Days | Rapid Antigen | National Institute of Allergy and Infectious Diseases | 209 (37.6) | Median:36 | NR | C: 150 (27.0)<br>B: 18 (3.2)<br>A: 385 (69.2)<br>O: 3 (0.5) | 387 (69.6) |
| Hayden (2018) [15] | 231 - 377 | Placebo | 21 Days | RT-PCR | Shionogi | 338 (55.6) | 35.2 | 68.3 kg | C: 100 (16.4)<br>B: 20 (3.3)<br>A: 483 (79.4)<br>O: 5 (0.8) | 537 (88.3) |
| Ison (2020) [14] | 386 - 389 | Placebo | 21 Days | RT-PCR | Shionogi | 371 (47.9) | 51.5 | 79.3 kg | C: 382 (49.6)<br>B: 59 (7.7)<br>A: 320 (41.6)<br>O: 9 (1.2) | 427 (55.1) |
| Lin (2006)* [27] | 29 - 27 | Placebo | 21 Days | Viral Culture | Shanghai Roche | 33 (58.9) | 50.3 | 65 kg | NR | NR |
| Roberts (2019) [28] | 7 - 7 | Placebo | 28 Days | Rapid Antigen | GlaxoSmithKline | 11 (78.6) | 34.9 | 30.5 kg/$m^2$ | C: 11(78.6)<br>B: 1 (7.1)<br>A: 2 (14.3)<br>O: 0 (0) | 7 (50.0) |
| Dorkings WV15670 (1998)* [30] | 161 - 158 | Placebo | 21 Days | Viral Culture | Roche | 238 (49.9) | 37.8 | 74.1 kg | C: 448 (93.9)<br>B: 6 (1.3)<br>A: 21 (4.4)<br>O: 2 (0.4) | 302 (64.3) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dorkings WV15671 (1999)* [31] | 129 - 124 | Placebo | 21 Days | Viral Culture | Roche | 196 (46.9) | 32.3 | 80.5 kg | C: 341 (81.6)<br>B: 41 (9.8)<br>A: 6 (1.4)<br>O: 30 (7.2) | 235 (56.1) |
| McGarty M76001 (2000)* [29] | 361 - 702 | Placebo | 21 Days | Viral Culture | Roche | 639 (44.2) | 35.2 | 78.1 kg | C: 1184 (81.8)<br>B: 117 (8.1)<br>A: 25 (1.7)<br>O: 121 (8.4) | 866 (59.8) |
| Grosse WV15707 (1999)* [32] | 6 - 6 | Placebo | 21 Days | Viral Culture | Roche | 14 (53.8) | 71.6 | 77.0 kg | C: 14 (53.8)<br>B: 0 (0)<br>A: 1 (3.8)<br>O: 11 (42.3) | 12 (46.2) |
| McCarvil WV15812 + WV15872 (2000)* [33] | 133 - 118 | Placebo | 21 Days | Viral Culture | Roche | 177 (44.1) | 51.8 | 77.8 kg | C: 375 (93.5)<br>B: 7 (1.7)<br>A: 4 (1.0)<br>O: 15 (3.7) | 205 (51.0%) |
| WV15819 + WV15876 + WV15978 (2000)* [34] | 254 - 223 | Placebo | 21 Days | Viral Culture | Roche | 316 (43.0) | 72.9 | 74.6 kg | C: 721 (98.1)<br>B: 9 (1.2)<br>A: 2 (0.3)<br>O: 3 (0.4) | 449 (61.1%) |
| WV16277 (2003)* [35] | 109 - 119 | Placebo | 21 Days | Viral Culture | Roche | 224 (49.7) | 34.9 | 72.8 kg | C: 445 (98.7)<br>B: 3 (0.7)<br>A: 2 (0.4)<br>O: 1 (0.2) | 205 (45.5%) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dorkings WV15730 (1999)* [36] | 19 - 19 | Placebo | 21 Days | Viral Culture | Roche | 30 (51.7) | 35.2 | 72.1 kg | C: 54 (93.1)<br>B: 1 (1.7)<br>A: 2 (3.4)<br>O: 1 (1.7) | 36 (62.1%) |
| Fry (2014) [26] | 64 - 76 | Placebo | Followed until 7 days after symptoms resolved | RT-PCR | Centers for Disease Control and Prevention | 627 (52.7) | NR | NR | NR | 762 (65.5) |
| Butler (2020) [13] | 674 - 702 | Standard of Care | 28 Days | PCR | European Commission's Seventh Framework Programme | 1438 (44.1) | NR | NR | NR | 948 (29.0) |

Overall trial demographics were based on the total study populations. NR = not reported within the study. C = Caucasian, B = black or African American, A = Asian or Asian American, O = other or not available. *Denotes studies that used serology alongside viral culture to confirm influenza diagnoses. Note: Demographics for the desired 12+ population extracted from Fry (2014) and the Butler (2020) data request were not provided, thus their entire populations are represented.

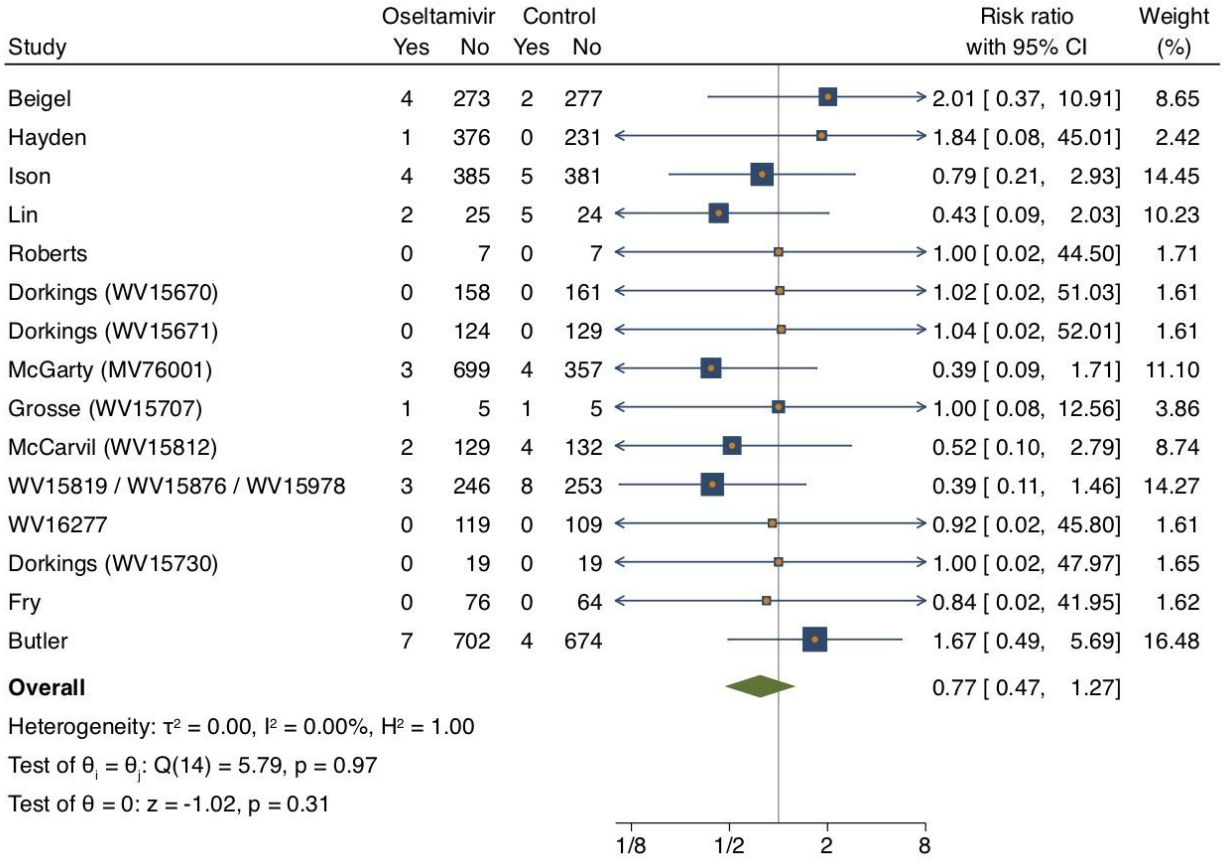


**Figure 2.** Random effects meta-analysis on the outcome of hospitalizations within the 12+ ITTi population. Yes = number of individuals hospitalized, No = number of individuals who were not.

**Table 2.** Random effects meta-analyses on adverse events and serious adverse events within the safety population.

| Event Type | Oseltamivir Frequency | Placebo Frequency | Risk Ratio (95% CI) | Heterogeneity | Risk Ratio p-value | Risk Difference (95% CI) | NNH (95% CI) |
|---|---|---|---|---|---|---|---|
| Nausea | 374 / 3892 | 218 / 3197 | 1.43 (1.13, 1.82) | 39.71% | <0.01 | 0.107 (0.048, 0.167) | 9.3 (6.0, 21.0) |
| Vomiting | 248 / 3120 | 103 / 2417 | 1.83 (1.28, 2.63) | 42.81% | <0.01 | 0.164 (0.088, 0.239) | 6.1 (4.2, 11.3) |
| Diarrhea | 222 / 3841 | 216 / 3142 | 0.76 (0.57, 1.00) | 39.72% | 0.05 | -0.082 (-0.161, -0.003) | -12.2 (-334.4, -6.2) |
| Gastrointestinal Disorders | 591 / 2305 | 356 / 1818 | 1.21 (1.02, 1.45) | 39.40% | 0.03 | 0.068 (0.009, 0.126) | 14.8 (7.9, 111.7) |
| Cardiac Disorders | 29 / 1991 | 32 / 1505 | 0.69 (0.42, 1.15) | 0.00% | 0.15 | -0.107 (-0.230, 0.017) | NA |
| Neurological Disorders | 179 / 2247 | 112 / 1758 | 1.15 (0.91, 1.45) | 0.00% | 0.25 | 0.034 (-0.023, 0.092) | NA |
| Psychiatric Disorders | 12 / 2247 | 16 / 1758 | 0.67 (0.29, 1.53) | 0.00% | 0.34 | -0.205 (-0.461, 0.051) | NA |
| Serious Adverse Events | 39 / 3765 | 49 / 3080 | 0.71 (0.46, 1.08) | 0.00% | 0.11 | -0.097 (-0.196, 0.003) | NA |

NNH= Number Needed to Harm

NA=Not applicable; NNH only reported when primary effect was statistically significant

**See Appendix A. Online Supplemental Figures and Table for Manuscript 1 (Chapter 2)**

**Supplemental eTable 1.** Search strategies.

**Supplemental eFigure 1.** Visualization of the risk of bias.

**Supplemental eFigure 2.** Random effects subgroup analyses on the outcome of hospitalization.

**Supplemental eFigure 3.** Random effects remove-one sensitivity analysis.

**Supplemental eFigure 4.** Random effects cumulative meta-analysis.

**Supplemental eFigure 5.** Random effects sensitivity analysis on the outcome of hospitalization.

**Supplemental eFigure 6.** Random effects sensitivity subgroup analyses.

**Supplemental eFigure 7.** Publication bias funnel plot.

## Chapter 3. Mortality outcomes of hospitalized influenza patients treated with oseltamivir and/or corticosteroids: a rapid review and meta-analysis

*Preamble*

Following a comprehensive systematic review and meta-analysis on the treatment of outpatients with influenza, I established that oseltamivir was not likely to substantially reduce the risk of hospitalization (RR: 0.77, 95% CI: 0.47 to 1.27). This finding was even consistent amongst high risk patients due to age (≥65) or other high risk factors (i.e. chronic illnesses). Thus, seeing that this study refuted the assertions of treatment guidelines that oseltamivir reduces complications, I questioned whether the same was true for its purported ability to decrease inpatient mortality.[43,44]

I began by briefly searching the literature on the effect of oseltamivir with respect to inpatient mortality. The initial results differed in their conclusions, so I decided to conduct a rapid review and meta-analysis. With a focus on hospitalized influenza patients, I also took the opportunity to review the role of corticosteroids in the same population. Inspired by the finding that steroids reduced mortality in inpatients with COVID-19, I wondered whether the benefit would translate to influenza.[35] While it is known that the use of corticosteroids for influenza is associated with a higher incidence of nosocomial infections, their ability to suppress immune responses by reversing the histone acetylation of activated inflammatory genes lends support to their potential utility as an immunomodulatory therapy.[45,46] Interestingly, randomized trials in COVID-19 featured another parallel: the antiviral remdesivir was found to reduce mortality for patients requiring oxygen, but had little to no effect for the least sick and potentially harmed the critically ill.[47] Noting that the effect of antivirals could be comparable between COVID-19 and influenza, this reinforced my need to study oseltamivir in hospitalized influenza patients.

Overall, despite not being conducted as a formal systematic review and meta-analysis (i.e. no screening in duplicate), this review provided substantial background information on the effect of oseltamivir and/or corticosteroids (with no other antiviral co-treatment). As a result, it greatly informed the construction of my subsequent RCT protocol manuscript and thesis in general.

With the reasoning for its execution now explained, the following chapter elaborates on my methodology, results, and discussion.

*Methodology*

To start, I searched the database Embase from its inception to June 1, 2022, using a search string (composed with the aid of a research librarian) consisting of terms related to: oseltamivir and/or corticosteroids, hospitalization, and influenza. Bibliographies of included articles and relevant literature reviews were also searched and no filters, limits, or language restrictions were applied. To be included, studies had to report in-hospital or 30-day mortality for influenza inpatients treated with oseltamivir and/or corticosteroids (with no other antiviral co-treatment). In addition, study populations were required to include patients 12 years of age and older that were confirmed to have influenza.

All search results were imported to the website Rayyan where each study was title and abstract screened. Remaining studies were then reviewed in full using the selection criteria outlined above. With every included study, targeted outcome and study demographic data were extracted using a pre-established guide. As for the meta-analysis, where there were direct comparisons between treatments and non-active controls, risk ratios with 95% confidence intervals (CIs) were calculated for both in-hospital and 30-day mortality. However, anticipating that there would be few, if any, RCTs without an active comparator, and that many observational studies would lack comparisons, both mortality outcomes were also computed as pooled proportions (PPs) with 95% CIs for each treatment.

*Results*

My search resulted in 1921 unique studies and after title and abstract screening, 1645 were excluded. From the 276 studies reviewed in full, an additional 247 were excluded due to not meeting one or more various selection criteria. Hand searching of relevant bibliographies resulted in 10 additional results, of which only 3 provided the necessary mortality data. In total, 32 studies were included in the review, 8 RCTs and 24 observational studies.[38, 48-78] Among the 8 RCTs, 4 had no comparator, 2 involved another antiviral, 1 compared a monoclonal antibody, and 1 utilized standard of care for its control group.

The intention-to-treat infected population involved a total of 5774 individuals (731 from randomized controlled trials and 5043 from observational studies). Treatments included: 5279 receiving oseltamivir alone, 105 receiving corticosteroids alone, 143 receiving oseltamivir and corticosteroids, and 247 receiving supportive care only. Altogether, 53.5% of participants were male, most studies (19/32) had averages of age between 55-70 years, and 1812 (31.5%) patients were treated within an intensive care unit (ICU). At the study level, the most frequent influenza strain and treatment investigated were seasonal influenza (17/32) and 75mg of oral oseltamivir twice a day (19/32), respectively.

In direct comparisons to standard of care, oseltamivir had a non-significant effect on the in-hospital mortality rate [risk ratio (RR) 0.71, (95% CI: 0.34 to 1.47). Likewise, oseltamivir was found to have no observed efficacy on 30-day mortality (RR: 0.45, 95% CI: 0.04 to 5.72). However, no risk ratio estimates were computed for corticosteroids or combination therapy as no studies compared either treatment to supportive care.

The in-hospital mortality pooled proportion for those treated with oseltamivir was 6.9% (95% CI: 3.2 to 13.9%). In particular, mortality was significantly lower in RCTs (PP: 0.7%, 95% CI: 0.1 to 8.9%) than in observational studies (PP: 8.2%, 95% CI: 4.0 to 16.2%). The pooled mortality rate for patients who received supportive care was 2.8% (95% CI: 1.4 to 5.8%). Meanwhile, corticosteroid treatment resulted in a PP of 41.9% (95% CI: 32.9 to 51.5%) while corticosteroids and oseltamivir together yielded a PP of 23.6% (95% CI: 16.3 to 32.8%).

For 30-day mortality, oseltamivir had a lower PP of 3.1% (95% CI: 1.6 to 6.0%) with similar subtotals between RCTs (PP: 2.1%, 95% CI: 0.6 to 6.5%) and observational studies (PP: 4.8%, 95% CI: 2.2 to 10.1%). No studies reported 30-day mortality for corticosteroid treatment and only one examined the combined treatments, producing a PP of 19.7% (95% CI: 11.2 to 30.9%). In comparison, standard of care had a pooled proportion of 1.0% (95% CI: 0.1 to 6.8%).

When grouped according to clinical setting, patients in acute care given oseltamivir had significantly lower in-hospital mortality (PP: 3.9%, 95% CI: 1.8 to 8.2%) than those treated in

ICUs (PP: 36.7%, 95% CI: 26.2 to 48.6%). Moreover, acute care patients treated with oseltamivir and corticosteroids had lower in-hospital mortality (PP: 16.4%, 95% CI: 8.2 to 28.1%) than their ICU peers (PP: 29.3%, 95% CI: 20.5 to 40.0%). But, because each corticosteroid and 30-day mortality estimate was based upon pooled studies with the same clinical setting, no subgroup analyses could be conducted for these outcomes.

*Discussion*

Overall, there is no randomized controlled trial evidence in support of oseltamivir or corticosteroids in the treatment of hospitalized patients with influenza. In primarily observational data, patients given oseltamivir alone had lower in-hospital and 30-day mortality compared to those given corticosteroids or combination therapy. Yet, oseltamivir still had a non-significant effect versus standard of care for both mortality outcomes.

Upon deeper examination, the advantage of oseltamivir diminished even further following subgroup adjustments. When categorized based on hospital setting, oseltamivir's in-hospital ICU mortality equaled the overall rates of the two other treatments whose estimates were composed primarily by ICU-based studies. Thus, despite the recommendation of initiating oseltamivir for severe influenza cases, the results suggest that the parallel to remdesivir in COVID may be true depending on the patients.[28,79] However, because the supporting evidence is limited, the drug should be evaluated as part of a randomized controlled trial.

Likewise, the usage of corticosteroids for the most critically ill may also be dangerous. Although no direct comparison could be made to standard of care or oseltamivir, patients who received corticosteroids had a mortality much greater than the 15-20% general average for severe influenza cases.[80] Yet, steroids should not be dismissed as a need remains for an adequately powered placebo controlled RCT. Only 4 studies, all of which were observational, provided corticosteroid data based upon a total of 248 patients. As a result, many questions went unanswered (i.e. 30-day mortality) and the acquired findings require confirmation with high-quality evidence. Hence, a RCT would effectively achieve these objectives and may identify specific subgroups (i.e. patients requiring mechanical ventilation) or treatment criteria (i.e. early administration) where corticosteroids could yield selective benefit.

However, it should be acknowledged that there would be a complexity to designing a RCT which incorporates both oseltamivir and corticosteroids. Not only would a large sample size be needed to detect statistical differences due to the low control event rate for inpatient mortality, but both drugs require significantly different timings of administration and patient populations. For instance, treatment guidelines recommend oseltamivir be given to all influenza patients, regardless of illness severity, within 48 hours of symptom onset for "optimal benefits".[27,28] In comparison, steroids are only utilized following a pulmonary inflammatory complication and even then, are primarily saved for the most severe cases. Therefore, while such a RCT would have multiple benefits as outlined above, one would require careful planning to account for these variabilities and ensure both treatments were accurately evaluated in the proper clinical settings.

This review also has several limitations. First, due to the limited number of corticosteroid studies and the minimal treatment details they report, no steroid subgroup analyses could be conducted to determine whether certain drugs or potencies provide greater benefit. Second, in addition to very few steroid studies meeting the pre-specified selection criteria, most involved ICU populations. Consequently, this made it difficult to compare the pooled efficacies versus the more generalized oseltamivir or standard of care studies which primarily included acute care patients outside of ICUs. Third, due to pooling RCT and observational studies together and no restrictions on treatment duration or dosages, the PP estimates had significant heterogeneity. However, attempts were made to minimize this issue by presenting subtotal estimates per study type. Fourth, patients in observational studies that received corticosteroids were especially confounded by indication. Since patients in the most critical conditions were primarily the ones to receive the drug, this may have created bias within the results against corticosteroids.

Nevertheless, this review focused on influenza inpatients given oseltamivir and/or corticosteroids provides impetus for an adequately powered, placebo-controlled factorial design RCT to assess these treatments on the outcome of inpatient mortality. As a result, this inspired the creation of the RCT protocol that comprises the final manuscript of my thesis research.

## Chapter 4. Assessing the efficacy and safety of oseltamivir and dexamethasone for hospitalized influenza cases: protocol for a randomized, double blind, controlled study

### Preamble to Manuscript Two

In summary, my rapid review and meta-analysis unfortunately provided no clearer insight on the efficacy of oseltamivir or corticosteroids against inpatient mortality. Although patients treated with oseltamivir had lower mortality in terms of pooled proportions compared to those given only corticosteroids, there was no significant difference in oseltamivir versus standard of care (in-hospital RR: 0.71, 95% CI: 0.34 to 1.47, 30-day RR: 0.45, 95% CI: 0.04 to 5.72). Plus, the limited number of studies that reported direct standard of care comparisons (5) or corticosteroid usage (4) prevented the acquisition of precise effect sizes. As a result, these factors hindered my ability to confidently refute or support the efficacy of either treatment.

Therefore, in order to definitively establish whether oseltamivir or corticosteroids decrease inpatient mortality I realized an adequately powered placebo-controlled RCT was required. No prior RCTs have been conducted on the outcome with respect to steroids and only one with a non-active comparator has been done to assess the effect of oseltamivir.[38] Even then, it only incorporated 74 patients confirmed to have influenza and utilized standard of care as a control. Although standard of care is generally more ethical and easier to implement than placebo, selection bias can still influence mortality outcomes in open-label studies, supporting the necessity for a placebo-controlled RCT.[81] Thus, by filling this extensive need, my trial would assist 1) policy makers in updating treatment guidelines as their highest quality source of evidence, and 2) healthcare providers by clearly identifying optimal treatment strategies, resulting in improved patient outcomes.

Leveraging the wealth of information generated by the COVID-19 inpatient corticosteroid trials, the finding that dexamethasone had the largest evidence base and greatest efficacy in reducing mortality over other steroids like hydrocortisone led to its selection as my steroid candidate.[35] This choice was then further reaffirmed by the results of an ARDS inpatient trial wherein treatment with dexamethasone resulted in lower mortality than routine care.[82] However, in the design, corticosteroid usage will be restricted to individuals on oxygen due to the potential

increased mortality risk for those who do not require oxygen.[35,83] Still, despite the selective population, there is merit to establishing whether the benefit of corticosteroids translates to influenza. Considering its well-established safety record, inexpensiveness, and accessibility, should it prove to be effective in reducing inpatient mortality, dexamethasone would become a high value influenza therapeutic.[35]

Given that my M.Sc. was completed in under two years, the following manuscript contains the protocol for the clinical trial I developed which will be carried out by our team at a later date. While the protocol comprises the second manuscript in my thesis, the ultimate trial, which will be multi-centered and take several years to recruit to, is beyond the scope of my Masters. Nevertheless, the manuscript is intended to be submitted to the journal Trials, and the contents of this paper will inform the registration of the trial on clinicalstrials.gov as well as be used to apply for grants and research ethics board approval for the conduct of the study.

**Title Page**

**Assessing the efficacy and safety of oseltamivir and dexamethasone for hospitalized influenza cases: Study protocol for a randomized controlled trial**

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**Trial Sponsor:**Research Institute of the McGill University Health Centre

**Article Type:** Protocol

**Keywords:** influenza; hospitalization; oseltamivir; corticosteroid; inpatient; treatment

*Equal contributions

**Abstract**

**Background:** Every year influenza causes numerous hospitalizations, of which a small but significant percentage end in death. Despite this, no treatment has ever been shown to definitively reduce inpatient mortality. The antiviral oseltamivir (Tamiflu®) has been endorsed by several professional societies, however, the supporting evidence for hospitalized patients is mainly observational, with conflicting study results subject to confounding and immortal time bias. Meanwhile, corticosteroids have been shown to provide inpatient benefit against community-acquired pneumonia, acute respiratory distress syndrome, and most recently COVID-19, but have never been assessed in a randomized controlled trial (RCT) with respect to influenza. We therefore propose an adequately powered, placebo-controlled RCT to evaluate the effect on mortality of oseltamivir and corticosteroids for hospitalized patients with influenza.

**Methods:** This will be a multi-centred, international, double-blind, placebo-controlled, factorial design phase III trial. The study will include up to 13,804 adult patients, aged 18 years or older, hospitalized due to symptomatic influenza. Patients will be randomized to oseltamivir (75 mg BID for 5 days) or placebo and to dexamethasone (6 mg daily for 10 days) or placebo in 1:1 ratios to compare the efficacy and safety of both treatments. The primary outcome will be all-cause 30-day mortality. Outcomes will be reported as risk ratios (adjusted for stratification) with 95% confidence intervals.

**Discussion:** As the first inpatient placebo-controlled RCT of oseltamivir and corticosteroids in influenza, this trial will be practice and guideline changing. This trial will either validate or refute treatment with oseltamivir, which is commonly prescribed to hospitalized patients. Furthermore, it will establish if the mortality benefit of corticosteroids observed in COVID-19 translates to patients with influenza.

**Trial Registration:** The study will be registered on Clinicaltrials.gov at time of manuscript submission.

## Introduction

*Background and Rationale*

As one of the most common global respiratory infectious diseases, influenza presents a constant threat to human health via both recurring seasonal infections and future pandemics. While most infections self-resolve within a few days with supportive care alone, depending on the year and strain of influenza, anywhere between 140,000 - 710,000 hospitalizations occur in the United States, with 15-34% requiring the intensive care unit (ICU).[1,2] Once admitted, 4-12% of patients die as a result of complications such as respiratory failure, secondary bacterial pneumonia, exacerbation or worsening of underlying cardiopulmonary conditions, and/or advanced frailty.[2,3]

In spite of the substantial disease burden, no treatment has been demonstrated to reduce mortality in a randomized controlled trial (RCT). The antiviral oseltamivir (Tamiflu®), the predominant treatment for decades, has been used as a control therapy in RCTs for newer antivirals, but it itself has never been proven in RCTs to be of benefit in the inpatient population.[4,5] Nonetheless, major professional societies endorse oseltamivir for inpatient influenza based on expert opinion, theory, and observational evidence which suffers from differing conclusions and considerable risk of bias (e.g. immortal time bias, residual confounding in non-granular datasets, and confounding by indication).[6,7] Indeed, there is reason to believe that antiviral therapy, when prescribed to an at-risk population, may reduce mortality, but there may also be populations who experience harm from the treatment. For instance, during COVID-19, the antiviral remdesivir was shown to have a minimal impact on mortality for low risk hospitalized patients, it reduced mortality in those requiring oxygen, and on the contrary, it increased mortality among critically ill patients requiring mechanical ventilation.[8] As a result, it would be prudent to know whether we should or should not be giving oseltamivir to hospitalized influenza patients, and if so, within which populations.

With respect to the effectiveness of non-antiviral therapies against inpatient mortality, systemic corticosteroids have demonstrated strong benefit in acute respiratory distress syndrome,[9] potential benefit in community-acquired pneumonia,[10] and were revolutionary for the care of hypoxemic patients with COVID-19.[11] Dexamethasone, in particular, had the greatest efficacy in reducing mortality for COVID-19 patients, albeit with a harm signal in patients who did not

require oxygen, and the largest observable benefit among patients requiring invasive ventilation.[12] As for influenza, there has never been an RCT evaluating steroids and the observational data is conflicting and subject to substantial confounding by indication/severity. In particular, it was observational data in influenza that contributed to early guideline recommendations to avoid steroids in COVID-19. Without the courage of those who conducted early RCTs, a greater number of lives might have been lost later in the pandemic. Therefore, we postulate that for patients hospitalized due to influenza pneumonia, it is possible that dexamethasone could exhibit a similar benefit as COVID-19, and reduce inpatient mortality (alone or in combination with oseltamivir).

The COVID-19 pandemic taught us that randomization is possible, desirable, and beneficial. Based on the overall lack of high-quality evidence for inpatient influenza, we believe there is an urgent and unmet need for RCTs of oseltamivir and corticosteroids (in particular dexamethasone) as treatments for hospitalized patients. We propose this should be accomplished in a large, modern-day, placebo controlled trial which is adequately powered for mortality, evaluates for subgroup effects by oxygenation status, and utilizes a factorial trial design to maximize the available information from the minimum number of subjects.

*Objectives*

We aim to evaluate the efficacy and safety of both oseltamivir and dexamethasone for adults hospitalized with influenza.

*Study Design*

This will be a double-blind, double placebo-controlled, randomized, factorial-design trial of hospitalized adults (18+) with laboratory confirmed influenza. Eligible participants (by treatment) will be randomized to receive oseltamivir or placebo **and** to receive dexamethasone or placebo in 1:1 ratios, respectively. This protocol describes a phase III superiority trial with the primary outcome of 30-day all-cause mortality. Once implemented, the study will be conducted in accordance with Health Canada and other international requirements, Good Clinical Practice, and the Declaration of Helsinki.

**Methods**

This protocol is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[13] This protocol will be registered on clinicaltrials.gov.

*Study Setting*

This will be a multi-site RCT of hospitalized adults taking place on an international scale. The goal will be to involve at least 50 centers to achieve the intended sample size. The study will be led and coordinated from the Research Institute of the McGill University Health Centre (MUHC) in partnership with the Pan-Canadian Clinical Trials Consortium.

*Participants*

Adults (18 years of age and older) with laboratory (RT-PCR) confirmed influenza presenting to one of the participating centers will be eligible for inclusion. Eligible participants must be able to provide consent (either directly, via legal surrogate, or using deferred consent in emergency situations as allowed by law), be symptomatic (i.e. cough, dyspnea, sore throat, fever, myalgias, headache, nasal symptoms, fatigue, diarrhea, nausea, vomiting, malaise, delirium), and have symptom onset within 2 days of presenting to hospital. This period was specifically chosen to reduce bias against oseltamivir since treatment guidelines state that patients need to receive the drug within 48 hours of symptom onset for "optimal benefits". Furthermore, given the known signal for harm seen in patients on room air in COVID-19 RCTs, only hypoxemic patients (based on the conventional definition of requiring oxygen to maintain an $O_2$ saturation greater than or equal to 92%) will receive dexamethasone. This will eliminate an unnecessary harm, especially since the same signal has been possibly observed in influenza, albeit by a singular study.[14]

Exclusion criteria include: being unlikely to survive for 48 hours based on the opinion of the treating medical team, known and/or documented history of a sensitivity or allergy to any of the study medications, inability to take oral medication (e.g. short gut syndrome) or a history of gastrointestinal malabsorption that would preclude the use of oral medication, and currently receiving or have received neuraminidase inhibitors or treatment dose corticosteroids for more than 48 hours. Patients with known or suspected adrenal insufficiency will be excluded from the

dexamethasone arm as will those with COPD, asthma, or other respiratory condition exacerbation for which steroids are indicated.

*Trial Interventions*

Oseltamivir (Tamiflu®) will be administered orally at 75 milligrams (mg) twice daily for 5 days based on the Centers for Disease Control and Prevention's guidelines or at the appropriate adjusted renal dosing.[1] Dexamethasone will be administered per oral (preferred route) or intravenous at 6 mg once daily for 10 days, following the regimen given to COVID-19 patients in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial.[15] Placebo tablets and saline will be used as placebo controls for oral and intravenous treatments, respectively.

Oseltamivir/placebo will be given for the intended duration. Dexamethasone/placebo will be given for the intended duration or until hospital discharge, whichever is sooner. Usage of concomitant antivirals with activity against influenza will be discouraged; however, non-study antibiotics and other medications (i.e bronchodilators), will be allowed. Dose adjustments related to renal function will be permitted during treatment if needed. Given the inpatient setting, adherence should be excellent as the study drugs and placebos will be dispensed by nursing and be listed on the medication administration record along with all of the patient's other medications.

While all subjects will be encouraged to receive their full course of treatment, withdrawal at any point of the study for any reason at the request of the patient will be respected. In addition, patients will be withdrawn if the investigator determines they experience a medication-induced grade 4 adverse event (AE) or toxicity.

*Outcomes*

The primary outcome is all-cause mortality at 30-days.

Secondary outcomes include:

- influenza-related mortality at 30-days as adjudicated by blinded review
- all-cause in-hospital mortality

- for those not requiring ICU care at admission and who do not have pre-existing "DNR" orders which preclude transfer, need for ICU care within 30-days and ICU duration
- length of hospitalization
- for those not requiring it at admission, need for invasive and non-invasive (e.g., BiPAP, CPAP, and high flow nasal cannula) respiratory support
- occurrence of secondary bacterial and fungal infections
- serious treatment emergent adverse events at 30-days (NCI Common Terminology Criteria for Adverse Events (CTCAE) grades 3 and 4)
- change from EuroQol EQ-5D-5L baseline at 30-days

*Sample Size*

In general, the 30 day rate of mortality amongst patients admitted to the hospital is estimated at 7-10%.[16] We believe that a meaningful 20% relative reduction in mortality with oseltamivir would be clinically important. At 80% power with an alpha of 0.05, this will require between 6422-9738 patients. The sample size will be adjusted at an interim analysis based on the pooled mortality rate in the oseltamivir study at that time.

We estimate that the risk of mortality in patients who require oxygen will be higher, and that the mortality reduction seen with dexamethasone will approximate that seen in COVID-19. Assuming a baseline mortality rate of 15-20%, and a relative risk reduction of 20%, at 80% power with an alpha of 0.05, this will require 2890-4066 patients.[17] The sample size will be adjusted at an interim analysis based on the pooled mortality rate in the dexamethasone study at that time.

*Blinding and Randomization*

Participants will be randomized into the treatment arms via permuted block randomization by a web-based system. Block sizes will be randomly chosen from 2, 4 and 6. Construction of the randomization sequence will be performed by an independent statistician. Randomization will be stratified by age ($<65$ vs $\geq 65$), sex, oxygen requirements (no oxygen, supplemental oxygen, and non-invasive/invasive ventilation) and vaccination status for the year's seasonal influenza (yes, no, or unknown).

After obtaining consent and being confirmed eligible to participate, trained research assistants will enroll patients into the study and enter their respective information in the database. Increased communication between trial sites, training of recruiters, and eligibility screening will help improve recruitment and ensure enrollment will be met without the creation of methodological or ethical challenges.[18] The randomization code will then be revealed and study medications will be prepared in each of the sites' research pharmacies (by an unblinded pharmacy technician or pharmacist who has no contact with the participants). Once patients are assigned, they will receive their blinded study medication from their nurse. All other trial staff, hospital staff, data analysts, outcome assessors, as well as patients will be blinded to group assignment.

To protect the blinded nature of the trial, placebo tablets will serve as the non-active comparator for oral oseltamivir and dexamethasone and saline as the equivalent for intravenous dexamethasone. Specific placebo and saline formulations will be selected once funding is acquired, with the various strengths, sizes, colors, and absorption rates of the active treatments taken into consideration to select the most appropriate substitutes. We believe non-active comparators are a necessary measure for this study to highlight any potential placebo effect and minimize the possibility of selection bias and cross-over between arms. While mortality is considered to be less subject to bias, it has been demonstrated that open-label studies tend to have larger mortality effect size estimates than placebo controlled studies.[19]

Although the study is double-blinded, in cases of emergency, the investigator will be charged with deciding whether the unblinding of a patient's treatment is required, taking into consideration patient safety as the top priority. In the case of an inadvertent unblinding, the patient will be allowed to continue therapy and will be included in all analyses, but with the protocol deviation reported.

*Data Collection and Management*

Participants are identified when they have a positive nasopharyngeal swab for influenza by PCR within 72 hours of admission. In addition, all participants will have baseline laboratory testing

for the following: complete blood count, chemistry panel (electrolytes and renal function), blood glucose, liver enzymes, albumin and arterial blood gas (if necessary) (**Figure 1**). These samples will be collected as part of usual care.

Patients will be followed daily (on weekdays) while admitted to the hospital and on study drugs. A member of the research team will review events since the last visit and record adherence and outcomes. After the study drugs have ended, patients will be seen weekly by the study team while in hospital and will have an in-person or virtual visit at day 30-35 to obtain final outcomes. If a patient is unreachable at days 30-35, we will seek proof of life from electronic medical records including outpatient pharmacy dispensing records. Should this be unsuccessful, we will contact their next of kin and send a registered letter to their home address before concluding loss to follow up. A variation of this technique was able to achieve 100% follow up for vital status in our *S. aureus* bacteremia trial.[20]

Pertinent information will be collected through the examination of medical charts as well as asking patients if their symptoms or condition have changed. Given that medical record abstraction is one of the most significant areas of error in trials, database entries will be periodically audited by trained monitors to ensure accuracy.[21] Study data will be contained in RedCap or another capable database system. Relevant case report forms (CRFs) will be completed directly within the electronic data capture system. No paper copies will be maintained. Access to the database will be restricted only to those who possess login authentication (including 2-factor authentication) and be available at all hours remotely from selected secure computer locations.

*Monitoring*

During treatment, site personnel will monitor participants for AEs and report them in the electronic CRF, should they occur. Moreover, all serious AEs will be reported as required to the research ethics board and/or to Health Canada or other regulatory bodies within the stipulated time frames depending on the severity and whether the study drug is responsible. Any serious AEs that occur will be monitored until resolution, or an adequate explanation is provided on why they may indefinitely continue.

Adverse events will be defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of any study medications, regardless of whether it is considered related to the medical treatment. As both oseltamivir and dexamethasone have been extensively used in humans, we will limit data collection to adverse events which are considered serious or life threatening. AEs will be assessed by blinded reviewers using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) with all grade 3 and 4 AEs validated and classified for severity and relatedness.[22] AEs will have the following relatedness categories: (i) Not related: if another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event. (ii) Possibly related: if the event follows a reasonable temporal sequence from the initiation of study procedures, but that could have readily been produced by a number of other factors. (iii) Related: the AE is clearly related to the study procedures.[23]

*Statistical Analysis*

In addition to the previously stated outcomes of interest, demographic items will also be collected from each patient. These will include: age, sex, weight, ethnicity, smoking and influenza vaccination history, residency (nursing home or not), relevant comorbidities, influenza subtype (if known), and symptom duration at the time of admission.

All efficacy analyses will be based on the intention-to-treat infected population, defined as individuals confirmed to have influenza and randomized at least one of the study arms. Safety analyses will include individuals who took at least one dose of study medication.

The primary outcome for oseltamivir and dexamethasone, respectively, will be assessed by calculating a risk ratio [with 95% confidence interval (95% CI)] using binary regression adjusting for all stratification variables and for co-treatment with the other drug. The risk difference will be reported (with 95% CI) by using the risk ratio and the control event rate. Secondary binary outcomes will be reported in the same way. Kaplan-Meier survival curves for overall mortality at day 30 will be plotted and a hazard ratio reported using multivariable cox regression adjusting for the same factors. Total length of hospital stay and length of ICU care by

day 30 will be compared by Wilcoxon Rank-sum with patients who died being assigned 31 days. Among survivors, the change in EQ-5D-5L between enrollment and 30-days for each group will be reported using Canadian time tradeoff values.[24] Based on the success of other influenza trials using this timeframe, 30 days should be sufficient to compare the quality of life of patients before and after treatment.[25,26]

Prespecified subgroup analyses will be performed for the primary outcome based on age (≥65 or <65), biological sex, vaccination status, pulmonary, renal, cardiac, and transplant/immunodeficiency comorbidities, clinical setting (ICU vs. acute care), cotreatment with the other drug, and use of respiratory support. These will be visually reported as Forest plots of risk ratios in accordance with guidance.[27]

Interim analyses will be conducted for efficacy and futility at 25% and 50% completion as well as for futility at 75% completion. Each threshold will be met independently by both treatment arms, triggering analyses within the respective randomized groupings. With respect to efficacy, the O'Brien-Fleming boundary approach will be used to determine if premature statistical significance is achieved, with each boundary value derived from an appropriate alpha-spending function.[28] As for futility, a Bayesian predictive probability function will be used to compute the posterior probability of a clinically important treatment effect, with values less than 20% prompting a recommendation to prematurely stop the treatment.[29] The sample size for each question may be adjusted at the 50% point based on the pooled event rate in that group if recruitment of that target remains feasible. If this is the case, and the resulting sample size is expanded, the interim analysis for benefit and futility will be delayed until 50% of the new sample size is achieved.

Missing data is not expected to be a significant concern due to the hospitalized nature of patients. However, in the event it is, variables with less than 5% missingness will be ignored due to the low probability of bias and variables having more than 20% missingness will be replaced with a last observation carried forward single imputation method.

**Discussion**

This pragmatic RCT will be among the first influenza inpatient trials to be powered on mortality and to incorporate placebo as a control. In addition, it will prove or disprove the benefits of oseltamivir (which has been recommended due to observational evidence of benefit) and dexamethasone (which has not been recommended due to observational evidence of harm). If oseltamivir reduces mortality, we should be using it in most patients and as an active comparator for newer agents; but if it does not, we should stop using it and devote effort into looking for more effective therapies. Similarly, while it would be tempting to infer that dexamethasone will have benefit in influenza based on COVID-19 data, demonstrating benefit is important to avoid harming patients simply due to lack of clinical trial evidence. Importantly, we must learn from the lessons of COVID-19 that large randomized trials are not only possible, but that they help clarify conflicting observational evidence and lead to evidence-based standards of care.

We are aware that this trial has potential limitations. First, there may be a treatment interaction between dexamethasone and oseltamivir. While we will provide an adjusted analysis for co-treatment and report the appropriate subgroups, we may not have adequate sample size to characterize it fully. Such an increase in sample size (up to 4x) may make the study unfeasible.[30] We believe it is important to control for the use of both antiviral and anti-inflammatory therapy given the risks of confounding by indication and believe that dual randomization is the best way to achieve balance. Second, our choice to use placebos makes the trial more complicated and will reduce the number of centers which have the ability to participate. Nonetheless, given that even mortality may be impacted by open-label design, and given the potential for cross-over or contamination between arms, we believe this is justified.[19] Thirdly, we hope to enroll quickly to arrive at an answer; however, by enrolling all patients within a limited number of influenza seasons, the trial may not be exposed to the temporal patterns of seasonal influenza with respect to quality of vaccine match, virulence of circulating strains, or to oseltamivir resistance levels.

**Conclusion**

In conclusion, this trial will assess if guideline recommendations for inpatient oseltamivir are justified and whether dexamethasone can translate the observed mortality benefit in COVID-19 patients to those hospitalized with influenza. Determining efficacy of these two treatments will

help clarify their respective evidence bases and enable healthcare providers to make more informed choices with respect to their usage, which populations are most likely to benefit, and ensure there is no harm in any major subgroup. It is time to move beyond the era of eminence and opinion based treatments and proceed with establishing the appropriate clinical trial evidence for effective treatments for this extremely common highly morbid infection.

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**Conflict of interest:** All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Author Contributions:**

R.H., T.C.L. and E.G.M. conceptualized the protocol. R.H., T.C.L., and E.G.M. drafted the manuscript. All authors helped review and edit the manuscript as well as approve the final version. The corresponding author attests that all listed authors fulfill the ICMJE authorship criteria and that no others meeting the criteria have been omitted.

**Ethics**

This study will submit for ethics approval from the McGill University Health Center Research Ethics Board (MUHC-REB). Any protocol modifications will be communicated to all required parties (MUHC-REB, regulators, patients, clinicaltrials.gov and journal in which this protocol is published). De-identified trial data to replicate all tables, figures and analyses will be made available at the time of eventual publication.

**References (Manuscript 2)**


1. Disease Burden of Flu: Centers for Disease Control and Prevention; 2022
2. Groeneveld GH, Marbus SD, Ismail N, de Vries JJC, Schneeberger P, Oosterheert JJ, et al. Effectiveness of oseltamivir in reduction of complications and 30-day mortality in severe seasonal influenza infection. Int J Antimicrob Agents. 2020;56(5):106155.
3. Beard K, Brendish N, Malachira A, Mills S, Chan C, Poole S, et al. Pragmatic multicentre randomised controlled trial evaluating the impact of a routine molecular point-of-care 'test-and-treat' strategy for influenza in adults hospitalised with acute respiratory illness (FluPOC): trial protocol. BMJ Open. 2019;9(12):e031674.
4. Kumar D, Ison MG, Mira JP, Welte T, Hwan Ha J, Hui DS, et al. Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial. Lancet Infect Dis. 2022;22(5):718-30.
5. Chen H-D, Wang X, Yu S-L, Ding Y-H, Wang M-L, Wang J-N. Clinical Effectiveness of Intravenous Peramivir Compared With Oseltamivir in Patients With Severe Influenza A With Primary Viral Pneumonia: A Randomized Controlled Study. Open Forum Infectious Diseases. 2020;8(1).
6. Aoki F, Papenburg J, Mubareka S, Allen U, Hatchette T, Evans G. 2021–2022 AMMI Canada guidance on the use of antiviral drugs for influenza in the COVID-19 pandemic setting in Canada. Official Journal of the Association of Medical Microbiology and Infectious Disease Canada. 2022;7.
7. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Jr, Fry AM, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. Clin Infect Dis. 2018;68(6):e1-e47.
8. Lee TC, Murthy S, Del Corpo O, Senécal J, Butler-Laporte G, Sohani ZN, et al. Remdesivir for the treatment of COVID-19: a systematic review and meta-analysis. Clin Microbiol Infect. 2022;28(9):1203-10.
9. Meduri GU, Siemieniuk RAC, Ness RA, Seyler SJ. Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS. *Journal of Intensive Care*. 2018/08/24 2018;6(1):53. doi:10.1186/s40560-018-0321-9
10. Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. *Ann Intern Med*. Oct 6 2015;163(7):519-28. doi:10.7326/m15-0715
11. Lee TC, Bortolussi-Courval É, Belga S, Daneman N, Chan AK, Hanula R, et al. Inhaled corticosteroids for outpatients with Covid-19: a meta-analysis. Eur Respir J. 2022:2102921.

12. Lee TC, McDonald EG, Butler-Laporte G, Harrison LB, Cheng MP, Brophy JM. Remdesivir and systemic corticosteroids for the treatment of COVID-19: A Bayesian re-analysis. Int J Infect Dis. 2021;104:671-6.
13. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ : British Medical Journal*. 2013;346:e7586. doi:10.1136/bmj.e7586
14. Li H, Yang SG, Gu L, et al. Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1)pdm09 viral pneumonia. *Influenza Other Respir Viruses*. Jul 2017;11(4):345-354. doi:10.1111/irv.12456
15. Horby P, Lim WS, Emberson J, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2020;384(8):693-704.
16. Hamilton MA, Liu Y, Calzavara A, Sundaram ME, Djebli M, Darvin D, et al. Predictors of all-cause mortality among patients hospitalized with influenza, respiratory syncytial virus, or SARS-CoV-2. Influenza Other Respi Viruses. 2022;16(6):1072-81.
17. Cobb NL, Sathe NA, Duan KI, et al. Comparison of Clinical Features and Outcomes in Critically Ill Patients Hospitalized with COVID-19 versus Influenza. *Ann Am Thorac Soc*. Apr 2021;18(4):632-640. doi:10.1513/AnnalsATS.202007-805OC
18. Treweek S, Lockhart P, Pitkethly M, Cook JA, Kjeldstrøm M, Johansen M, et al. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. BMJ Open. 2013;3(2):e002360.
19. Martin GL, Trioux T, Gaudry S, Tubach F, Hajage D, Dechartres A. Association Between Lack of Blinding and Mortality Results in Critical Care Randomized Controlled Trials: A Meta-Epidemiological Study. Crit Care Med. 2021;49(10):1800-11.
20. Cheng MP, Lawandi A, Butler-Laporte G, De l'Étoile-Morel S, Paquette K, Lee TC. Adjunctive Daptomycin in the Treatment of Methicillin-susceptible Staphylococcus aureus Bacteremia: A Randomized, Controlled Trial. Clin Infect Dis. 2021;72(9):e196-e203.
21. Nahm ML, Pieper CF, Cunningham MM. Quantifying Data Quality for Clinical Trials Using Electronic Data Capture. PLoS One. 2008;3(8):e3049.
22. Health UDo, Services H. Common Terminology Criteria for Adverse Events. Version 5.0. Published November 27, 2017. 2020
23. Sohani ZN, Butler-Laporte G, Aw A, Belga S, Benedetti A, Carignan A, et al. Low-dose trimethoprim-sulfamethoxazole for the treatment of Pneumocystis jirovecii pneumonia (LOW-TMP): protocol for a phase III randomised, placebo-controlled, dose-comparison trial. BMJ Open. 2022;12(7):e053039.
24. Xie F, Pullenayegum E, Gaebel K, Bansback N, Bryan S, Ohinmaa A, et al. A Time Trade-off-derived Value Set of the EQ-5D-5L for Canada. Med Care. 2016;54(1):98-105.
25. Bongard E, van der Velden AW, Cook J, et al. Antivirals for influenza-Like Illness? A randomised Controlled trial of Clinical and Cost effectiveness in primary CarE (ALIC(4)

E): the ALIC(4) E protocol. *BMJ Open*. Jul 12 2018;8(7):e021032. doi:10.1136/bmjopen-2017-021032
26. Rombach I, Wang K, Tonner S, Grabey J, Harnden A, Wolstenholme J. Quality of life, healthcare use and costs in 'at-risk' children after early antibiotic treatment versus placebo for influenza-like illness: within-trial descriptive economic analyses of the ARCHIE randomised controlled trial. *BMJ Open*. 2022;12(4):e049373. doi:10.1136/bmjopen-2021-049373
27. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in Medicine — Reporting of Subgroup Analyses in Clinical Trials. N Engl J Med. 2007;357(21):2189-94.
28. Kumar A, Chakraborty BS. Interim analysis: A rational approach of decision making in clinical trial. J Adv Pharm Technol Res. 2016;7(4):118-22.
29. Snapinn S, Chen MG, Jiang Q, Koutsoukos T. Assessment of futility in clinical trials. Pharm Stat. 2006;5(4):273-81.
30. Wolbers M, Heemskerk D, Chau TT, Yen NT, Caws M, Farrar J, et al. Sample size requirements for separating out the effects of combination treatments: randomised controlled trials of combination therapy vs. standard treatment compared to factorial designs for patients with tuberculous meningitis. Trials. 2011;12:26.

## Figures and Tables

| | STUDY PERIOD | | | | |
|---|---|---|---|---|---|
| | **Enrollment** | **Post-allocation** | | | |
| **TIMEPOINT*** | ***Day 1*** | ***Days 1-5*** | ***Days 6-10*** | ***Days 11-29*** | ***Days 30-35*** |
| **ENROLLMENT:** | | | | | |
| **Eligibility Screen** | **X** | | | | |
| **Informed Consent** | **X** | | | | |
| ***Demographic Data*** | **X** | | | | |
| **Allocation** | **X** | | | | |
| **INTERVENTIONS:** | | | | | |
| ***Oseltamivir or Placebo*** | | **X** | | | |
| ***Dexamethasone or Placebo*** | | **X** | **X** | | |
| **ASSESSMENTS:** | | | | | |
| ***Physical Examination*** | **X** | | | | |
| ***Checking Vital Signs*** | **X** | **X** | **X** | **X** | |
| ***Medical History*** | **X** | | | | |
| ***Baseline Blood Sample (CBC, SMA7, liver function tests)*** | **X** | | | | |
| ***Medical Record Check for Outcomes*** | | **X** | **X** | **X** | **X** |
| ***Daily Follow-Ups*** | | **X** | **X** | | |
| ***Weekly Follow-Up*** | | | | **X** | |

| | | | | | |
|---|---|---|---|---|---|
| ***PRIMARY OUTCOMES:*** | | | | | |
| ***All-Cause Mortality*** | | | | | **X** |
| ***SECONDARY OUTCOMES:*** | | | | | |
| ***In-Hospital Mortality, ICU Care, Respiratory Support, Secondary Infections*** | | **X** | **X** | **X** | **X** |
| ***EuroQol EQ-5D-5L*** | **X** | | | | **X** |

**Figure 1.** Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) study schedule of planned enrollment, interventions, assessments and outcomes

## Chapter 5. Discussion

Having now presented the entirety of my thesis research, I soundly believe I achieved each of my objectives. As proposed, I reviewed and synthesized the literature on oseltamivir for influenza outpatients (manuscript under revision at JAMA Internal Medicine) as well as the literature on oseltamivir and corticosteroids for hospitalized patients. I then used the findings of the latter review to inform the creation of a randomized controlled trial protocol which can be taken forward to conduct. Thus, I have produced two high-quality first-author papers which will advance our knowledge with respect to influenza treatment. In this chapter, I will subsequently explain the contributions and implications of my findings and the research still needed to further advance the field of influenza therapeutics.

### *Contributions of My Work*

Throughout my thesis, I made several contributions to advance the knowledge of the benefits, risks, and gaps in literature related to influenza therapeutics for both outpatients and hospitalized individuals.

To start, I conducted a systematic review and meta-analysis that reviewed and synthesized the literature on the risk of hospitalization for influenza outpatients given oseltamivir. This resolved the conflicting conclusions of previous studies and established that oseltamivir is unlikely to provide a clinically meaningful benefit over placebo with respect to hospitalization. Although prior reviews have investigated the same topic, mine consists of the most up-to-date and extensive search strategy with the inclusion of 8 databases.[29,39,40] By subsequently including 3400 more patients, my hospitalization estimate (RR: 0.77, 95% CI: 0.47 to 1.27) also represents the most accurate value within the literature. As a result, my study will serve as the primary body of evidence on the subject rather than simply add to the collection of previous publications.

The manuscript contributed as well by imparting new knowledge with several of its findings. One example is that it produced a hospitalization estimate that was more precise, better encompassed the current clinical field, and accounted for admissions due to oseltamivir, an aspect often overlooked. This was achieved by being the first review to include six large, recent

RCTs and one of the few to examine all-cause admissions rather than influenza-related cases. Another new finding was the disparity in subgroup estimates between studies funded by Roche (RR: 0.50, 95% CI: 0.25 to 0.97) and other sponsors (RR: 1.32, 95% CI: 0.63 to 2.75). Despite allegations that the initial oseltamivir trials suffer from reporting bias, I was the first to investigate, quantify and acknowledge that the claim may be correct.[21] Finally, one other discovery made by my review was that psychiatric disorders were less frequent for patients given oseltamivir compared to placebo. Long thought to have a hazardous association as evidenced by the ban for Japanese teenagers and FDA safety review, this finding will ease fears and indicate many neuropsychiatric episodes were caused by influenza instead.[84]

Although not its own manuscript, another component contributing to the collective knowledge on influenza therapeutics is my review on the efficacy of oseltamivir and corticosteroids against inpatient mortality. As the first to synthesize the conflicted literature for both treatments, I discovered there were no high quality RCTs involving either drug, a notable discovery given that influenza causes 12,200 Canadians to be hospitalized every year.[8] Moreover, I found that in-hospital mortality was more frequently reported (26/32 studies) than 30-day rates (14/32 studies). Considering that placebo-controlled RCTs are the highest level of evidence and 30-day outcomes are the benchmark in assessing risk, I identified the need for an RCT that incorporated these elements.[85,86] Furthermore, despite the inability to produce conclusive corticosteroid estimates, I did establish that oseltamivir had a non-significant effect compared to standard of care based on substantial observational evidence. While an RCT is needed for confirmation, this finding will spark deliberation on whether oseltamivir truly has value in inpatient settings.

As a result, inspired by the findings of that review, the final element that will advance influenza inpatient care is my second thesis manuscript, my randomized controlled trial protocol. Once implemented, on account of being the first inpatient placebo-controlled RCT focused on oseltamivir and corticosteroids (without antiviral co-treatment), original data will be produced on not only mortality, but ICU admittance, respiratory support and adverse event rates. In addition, depending on the results, the trial may be the first to demonstrate an influenza treatment with definitive efficacy against inpatient mortality.[87] Thus, this trial protocol will serve as the

foundation for establishing whether oseltamivir and dexamethasone are important influenza inpatient treatments.

*Implications*

With the significant addition of knowledge and insight provided by my thesis, multiple clinical and public health implications will subsequently occur. Many of those stem from my finding that oseltamivir has no effect on hospitalization, but does increase the risk of gastrointestinal adverse events. On an individual basis, healthcare providers are expected to transition away from oseltamivir as an outpatient treatment for two reasons. First, if hospitalization is a concern for any patient, then the drug has little value given its ineffectiveness in preventing the outcome. Second, for those less at risk, the increased rate of side effects may outweigh the chance of experiencing any modest clinical benefit. Instead, healthcare providers may turn to alternative antivirals with greater efficacy in preventing complications like baloxavir or even home remedies (i.e. vitamin C, fluids) for low-risk patients to avoid risking the harms of any treatment.[88] Admittedly, this movement has already begun in Canada with many physicians abandoning oseltamivir because of the general sentiment that the drug is futile. However, for those yet to react, my review should persuade a further percent to follow suit, although some may resist due to the opinion that the drug's modest reduction in symptom duration still warrants its usage.[21]

On a broader level, my conclusion will force policy makers to re-examine their outpatient treatment guidelines regarding oseltamivir, especially for high-risk populations. Those decisions may also have economic consequences for Roche who recently negotiated over-the-counter rights for oseltamivir in the United States.[89] Without recommendations from trusted international and community guidelines, patients may become hesitant, resulting in lost sales which have already decreased by 29% from 2018 to 2019.[90] Furthermore, the finding will also compel policy makers in at least 95 countries including Canada and the United States to re-evaluate their pandemic plans since oseltamivir comprises the majority of their antiviral stockpiles.[26] As unfortunately learned during COVID-19, minimizing hospitalization is essential in pandemic responses to prevent the collapse of healthcare systems.[91] With oseltamivir providing no substantial benefit, the drug will be replaced with a therapeutic that has greater efficacy and fewer harms in terms of adverse events to minimize the clinical burden of any future

pandemic. Whether this will be achieved by another antiviral, a monoclonal antibody, or a brand new treatment should all current options be unsatisfactory, remains to be seen.

Last but not least, influenza deserves a well-designed randomized controlled trial. As a result, the initial backbone which I developed will also have several implications on influenza inpatient care upon its execution. In the event dexamethasone is found to reduce inpatient mortality, inpatient treatment guidelines will need to be updated given its cost-effectiveness and accessibility.[92] Additionally, the success of translating its usage from COVID-19 to influenza would raise questions on whether other effective COVID-19 treatments, like tocilizumab or baricitinib in regards to mortality, could be utilized as well.[93,94] With respect to oseltamivir, should it demonstrate benefit against inpatient mortality, this would validate the findings presented by several guidelines such as the CDC and European CDC.[28,95] However, if it does not, the repercussions could be profound given that more than a decade of incorrect practice would have occurred. Since the original inpatient recommendations were based on observational data and expert opinion, the finding would cast a spotlight on the issues of relying on low-quality evidence and the need for RCTs. In addition, aside from modifying treatment guidelines, antiviral stockpiles and prescription patterns, a second efficacy outcome to be refuted would cast doubt on oseltamivir's remaining reported benefits on symptom alleviation and prophylaxis.

*Limitations*

It should be acknowledged that my thesis does possess some limitations though. One example is that with the inclusion criteria of my studies requiring individuals at least 12 years of age, I was unable to evaluate the effect of oseltamivir or corticosteroids on pediatric populations. Although this was done to minimize heterogeneity since children receive lesser dosages and face innately higher risks of complications, as the age cohort most likely to develop symptomatic influenza, there is ample merit for similar pediatric-based studies.[96] The other major limitation within my thesis was that I only assessed two influenza therapeutics. By omitting all other treatments, I was limited in my comparisons and may have overlooked other choices. For example, I was unable to confirm if salvage peramivir with oseltamivir is more effective in reducing inpatient mortality than oseltamivir and corticosteroids.[97] Even within my own inpatient literature review, the restriction on oseltamivir being the only antiviral permitted as co-treatment in corticosteroid

studies caused the exclusion of some larger observational studies. As a result, by focusing on oseltamivir and/or steroids, I bypassed individual or combined therapies that may be even more optimal in preventing hospitalization or inpatient mortality.

*Future Research*

Despite the significant progress made by my thesis, additional research is required to address lingering questions on both treatments. Focusing on outpatients to start, studies should be done to see if oseltamivir reduces the risk of hospitalization for specific subgroups. While it is evident that oseltamivir is unlikely to benefit the general public or high-risk individuals as a whole, it may possess some utility to select groups who were not isolated in my review. Some examples include: pregnant women; patients with immunodeficiency (e.g. transplant); or the advanced elderly including those with severe frailty or who live in nursing homes. Given that they all face a greater risk of complications but experience fewer severe outcomes when given antivirals, oseltamivir may still yield some benefit for them.[98,99] Second, due to my review on hospitalization restricting oseltamivir to its normal regimen of 75mg twice a day, studies could be done to see if higher dosages lead to increased efficacy on the outcome. Although previous inpatient trials have found double dosages to have no clinical advantages and a potential for increased toxicity, a change in clinical settings and outcome may produce favorable results.[100,101] Finally, with respect to inpatient care, should corticosteroids prove to be effective in reducing mortality in my RCT, another trial focused on pediatric patients could be advantageous. Since children admitted with influenza almost always require oxygen therapy, the addition of steroids to treatment protocols could significantly help reduce lung inflammation and mitigate the number of complications.[102]

**Conclusion**

In conclusion, my thesis concretely summarized the current state of two key influenza therapeutics and provided the groundwork to further advance our understanding of them. In particular, despite a belief that oseltamivir reduces complications due to influenza, I demonstrated that it is unlikely to be effective against hospitalization. Within the inpatient population, I also identified that a controlled trial for oseltamivir and corticosteroids remains a necessity and subsequently provided a RCT protocol to meet this demand. As a result, my

research created a robust evidence base that will help serve multiple populations in both pandemics and seasonal epidemics. However, considering that influenza annually infects a billion individuals and yet only a few thousand have been part of high quality studies for either drug, my thesis has only just begun the work still needed to fully optimize influenza treatment strategies.

**Master Reference List (Excluding Manuscripts)**


1. Influenza Virus. *Transfus Med Hemother*. 2009;36(1):32-39. doi:10.1159/000197314
2. Boktor SW, Hafner JW. Influenza. *StatPearls*. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.
3. Ghebrehewet S, MacPherson P, Ho A. Influenza. *BMJ*. Dec 7 2016;355:i6258. doi:10.1136/bmj.i6258
4. Barberis I, Myles P, Ault SK, Bragazzi NL, Martini M. History and evolution of influenza control through vaccination: from the first monovalent vaccine to universal vaccines. *J Prev Med Hyg*. Sep 2016;57(3):E115-e120.
5. Flu (influenza): Prevention and risks (Government of Canada) (2021).
6. Flu (influenza): Symptoms and treatment (Government of Canada) (2020).
7. Godman H. How long does the flu last? *Harv Health Lett*. Harvard Health Publishing; 2020. October 1, 2020.
8. Seasonal Influenza, Avian Influenza and Pandemic Influenza. Infection Prevention and Control Canada. 2022.
9. Black CL, O'Halloran A, Hung MC, et al. Vital Signs: Influenza Hospitalizations and Vaccination Coverage by Race and Ethnicity-United States, 2009-10 Through 2021-22 Influenza Seasons. *MMWR Morb Mortal Wkly Rep*. Oct 28 2022;71(43):1366-1373. doi:10.15585/mmwr.mm7143e
10. Putri WCWS, Muscatello DJ, Stockwell MS, Newall AT. Economic burden of seasonal influenza in the United States. *Vaccine*. 2018/06/22/ 2018;36(27):3960-3966. doi:https://doi.org/10.1016/j.vaccine.2018.05.057
11. Ferguson N. Poverty, death, and a future influenza pandemic. *The Lancet*. 2006;368(9554):2187-2188. doi:10.1016/S0140-6736(06)69870-X
12. Fan VY, Jamison DT, Summers LH. Pandemic risk: how large are the expected losses? *Bull World Health Organ*. Feb 1 2018;96(2):129-134. doi:10.2471/blt.17.199588
13. Jester BJ, Uyeki TM, Patel A, Koonin L, Jernigan DB. 100 Years of Medical Countermeasures and Pandemic Influenza Preparedness. *Am J Public Health*. Nov 2018;108(11):1469-1472. doi:10.2105/ajph.2018.304586
14. Influenza Treatment. National Institute of Allergy and Infectious Diseases; 2017.
15. Sloan SE, Szretter KJ, Sundaresh B, et al. Clinical and virological responses to a broad-spectrum human monoclonal antibody in an influenza virus challenge study. *Antiviral Res*. 2020/12/01/ 2020;184:104763. doi:https://doi.org/10.1016/j.antiviral.2020.104763
16. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. *N Engl J Med*. 2021;385(15):1382-1392. doi:10.1056/NEJMoa2102685
17. Vigil A, Frias-Staheli N, Carabeo T, Wittekind M. Airway Delivery of Anti-influenza Monoclonal Antibodies Results in Enhanced Antiviral Activities and Enables Broad-Coverage Combination Therapies. *J Virol*. 2020;94(22):e00052-20. doi:doi:10.1128/JVI.00052-20

18. Chai N, Swem LR, Reichelt M, et al. Two Escape Mechanisms of Influenza A Virus to a Broadly Neutralizing Stalk-Binding Antibody. *PLoS Pathog*. Jun 2016;12(6):e1005702. doi:10.1371/journal.ppat.1005702
19. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. *Critical Care*. 2020/12/14 2020;24(1):696. doi:10.1186/s13054-020-03400-9
20. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA*. 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023
21. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ : British Medical Journal*. 2014;348:g2545. doi:10.1136/bmj.g2545
22. Shim SJ, Chan M, Owens L, Jaffe A, Prentice B, Homaira N. Rate of use and effectiveness of oseltamivir in the treatment of influenza illness in high-risk populations: A systematic review and meta-analysis. *Health Sci Rep*. Mar 2021;4(1):e241. doi:10.1002/hsr2.241
23. Mudur G. Indian firm to produce oseltamivir for developing countries. *BMJ*. Jan 7 2006;332(7532):5. doi:10.1136/bmj.332.7532.5-a
24. Prescribed Medicines Files (Agency for Healthcare Research and Quality) (2022).
25. Reuters Staff. Roche touts new flu drug as Tamiflu suffers generics hit. *Reuters*. Thomson Reuters Corporation; 2018.
26. Vilhelmsson A, Mulinari S. Pharmaceutical lobbying and pandemic stockpiling of Tamiflu: a qualitative study of arguments and tactics. *Journal of Public Health*. 2018;40(3):646-651. doi:10.1093/pubmed/fdx101
27. Papenburg J, Mubareka S, Allen UD, et al. Guidance on the use of antiviral agents for the 2019-2020 influenza season. *J Assoc Med Microbiol Infect Dis Can*. Jun 2020;5(2):57-60. doi:10.3138/jammi.2020-01-13
28. Influenza Antiviral Medications: Summary for Clinicians (Centers for Disease Control and Prevention) (2022).
29. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database Syst Rev*. Apr 10 2014;2014(4):Cd008965. doi:10.1002/14651858.CD008965.pub4
30. Kelton E. Whistleblower Cases Are A Warning To Covid-19 Vaccine Makers. Forbes: Forbes Media LLC; 2020.
31. Cruz-Topete D, Cidlowski JA. One Hormone, Two Actions: Anti- and Pro-Inflammatory Effects of Glucocorticoids. *Neuroimmunomodulation*. 2015;22(1-2):20-32. doi:10.1159/000362724
32. Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. *Br J Pharmacol*. Jun 2006;148(3):245-54. doi:10.1038/sj.bjp.0706736

33. Huang J, Guo J, Li H, Huang W, Zhang T. Efficacy and safety of adjunctive corticosteroids therapy for patients with severe community-acquired pneumonia: A systematic review and meta-analysis. *Medicine (Baltimore)*. Mar 2019;98(13):e14636. doi:10.1097/md.0000000000014636
34. Hirano Y, Madokoro S, Kondo Y, Okamoto K, Tanaka H. Corticosteroid treatment for early acute respiratory distress syndrome: a systematic review and meta-analysis of randomized trials. *Journal of Intensive Care*. 2020/12/07 2020;8(1):91. doi:10.1186/s40560-020-00510-y
35. Lee TC, McDonald EG, Butler-Laporte G, Harrison LB, Cheng MP, Brophy JM. Remdesivir and systemic corticosteroids for the treatment of COVID-19: A Bayesian re-analysis. *Int J Infect Dis*. Mar 2021;104:671-676. doi:10.1016/j.ijid.2021.01.065
36. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care*. Mar 27 2019;23(1):99. doi:10.1186/s13054-019-2395-8
37. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam JS, Lim WS. Effect of Corticosteroid Therapy on Influenza-Related Mortality: A Systematic Review and Meta-analysis. *The Journal of Infectious Diseases*. 2015;212(2):183-194. doi:10.1093/infdis/jiu645
38. Ramirez J, Peyrani P, Wiemken T, Chaves SS, Fry AM. A Randomized Study Evaluating the Effectiveness of Oseltamivir Initiated at the Time of Hospital Admission in Adults Hospitalized With Influenza-Associated Lower Respiratory Tract Infections. *Clin Infect Dis*. Aug 16 2018;67(5):736-742. doi:10.1093/cid/ciy163
39. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet*. May 2 2015;385(9979):1729-1737. doi:10.1016/s0140-6736(14)62449-1
40. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of Oseltamivir Treatment on Influenza-Related Lower Respiratory Tract Complications and Hospitalizations. *Arch Intern Med*. 2003;163(14):1667-1672. doi:10.1001/archinte.163.14.1667
41. McDonald EG, Prosty C, Hanula R, et al. Observational versus randomized controlled trials to inform antibiotic treatment durations: a narrative review. *Clin Microbiol Infect*. Sep 13 2022;doi:10.1016/j.cmi.2022.09.002
42. PROSPERO. Oseltamivir and the rate of hospitalizations for influenza-infected outpatients: a systematic review and meta-analysis of randomized controlled trials. National Institute of Health Research.
43. Antiviral Medications for Treatment of Influenza (Public Health Ontario) (2019).
44. WHO Guidelines Approved by the Guidelines Review Committee. *Guidelines for the clinical management of severe illness from influenza virus infections*. World Health Organization © World Health Organization 2022.; 2022.
45. Martin-Loeches I, Torres A. Corticosteroids for CAP, influenza and COVID-19: when, how and benefits or harm? *European Respiratory Review*. 2021;30(159):200346. doi:10.1183/16000617.0346-2020

46. Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. *Br J Pharmacol*. Jun 2006;148(3):245-54. doi:10.1038/sj.bjp.0706736
47. Lee TC, Murthy S, Del Corpo O, et al. Remdesivir for the treatment of COVID-19: a systematic review and meta-analysis. *Clin Microbiol Infect*. Sep 2022;28(9):1203-1210. doi:10.1016/j.cmi.2022.04.018
48. Clark TW, Beard KR, Brendish NJ, et al. Clinical impact of a routine, molecular, point-of-care, test-and-treat strategy for influenza in adults admitted to hospital (FluPOC): a multicentre, open-label, randomised controlled trial. *The Lancet Respiratory Medicine*. April 2021;9(4):419-429. doi:https://dx.doi.org/10.1016/S2213-2600%2820%2930469-0
49. Hung IFN, To KKW, Chan JFW, et al. Efficacy of Clarithromycin-Naproxen-Oseltamivir Combination in the Treatment of Patients Hospitalized for Influenza A(H3N2) Infection: An Open-label Randomized, Controlled, Phase IIb/III Trial. *Chest*. May 2017;151(5):1069-1080. doi:10.1016/j.chest.2016.11.012
50. Ison MG, Hui DS, Clezy K, et al. A clinical trial of intravenous peramivir compared with oral oseltamivir for the treatment of seasonal influenza in hospitalized adults. *Antiviral Therapy*. 2013;18(5):651-661. doi:http://dx.doi.org/10.3851/IMP2442
51. Lee N, Wong CK, Chan MCW, et al. Anti-inflammatory effects of adjunctive macrolide treatment in adults hospitalized with influenza: A randomized controlled trial. *Antiviral Research*. August 2017;144:48-56. doi:http://dx.doi.org/10.1016/j.antiviral.2017.05.008
52. Lim JJ, Nilsson AC, Silverman M, et al. A phase 2 randomized, double-blind, placebo-controlled trial of MHAA4549A, a monoclonal antibody, plus oseltamivir in patients hospitalized with severe influenza a virus infection. *Antimicrobial Agents and Chemotherapy*. July 2020;64(7) (no pagination)e00352-20. doi:http://dx.doi.org/10.1128/AAC.00352-20
53. Marty FM, Vidal-Puigserver J, Clark C, et al. Intravenous zanamivir or oral oseltamivir for hospitalised patients with influenza: an international, randomised, double-blind, double-dummy, phase 3 trial. *The Lancet Respiratory Medicine*. 01 Feb 2017;5(2):135-146. doi:http://dx.doi.org/10.1016/S2213-2600%2816%2930435-0
54. O'Neil B, Ison MG, Hallouin-Bernard MC, et al. A Phase 2 Study of Pimodivir (JNJ-63623872) in Combination with Oseltamivir in Elderly and NonElderly Adults Hospitalized with Influenza A Infection: OPAL study. *The Journal of infectious diseases*. 2020;30doi:http://dx.doi.org/10.1093/infdis/jiaa376
55. Akinci E, Kayaaslan B, Yetkin MA, et al. Analysis of 113 hospitalized patients with confirmed 2009 influenza a (H1N1) virus infection. [Turkish]. 2009 influenza A (H1N1) enfeksiyonu tanisiyla yatirilan 113 hastanin analizi. *Turkish Journal of Medical Sciences*. 2011;41(3):507-514. doi:http://dx.doi.org/10.3906/sag-1003-688
56. Al Salman J, Al Sharbati W, Al Hajeri M, Abdalla M, Hassan E, Alzaimoor K. Adult cases of H1N1 influenza admitted from 2015 to 201. *Bahrain Medical Bulletin*. September 2018;40(3):145-149.

57. Belucci TR, Marra AR, Edmond MB, et al. Evaluation of Influenza A H1N1 infection and antiviral utilization in a tertiary care hospital 11 Medical and Health Sciences 1103 Clinical Sciences 11 Medical and Health Sciences 1117 Public Health and Health Services. *BMC Infectious Diseases*. 16 Nov 2018;18(1) (no pagination)579. doi:http://dx.doi.org/10.1186/s12879-018-3492-z
58. Chao CM, Lai CC, Chan KS, et al. Outcomes of patients with severe influenza infection admitted to intensive care units: A retrospective study in a medical centre. *Journal of Medical Microbiology*. October 2017;66(10):1421-1428. doi:http://dx.doi.org/10.1099/jmm.0.000593
59. Groeneveld GH, Marbus SD, Ismail N, et al. Effectiveness of oseltamivir in reduction of complications and 30-day mortality in severe seasonal influenza infection. *Int J Antimicrob Agents*. Nov 2020;56(5):106155. doi:10.1016/j.ijantimicag.2020.106155
60. Hegde S, Thyagaraj V, Prabhu D. "H1N1 influenza revisited: Our experience of the 2019 outbreak". *Bangladesh Journal of Medical Science*. 02/25 2022;21(2):426-431. doi:10.3329/bjms.v21i2.58077
61. Hernu R, Chroboczek T, Madelaine T, et al. Early oseltamivir therapy improves the outcome in critically ill patients with influenza: a propensity analysis. *Intensive Care Med*. Feb 2018;44(2):257-260. doi:10.1007/s00134-017-4953-3
62. Hiba V, Chowers M, Levi-Vinograd I, Rubinovitch B, Leibovici L, Paul M. Benefit of early treatment with oseltamivir in hospitalized patients with documented 2009 influenza A (H1N1): Retrospective cohort study. *Journal of Antimicrobial Chemotherapy*. May 2011;66(5):1150-1155. doi:http://dx.doi.org/10.1093/jac/dkr089
63. Joshi M, Chandra D, Mittadodla P, Bartter T. The impact of vaccination on influenza-related respiratory failure and mortality in hospitalized elderly patients over the 2013-2014 season. *Open Respiratory Medicine Journal*. 2015;9:9-14.
64. Katzen J, Kohn R, Houk JL, Ison MG. Early oseltamivir after hospital admission is associated with shortened hospitalization: A 5-year analysis of oseltamivir timing and clinical outcomes. *Clinical Infectious Diseases*. 18 Jun 2019;69(1):52-58. doi:http://dx.doi.org/10.1093/cid/ciy860
65. Khanum I, Ahmed AS, Awan S, Bano S, Jamil B. Predictors of mortality in hospitalized patients with influenza: A five-year experience from a tertiary care centre in Pakistan. *Monaldi Archives for Chest Disease*. 28 Dec 2021;90(4):692-697. doi:https://dx.doi.org/10.4081/MONALDI.2020.1456
66. Kositpantawong N, Surasombatpattana S, Siripaitoon P, et al. Outcomes of early oseltamivir treatment for hospitalized adult patients with community-acquired influenza pneumonia. *PLoS ONE*. December 2021;16(12 December) (no pagination)e0261411. doi:https://dx.doi.org/10.1371/journal.pone.0261411
67. Lee IK, Chen YH, Huang CH, et al. A multicenter cohort study of severe dengue and critically ill influenza patients with elevated cardiac troponin-I: Difference clinical features

and high mortality. *Travel Medicine and Infectious Disease*. 01 May 2022;47 (no pagination)102281. doi:https://dx.doi.org/10.1016/j.tmaid.2022.102281
68. Lee N, Hui DSC, Zuo Z, et al. A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with influenza A and B infections. *Clinical Infectious Diseases*. 01 Dec 2013;57(11):1511-1519. doi:http://dx.doi.org/10.1093/cid/cit597
69. Ling LM, Chow AL, Lye DC, et al. Effects of early oseltamivir therapy on viral shedding in 2009 pandemic influenza A (H1N1) virus infection. *Clin Infect Dis*. Apr 1 2010;50(7):963-9. doi:10.1086/651083
70. Lytras T, Mouratidou E, Andreopoulou A, Bonovas S, Tsiodras S. Effect of Early Oseltamivir Treatment on Mortality in Critically Ill Patients with Different Types of Influenza: A Multiseason Cohort Study. *Clinical Infectious Diseases*. 13 Nov 2019;69(11):1896-1902. doi:http://dx.doi.org/10.1093/cid/ciz101
71. Ramakrishna K, Sampath S, Chacko J, et al. Clinical profile and predictors of mortality of severe pandemic (H1N1) 2009 virus infection needing intensive care: A multi-centre prospective study from South India. *Journal of Global Infectious Diseases*. July-September 2012;4(3):145-152. doi:http://dx.doi.org/10.4103/0974-777X.100569
72. Reyes S, Montull B, Martinez R, et al. Risk factors of A/H1N1 etiology in pneumonia and its impact on mortality. *Respiratory Medicine*. September 2011;105(9):1404-1411. doi:http://dx.doi.org/10.1016/j.rmed.2011.04.011
73. Segaloff HE, Evans R, Arshad S, et al. The impact of obesity and timely antiviral administration on severe influenza outcomes among hospitalized adults. *Journal of Medical Virology*. February 2018;90(2):212-218. doi:http://dx.doi.org/10.1002/jmv.24946
74. Sertogullarindan B, Ozbay B, Gunini H, et al. Clinical and prognostic features of patients with pandemic 2009 influenza A (H1N1) virus in the intensive care unit. *Afr Health Sci*. Jun 2011;11(2):163-70.
75. Shah S, McManus D, Bejou N, et al. Clinical outcomes of baloxavir versus oseltamivir in patients hospitalized with influenza A. *J Antimicrob Chemother*. Oct 1 2020;75(10):3015-3022. doi:10.1093/jac/dkaa252
76. Sharma Y, Horwood C, Hakendorf P, Thompson C. Effectiveness of Oseltamivir in reducing 30-day readmissions and mortality among patients with severe seasonal influenza in Australian hospitalized patients. *Int J Infect Dis*. Mar 2021;104:232-238. doi:10.1016/j.ijid.2021.01.011
77. Tsai MJ, Yang KY, Chan MC, et al. Impact of corticosteroid treatment on clinical outcomes of influenza-associated ARDS: a nationwide multicenter study. *Ann Intensive Care*. Feb 27 2020;10(1):26. doi:10.1186/s13613-020-0642-4
78. Xiao H, Lu SH, Ou Q, Chen YY, Huang SP. Hospitalized patients with novel influenza A (H1N1) virus infection: Shanghai, June - July 2009. *Chin Med J (Engl)*. Feb 20 2010;123(4):401-5.
79. Influenza (Seasonal). World Health Organization 2018.

80. Cobb NL, Sathe NA, Duan KI, et al. Comparison of Clinical Features and Outcomes in Critically Ill Patients Hospitalized with COVID-19 versus Influenza. *Ann Am Thorac Soc*. Apr 2021;18(4):632-640. doi:10.1513/AnnalsATS.202007-805OC
81. Martin GL, Trioux T, Gaudry S, Tubach F, Hajage D, Dechartres A. Association Between Lack of Blinding and Mortality Results in Critical Care Randomized Controlled Trials: A Meta-Epidemiological Study. *Crit Care Med*. Oct 1 2021;49(10):1800-1811. doi:10.1097/ccm.0000000000005065
82. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. Mar 2020;8(3):267-276. doi:10.1016/s2213-2600(19)30417-5
83. Li H, Yang SG, Gu L, et al. Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1)pdm09 viral pneumonia. *Influenza Other Respir Viruses*. Jul 2017;11(4):345-354. doi:10.1111/irv.12456
84. Lee BY. Hallucinations After Taking Tamiflu: How Much Is Real Versus Not Real? *Forbes*.
85. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg*. Jul 2011;128(1):305-310. doi:10.1097/PRS.0b013e318219c171
86. Joung RH-S, Merkow RP. Is it Time to Abandon 30-Day Mortality as a Quality Measure? *Ann Surg Oncol*. 2021/03/01 2021;28(3):1263-1264. doi:10.1245/s10434-020-09262-3
87. Principi N, Camilloni B, Alunno A, Polinori I, Argentiero A, Esposito S. Drugs for Influenza Treatment: Is There Significant News? Review. *Frontiers in Medicine*. 2019-May-28 2019;6doi:10.3389/fmed.2019.00109
88. Liu J-W, Lin S-H, Wang L-C, Chiu H-Y, Lee J-A. Comparison of Antiviral Agents for Seasonal Influenza Outcomes in Healthy Adults and Children: A Systematic Review and Network Meta-analysis. *JAMA Network Open*. 2021;4(8):e2119151-e2119151. doi:10.1001/jamanetworkopen.2021.19151
89. Sanofi signs strategic deal for exclusive US over-the-counter rights to Tamiflu® in Flu Care. Sanofi; 2019.
90. Blankenship K. Roche's Tamiflu follow-up Xofluza scores in flu-spreading study. *Fierce Pharma*.
91. Vercammen P, Yan H, Maxouris C. ‘This is about total collapse of the health care system if we have another spike’ of Covid-19. *CNN*.
92. Águas R, Mahdi A, Shretta R, Horby P, Landray M, White L. Potential health and economic impacts of dexamethasone treatment for patients with COVID-19. *Nat Commun*. Feb 10 2021;12(1):915. doi:10.1038/s41467-021-21134-2
93. Avni T, Leibovici L, Cohen I, et al. Tocilizumab in the treatment of COVID-19-a meta-analysis. *QJM*. Nov 5 2021;114(8):577-586. doi:10.1093/qjmed/hcab142
94. Abizanda P, Calbo Mayo JM, Mas Romero M, et al. Baricitinib reduces 30-day mortality in older adults with moderate-to-severe COVID-19 pneumonia. *J Am Geriatr Soc*. Oct 2021;69(10):2752-2758. doi:10.1111/jgs.17357

95. Penttinen P. Expert opinion on neuraminidase inhibitors for the prevention and treatment of influenza – review of recent systematic reviews and meta-analyses. ECDC Scientific Advice: European Centers for Disease and Control; 2017.
96. Tokars JI, Olsen SJ, Reed C. Seasonal Incidence of Symptomatic Influenza in the United States. *Clin Infect Dis*. 2018;66(10):1511-1518. doi:10.1093/cid/cix1060
97. Huang S-F, Fung C-P, Perng D-W, Wang F-D. Effects of corticosteroid and neuraminidase inhibitors on survival in patients with respiratory distress induced by influenza virus. *Journal of Microbiology, Immunology and Infection*. 2017/10/01/ 2017;50(5):586-594. doi:https://doi.org/10.1016/j.jmii.2015.08.016
98. Antiviral Annex: Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector (Government of Canada) (2022).
99. Yoshikawa TT, Stefan G, Davidson HE. Current Strategies for Management of Influenza in the Elderly Population. *Clin Infect Dis*. 2002;35(6):729-737. doi:10.1086/341246
100. South East Asia Infectious Disease Clinical Research Network. Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. *BMJ*. May 30 2013;346:f3039. doi:10.1136/bmj.f3039
101. Noel ZR, Bastin MLT, Montgomery AA, Flannery AH. Comparison of High-Dose Versus Standard Dose Oseltamivir in Critically Ill Patients With Influenza. *J Intensive Care Med*. Dec 2017;32(10):574-577. doi:10.1177/0885066616638649
102. Suran M. Preparing Hospitals' Medical Oxygen Delivery Systems for a Respiratory "Twindemic". *JAMA*. 2022;327(5):411-413. doi:10.1001/jama.2021.23392

## Appendices
## Appendix A. Supplemental Material for Manuscript 1 (Chapter 2)

**Supplemental Table 1.** Search Strategies
**Ovid Medline**

| # | Search | Results |
|---|---|---|
| 1 | Influenza A virus/ | 22175 |
| 2 | Influenza B virus/ | 4528 |
| 3 | Influenza*.mp. | 145690 |
| 4 | flu.mp. | 15249 |
| 5 | Influenza, Human/ | 54694 |
| 6 | 1 or 2 or 3 or 4 or 5 | 153306 |
| 7 | randomized controlled trial.pt. | 566020 |
| 8 | controlled clinical trial.pt. | 94836 |
| 9 | random*.ab. | 1271612 |
| 10 | placebo.ab. | 227506 |
| 11 | trial.ab. | 596535 |
| 12 | groups.ab. | 2340038 |
| 13 | 7 or 8 or 9 or 10 or 11 or 12 | 3624063 |
| 14 | Exp animals/ not humans.sh. | 4997861 |
| 15 | 13 not 14 | 3114255 |
| 16 | Oseltamivir/ | 3151 |
| 17 | Oseltamivir*.mp. | 4908 |
| 18 | Tamiflu*.mp. | 518 |
| 19 | 16 or 17 or 18 | 4986 |
| 20 | 6 and 15 and 19 | 589 |

**Embase**

| # | Search | Results |
|---|---|---|
| 1 | Influenza virus A/ or Influenza A virus/ | 24615 |
| 2 | Influenza virus B/ or Influenza B virus/ | 7198 |
| 3 | influenza B/ or influenza/ or influenza B/ | 84196 |
| 4 | influenza*.mp. | 223242 |
| 5 | flu*.mp. | 3178533 |
| 6 | 1 or 2 or 3 or 4 or 5 | 3362888 |
| 7 | Randomized controlled trial/ | 708162 |
| 8 | Controlled clinical trial/ | 465854 |
| 9 | random*.ti,ab. | 1792299 |
| 10 | randomization/ | 93918 |
| 11 | Intermethod comparison/ | 282433 |
| 12 | placebo.ti,ab. | 344616 |
| 13 | (compare or compared or comparison).ti. | 593655 |
| 14 | ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. | 2491458 |
| 15 | (open adj label).ti,ab. | 96390 |
| 16 | ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. | 261129 |
| 17 | double blind procedure/ | 196834 |
| 18 | parallel group*1.ti,ab. | 29275 |
| 19 | (crossover or cross over).ti,ab. | 117233 |
| 20 | ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or subject$1 or participant$1)).ti,ab. | 380014 |
| 21 | (assigned or allocated).ti,ab. | 447816 |
| 22 | (controlled adj7 (study or design or trial)).ti,ab. | 409163 |

| | | |
|---|---|---|
| 23 | (volunteer or volunteers).ti,ab. | 273118 |
| 24 | human experiment/ | 572817 |
| 25 | trial.ti. | 364746 |
| 26 | or/7-25 | 5815599 |
| 27 | (random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. Not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. Or randomly assigned.ti,ab.) | 9055 |
| 28 | Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) | 307281 |
| 29 | (((case adj control$) and random$) not randomi?ed controlled).ti,ab. | 19729 |
| 30 | (Systematic review not (trial or study)).ti. | 207099 |
| 31 | (nonrandom$ not random$).ti,ab. | 17850 |
| 32 | Random field$.ti,ab. | 2691 |
| 33 | (random cluster adj# sampl$).ti,ab. | 1430 |
| 34 | (review.ab. and review.pt.) not trial.ti. | 987121 |
| 35 | we searched.ab. And (review.ti. or review.pt.) | 41495 |
| 36 | update review.ab. | 122 |
| 37 | (databases adj4 searched).ab. | 50138 |
| 38 | (rat or rats or mouse or mice or swine or porcupine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout ot marmoset$1).ti. and animal experiment/ | 1146778 |
| 39 | Animal experiment/ not (human experiment/ or human/) | 2410619 |
| 40 | or/27-29 | 3948480 |
| 41 | 26 not 40 | 5160620 |

| | | |
|---|---|---|
| 42 | oseltamivir/ | 13392 |
| 43 | Oseltamivir*.mp. | 14030 |
| 44 | tamiflu*.mp. | 2317 |
| 45 | 42 or 43 or 44 | 14079 |
| 46 | 6 and 41 and 45 | 1121 |

## Cochrane CENTRAL

| # | Search | Results |
|---|---|---|
| 1 | (Influenza A virus):ti,ab,kw | 3139 |
| 2 | (Influenza B virus):ti,ab,kw | 1282 |
| 3 | (Influenza*):ti,ab,kw | 9988 |
| 4 | (flu*):ti,ab,kw | 111122 |
| 5 | MeSH descriptor: [Influenza, Human] this term only | 2902 |
| 6 | (Influenza A*):ti,ab,kw | 8029 |
| 7 | (Influenza B*):ti,ab,kw | 7399 |
| 8 | 1 or 2 or 3 or 4 or 5 or 6 or 7 | 119243 |
| 9 | (controlled clinical trial):pt | 331021 |
| 10 | (randomized controlled trial):pt | 545182 |
| 11 | (random*):ab | 950488 |
| 12 | (placebo):ab | 308565 |
| 13 | (trial):ab | 504148 |
| 14 | (groups):ab | 517708 |
| 15 | 9 or 10 or 11 or 12 or 3 or 14 | 1265774 |
| 16 | MeSH descriptor: [Oseltamivir] this term only | 252 |
| 17 | (oseltamivir*):ti,ab,kw | 577 |
| 18 | (tamiflu*):ti,ab,kw | 86 |
| 19 | 16 or 17 or 18 | 584 |

| | | |
|---|---|---|
| 20 | 8 and 15 and 19 | 356 |

**PubMed**

| # | Search | Results |
|---|---|---|
| 1 | (((((influenza a virus) OR (influenza b virus)) OR (influenza*)) OR (flu*)) OR (influenza a*)) OR (influenza b*) | 153288 |
| 2 | (((((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type])) OR (placebo[Title/Abstract])) OR (clinical trials as topic [MeSH Terms])) or (random*[Title/Abstract])) OR (trial[Title]) | 1804352 |
| 3 | (animals[MeSH Terms]) NOT (humans[MeSH Terms]) | 4937458 |
| 4 | 2 not 3 | 1659482 |
| 5 | ((oseltamivir[MeSH Terms]) OR (oseltamivir*)) OR (tamiflu*) | 4942 |
| 6 | 1 and 4 and 5 | 443 |

**Europe PMC**

| # | Search | Results |
|---|---|---|
| 1 | ((((TS=(influenza*)) OR TS=(flu*)) OR TS=(influenza a virus)) OR TS=(influenza b virus)) | 4110241 |
| 2 | (((((TS=(randomized controlled trial)) OR TS=(controlled clinical trial)) OR AB=(random*)) OR AB=(placebo)) OR AB=(trial)) OR AB=(groups) | 7021918 |
| 3 | ((TS=(oseltamivir)) OR TS=(tamiflu*)) or TS=(oseltamivir*) | 5870 |
| 4 | 1 and 2 and 3 | 1276 |

**Web of Science**

| # | Search | Results |
|---|---|---|
| 1 | TOPIC: (influenza a virus) OR TOPIC: (influenza b virus) OR TOPIC: (influenza*) OR TOPIC: (flu*) | 4115204 |

| | | |
|---|---|---|
| 2 | TS=(controlled clinical trial) OR TS=(randomized controlled trial) OR AB=(random*) OR AB=(placebo) OR AB=(groups) OR AB=(trial) | 7035023 |
| 3 | TOPIC: (Oseltamivir*) OR TOPIC: (tamiflu*) | 5881 |
| 4 | 1 and 2 and 3 | 1276 |

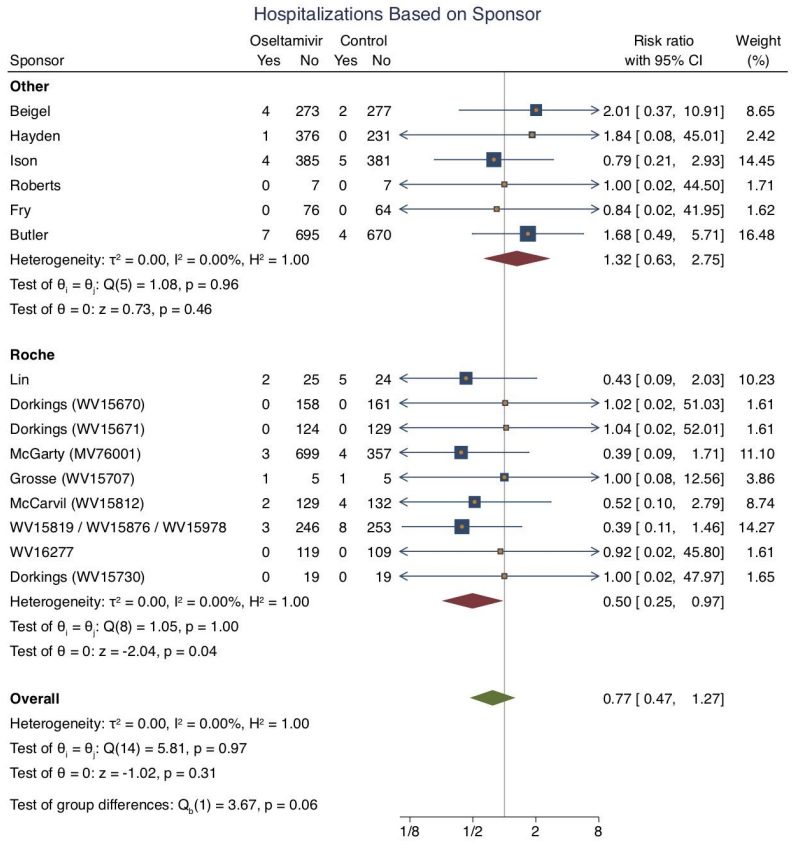
**Clinicaltrials.gov**

| # | Search | Results |
|---|---|---|
| 1 | Condition or disease: Influenza OR Influenza A OR Influenza B, Other terms: Oseltamivir OR Tamiflu Study Type: Interventional (Clinical Trial) | 68 |

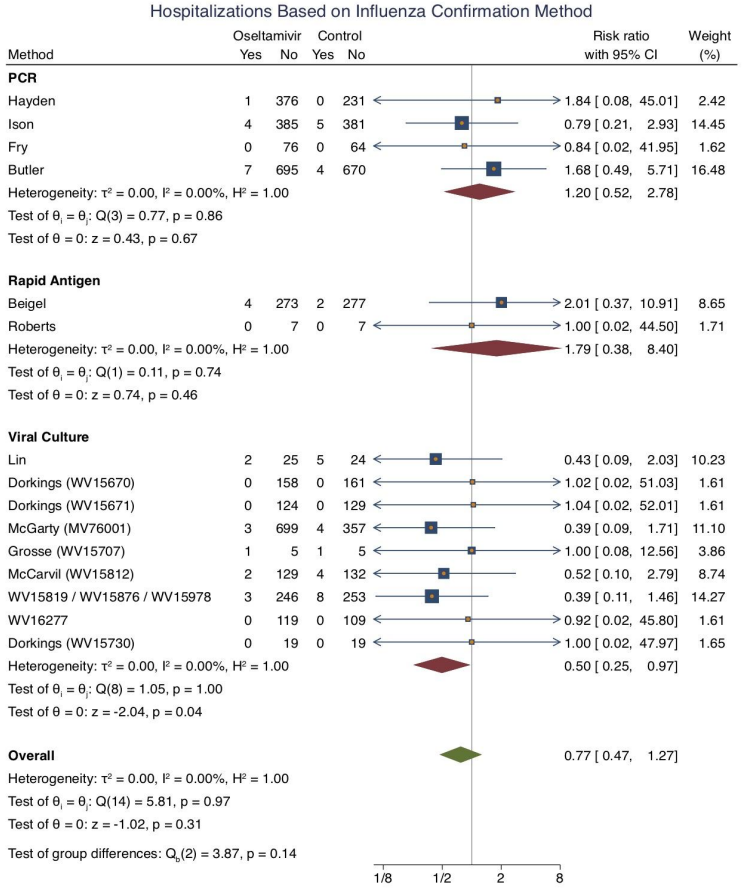
**World Health Organization International Clinical Trials Registry Platform (trialsearch.who.int)**

| # | Search | Results |
|---|---|---|
| 1 | influenza AND (oseltamivir OR tamiflu) | 188 |

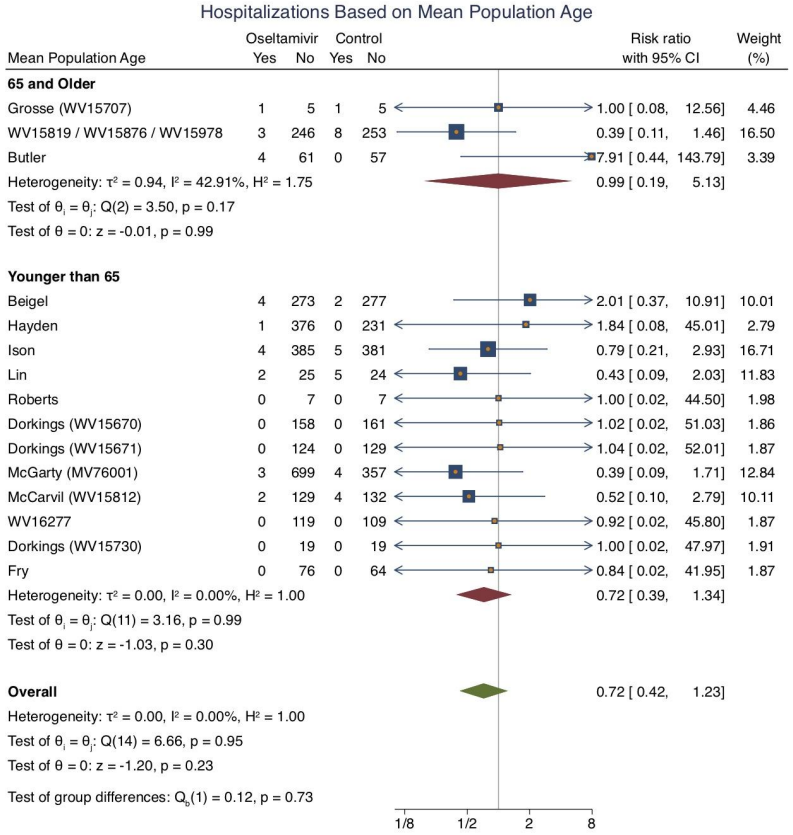

**Supplemental Figure 1.** Visualization of the risk of bias. Determined using the Cochrane Risk of Bias Tool 2.0.


Hospitalizations Based on Sponsor
Sponsor
Oseltamivir Yes No
Control Yes No
Risk ratio with 95% CI
Weight (%)
Other
Beigel 4 273 2 277 2.01 [ 0.37, 10.91] 8.65
Hayden 1 376 0 231 1.84 [ 0.08, 45.01] 2.42
Ison 4 385 5 381 0.79 [ 0.21, 2.93] 14.45
Roberts 0 7 0 7 1.00 [ 0.02, 44.50] 1.71
Fry 0 76 0 64 0.84 [ 0.02, 41.95] 1.62
Butler 7 695 4 670 1.68 [ 0.49, 5.71] 16.48
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 1.32 [ 0.63, 2.75]
Test of θi = θj: Q(5) = 1.08, p = 0.96
Test of θ = 0: z = 0.73, p = 0.46
Roche
Lin 2 25 5 24 0.43 [ 0.09, 2.03] 10.23
Dorkings (WV15670) 0 158 0 161 1.02 [ 0.02, 51.03] 1.61
Dorkings (WV15671) 0 124 0 129 1.04 [ 0.02, 52.01] 1.61
McGarty (MV76001) 3 699 4 357 0.39 [ 0.09, 1.71] 11.10
Grosse (WV15707) 1 5 1 5 1.00 [ 0.08, 12.56] 3.86
McCarvil (WV15812) 2 129 4 132 0.52 [ 0.10, 2.79] 8.74
WV15819 / WV15876 / WV15978 3 246 8 253 0.39 [ 0.11, 1.46] 14.27
WV16277 0 119 0 109 0.92 [ 0.02, 45.80] 1.61
Dorkings (WV15730) 0 19 0 19 1.00 [ 0.02, 47.97] 1.65
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.50 [ 0.25, 0.97]
Test of θi = θj: Q(8) = 1.05, p = 1.00
Test of θ = 0: z = -2.04, p = 0.04
Overall 0.77 [ 0.47, 1.27]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(14) = 5.81, p = 0.97
Test of θ = 0: z = -1.02, p = 0.31
Test of group differences: Qb(1) = 3.67, p = 0.06
1/8
1/2
2
8

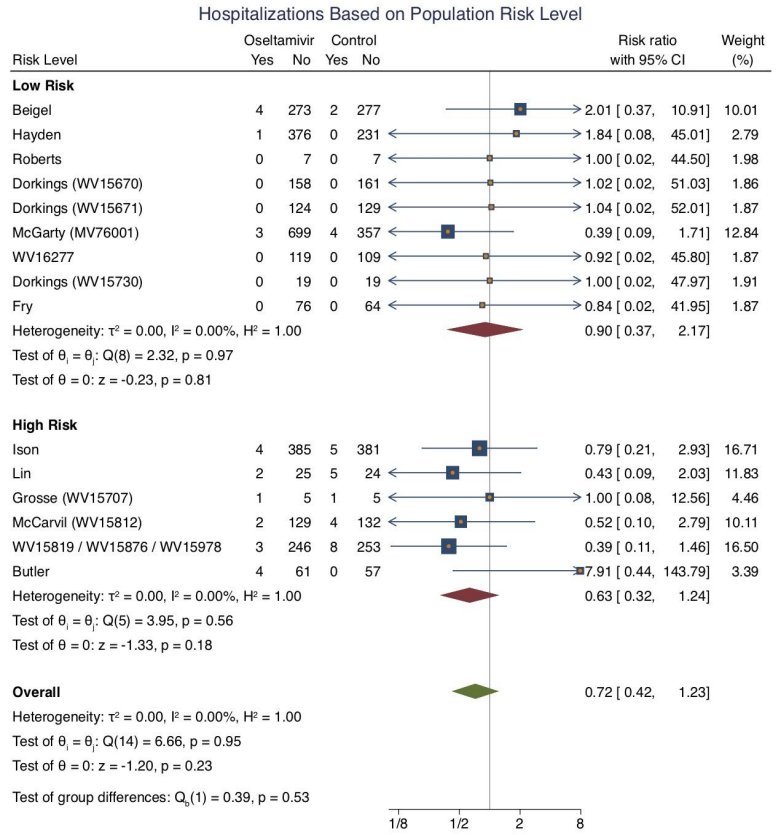
**A)**


Hospitalizations Based on Influenza Confirmation Method
Method
Oseltamivir Yes No
Control Yes No
Risk ratio with 95% CI
Weight (%)
PCR
Hayden 1 376 0 231 1.84 [ 0.08, 45.01] 2.42
Ison 4 385 5 381 0.79 [ 0.21, 2.93] 14.45
Fry 0 76 0 64 0.84 [ 0.02, 41.95] 1.62
Butler 7 695 4 670 1.68 [ 0.49, 5.71] 16.48
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 1.20 [ 0.52, 2.78]
Test of θi = θj: Q(3) = 0.77, p = 0.86
Test of θ = 0: z = 0.43, p = 0.67
Rapid Antigen
Beigel 4 273 2 277 2.01 [ 0.37, 10.91] 8.65
Roberts 0 7 0 7 1.00 [ 0.02, 44.50] 1.71
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 1.79 [ 0.38, 8.40]
Test of θi = θj: Q(1) = 0.11, p = 0.74
Test of θ = 0: z = 0.74, p = 0.46
Viral Culture
Lin 2 25 5 24 0.43 [ 0.09, 2.03] 10.23
Dorkings (WV15670) 0 158 0 161 1.02 [ 0.02, 51.03] 1.61
Dorkings (WV15671) 0 124 0 129 1.04 [ 0.02, 52.01] 1.61
McGarty (MV76001) 3 699 4 357 0.39 [ 0.09, 1.71] 11.10
Grosse (WV15707) 1 5 1 5 1.00 [ 0.08, 12.56] 3.86
McCarvil (WV15812) 2 129 4 132 0.52 [ 0.10, 2.79] 8.74
WV15819 / WV15876 / WV15978 3 246 8 253 0.39 [ 0.11, 1.46] 14.27
WV16277 0 119 0 109 0.92 [ 0.02, 45.80] 1.61
Dorkings (WV15730) 0 19 0 19 1.00 [ 0.02, 47.97] 1.65
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.50 [ 0.25, 0.97]
Test of θi = θj: Q(8) = 1.05, p = 1.00
Test of θ = 0: z = -2.04, p = 0.04
Overall 0.77 [ 0.47, 1.27]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(14) = 5.81, p = 0.97
Test of θ = 0: z = -1.02, p = 0.31
Test of group differences: Qb(2) = 3.87, p = 0.14
1/8
1/2
2
8

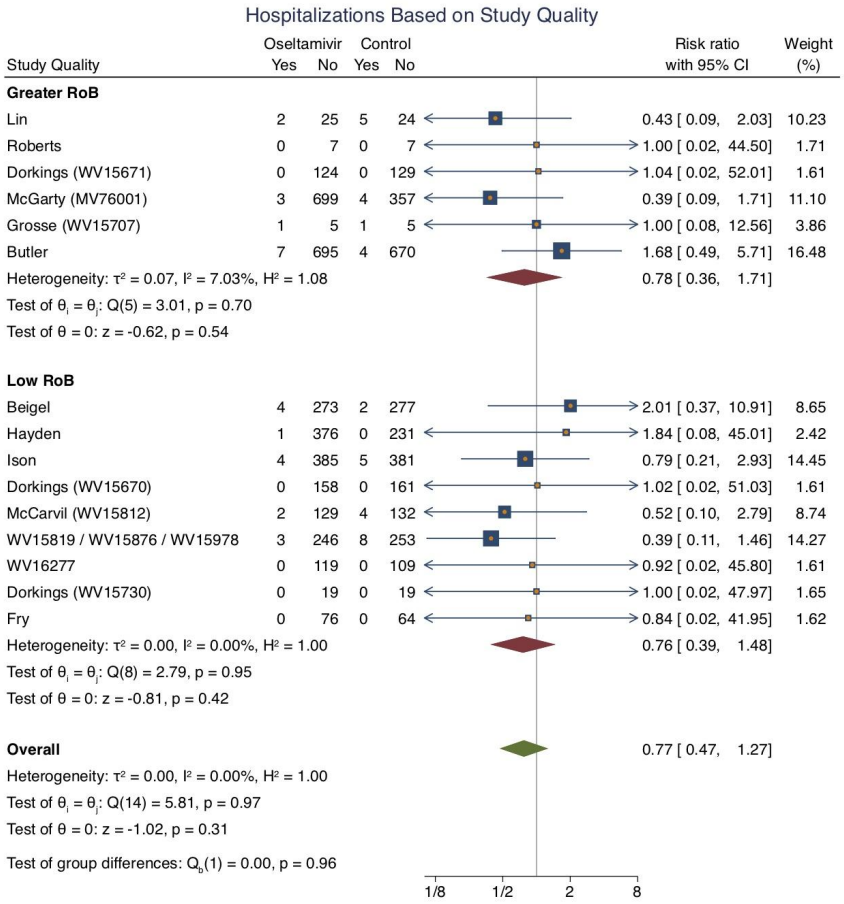
**B)**


Hospitalizations Based on Mean Population Age
Mean Population Age
Oseltamivir Yes No
Control Yes No
Risk ratio with 95% CI
Weight (%)
65 and Older
Grosse (WV15707) 1 5 1 5 1.00 [ 0.08, 12.56] 4.46
WV15819 / WV15876 / WV15978 3 246 8 253 0.39 [ 0.11, 1.46] 16.50
Butler 4 61 0 57 7.91 [ 0.44, 143.79] 3.39
Heterogeneity: τ² = 0.94, I² = 42.91%, H² = 1.75 0.99 [ 0.19, 5.13]
Test of θi = θj: Q(2) = 3.50, p = 0.17
Test of θ = 0: z = -0.01, p = 0.99
Younger than 65
Beigel 4 273 2 277 2.01 [ 0.37, 10.91] 10.01
Hayden 1 376 0 231 1.84 [ 0.08, 45.01] 2.79
Ison 4 385 5 381 0.79 [ 0.21, 2.93] 16.71
Lin 2 25 5 24 0.43 [ 0.09, 2.03] 11.83
Roberts 0 7 0 7 1.00 [ 0.02, 44.50] 1.98
Dorkings (WV15670) 0 158 0 161 1.02 [ 0.02, 51.03] 1.86
Dorkings (WV15671) 0 124 0 129 1.04 [ 0.02, 52.01] 1.87
McGarty (MV76001) 3 699 4 357 0.39 [ 0.09, 1.71] 12.84
McCarvil (WV15812) 2 129 4 132 0.52 [ 0.10, 2.79] 10.11
WV16277 0 119 0 109 0.92 [ 0.02, 45.80] 1.87
Dorkings (WV15730) 0 19 0 19 1.00 [ 0.02, 47.97] 1.91
Fry 0 76 0 64 0.84 [ 0.02, 41.95] 1.87
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.72 [ 0.39, 1.34]
Test of θi = θj: Q(11) = 3.16, p = 0.99
Test of θ = 0: z = -1.03, p = 0.30
Overall 0.72 [ 0.42, 1.23]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(14) = 6.66, p = 0.95
Test of θ = 0: z = -1.20, p = 0.23
Test of group differences: Qb(1) = 0.12, p = 0.73
1/8
1/2
2
8

C)

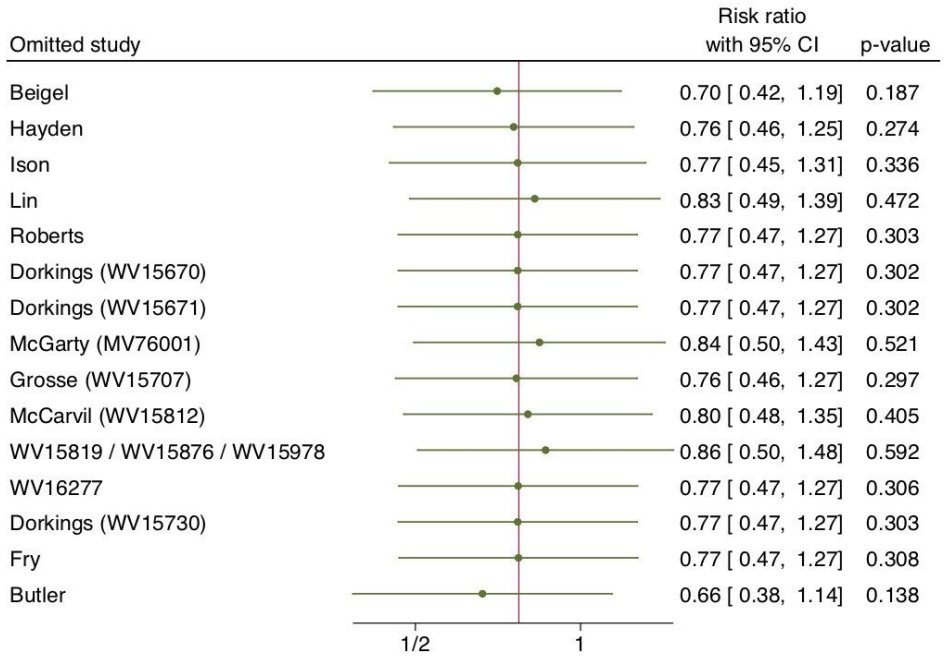

Hospitalizations Based on Population Risk Level
Risk Level
Oseltamivir Yes No
Control Yes No
Risk ratio with 95% CI
Weight (%)
Low Risk
Beigel 4 273 2 277 2.01 [ 0.37, 10.91] 10.01
Hayden 1 376 0 231 1.84 [ 0.08, 45.01] 2.79
Roberts 0 7 0 7 1.00 [ 0.02, 44.50] 1.98
Dorkings (WV15670) 0 158 0 161 1.02 [ 0.02, 51.03] 1.86
Dorkings (WV15671) 0 124 0 129 1.04 [ 0.02, 52.01] 1.87
McGarty (MV76001) 3 699 4 357 0.39 [ 0.09, 1.71] 12.84
WV16277 0 119 0 109 0.92 [ 0.02, 45.80] 1.87
Dorkings (WV15730) 0 19 0 19 1.00 [ 0.02, 47.97] 1.91
Fry 0 76 0 64 0.84 [ 0.02, 41.95] 1.87
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.90 [ 0.37, 2.17]
Test of θi = θj: Q(8) = 2.32, p = 0.97
Test of θ = 0: z = -0.23, p = 0.81
High Risk
Ison 4 385 5 381 0.79 [ 0.21, 2.93] 16.71
Lin 2 25 5 24 0.43 [ 0.09, 2.03] 11.83
Grosse (WV15707) 1 5 1 5 1.00 [ 0.08, 12.56] 4.46
McCarvil (WV15812) 2 129 4 132 0.52 [ 0.10, 2.79] 10.11
WV15819 / WV15876 / WV15978 3 246 8 253 0.39 [ 0.11, 1.46] 16.50
Butler 4 61 0 57 7.91 [ 0.44, 143.79] 3.39
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.63 [ 0.32, 1.24]
Test of θi = θj: Q(5) = 3.95, p = 0.56
Test of θ = 0: z = -1.33, p = 0.18
Overall 0.72 [ 0.42, 1.23]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(14) = 6.66, p = 0.95
Test of θ = 0: z = -1.20, p = 0.23
Test of group differences: Qb(1) = 0.39, p = 0.53
1/8
1/2
2
8

D)

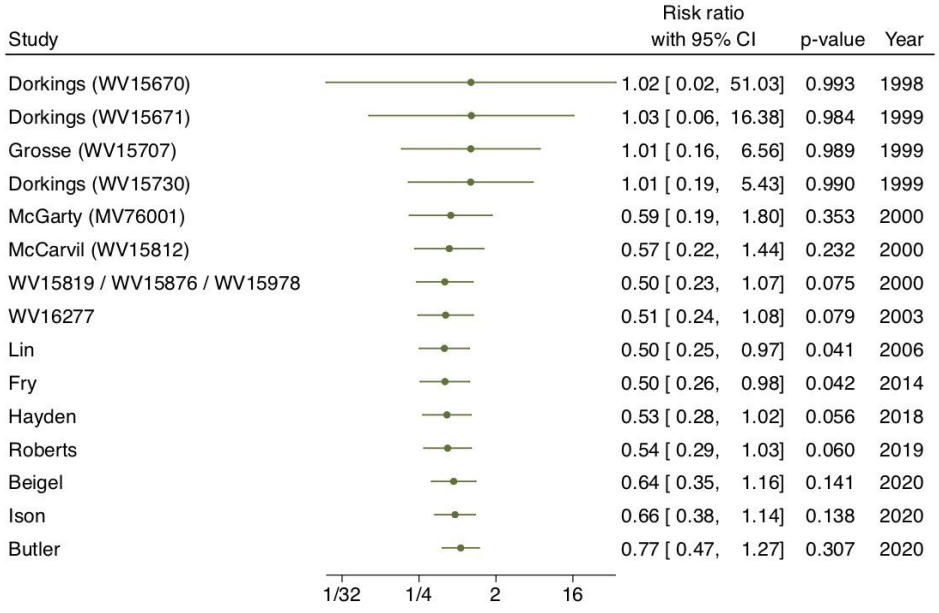



**E)**

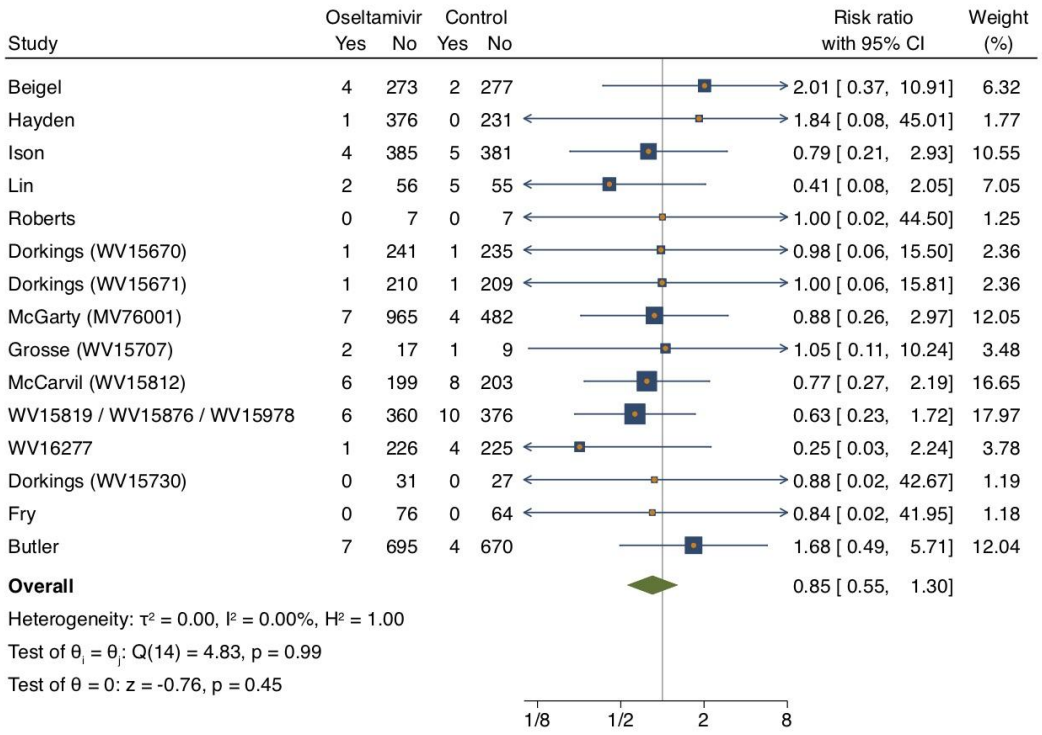
**Supplemental Figure 2.** Random effects subgroup analyses on the outcome of hospitalization. Studies were stratified according to A) Study Sponsor, B) Method of Confirming Influenza Infections, C) Mean Study Population Age, D) Population Risk Level, and E) Study Quality. Yes = number of individuals hospitalized, No = number of individuals who were not. Note: Butler's (2020) 12+ ITTi data provided via data request was used for the subgroup estimates in forest plots A, B, and E. However, the supplemental 65+ ITTi data also provided was used for the subgroup estimates in forest plots C and D.



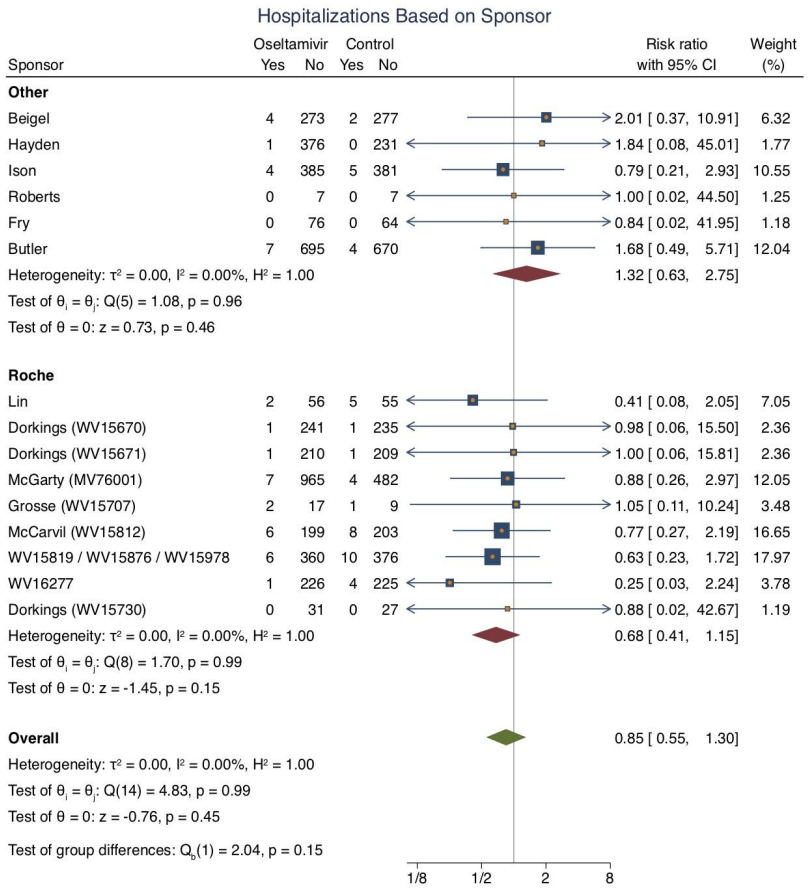

**Supplemental Figure 3.** Random effects remove-one sensitivity analysis. Based on the outcome of hospitalization within the 12+ ITTi population.



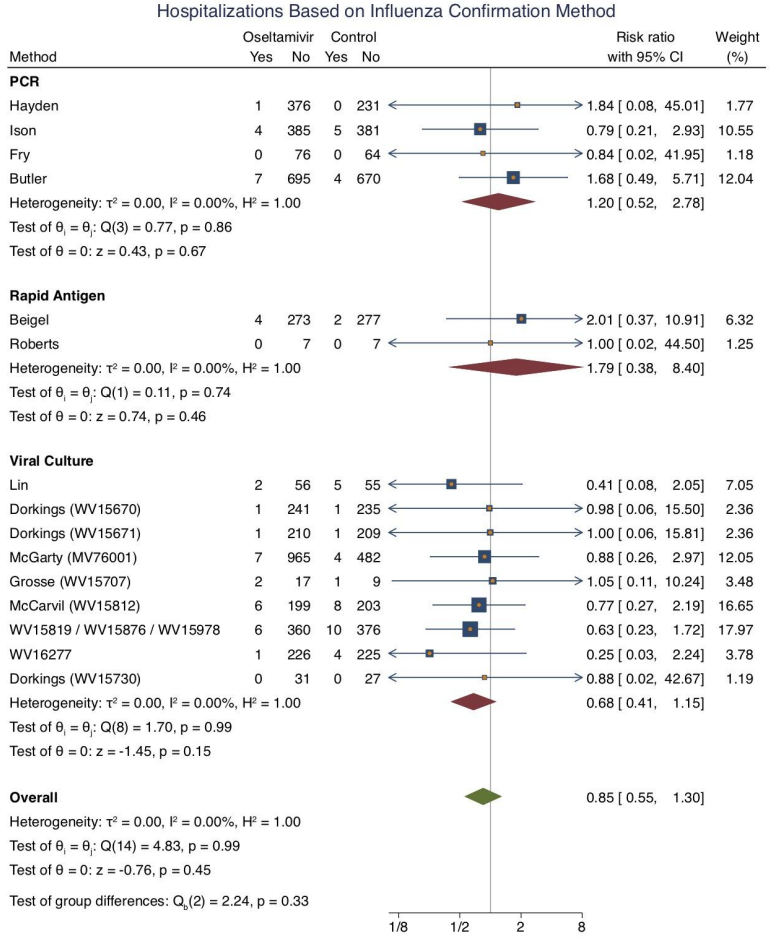

**Supplemental Figure 4.** Random effects cumulative meta-analysis. Based on the outcome of hospitalization within the 12+ ITTi population.



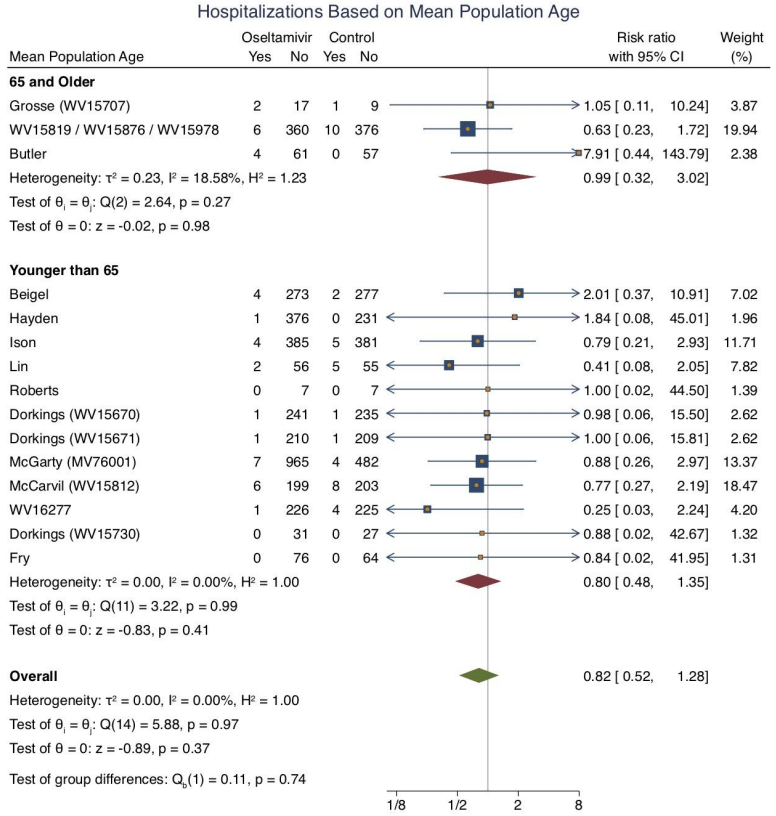

**Supplemental Figure 5.** Random effects sensitivity analysis on the outcome of hospitalization. Outcome data was based on the 12+ ITT populations for Roche-sponsored studies and 12+ ITTi populations for non-industry studies. Yes = number of individuals hospitalized, No = number of individuals who were not.


Hospitalizations Based on Sponsor
Sponsor
Oseltamivir Yes No
Control Yes No
Risk ratio with 95% CI
Weight (%)
Other
Beigel 4 273 2 277 2.01 [ 0.37, 10.91] 6.32
Hayden 1 376 0 231 1.84 [ 0.08, 45.01] 1.77
Ison 4 385 5 381 0.79 [ 0.21, 2.93] 10.55
Roberts 0 7 0 7 1.00 [ 0.02, 44.50] 1.25
Fry 0 76 0 64 0.84 [ 0.02, 41.95] 1.18
Butler 7 695 4 670 1.68 [ 0.49, 5.71] 12.04
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 1.32 [ 0.63, 2.75]
Test of θi = θj: Q(5) = 1.08, p = 0.96
Test of θ = 0: z = 0.73, p = 0.46
Roche
Lin 2 56 5 55 0.41 [ 0.08, 2.05] 7.05
Dorkings (WV15670) 1 241 1 235 0.98 [ 0.06, 15.50] 2.36
Dorkings (WV15671) 1 210 1 209 1.00 [ 0.06, 15.81] 2.36
McGarty (MV76001) 7 965 4 482 0.88 [ 0.26, 2.97] 12.05
Grosse (WV15707) 2 17 1 9 1.05 [ 0.11, 10.24] 3.48
McCarvil (WV15812) 6 199 8 203 0.77 [ 0.27, 2.19] 16.65
WV15819 / WV15876 / WV15978 6 360 10 376 0.63 [ 0.23, 1.72] 17.97
WV16277 1 226 4 225 0.25 [ 0.03, 2.24] 3.78
Dorkings (WV15730) 0 31 0 27 0.88 [ 0.02, 42.67] 1.19
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.68 [ 0.41, 1.15]
Test of θi = θj: Q(8) = 1.70, p = 0.99
Test of θ = 0: z = -1.45, p = 0.15
Overall 0.85 [ 0.55, 1.30]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(14) = 4.83, p = 0.99
Test of θ = 0: z = -0.76, p = 0.45
Test of group differences: Qb(1) = 2.04, p = 0.15
1/8
1/2
2
8

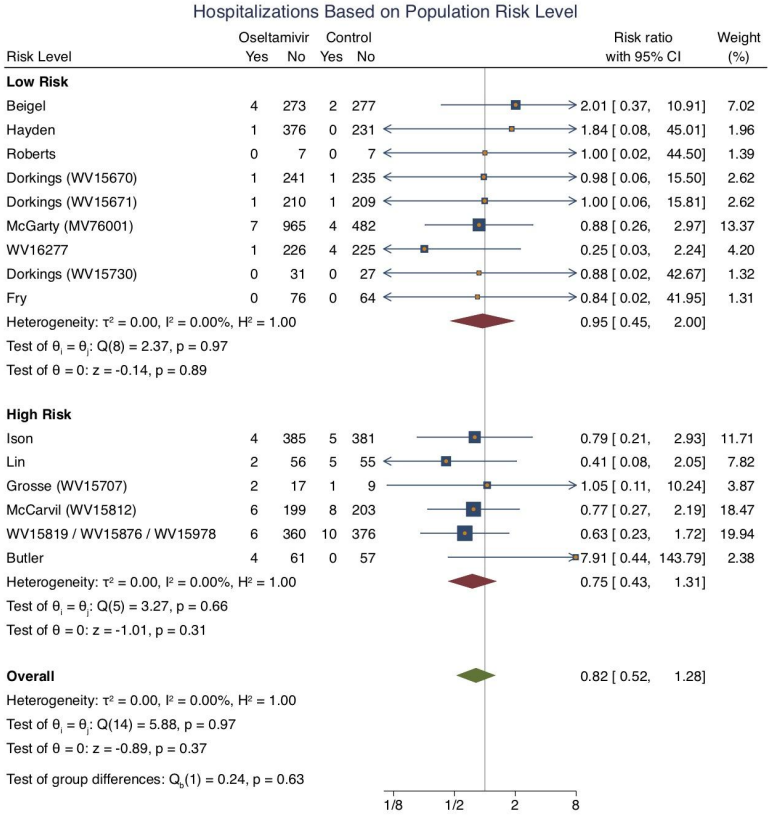
A)


Hospitalizations Based on Influenza Confirmation Method
Method
Oseltamivir Yes No
Control Yes No
Risk ratio with 95% CI
Weight (%)
PCR
Hayden 1 376 0 231 1.84 [ 0.08, 45.01] 1.77
Ison 4 385 5 381 0.79 [ 0.21, 2.93] 10.55
Fry 0 76 0 64 0.84 [ 0.02, 41.95] 1.18
Butler 7 695 4 670 1.68 [ 0.49, 5.71] 12.04
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 1.20 [ 0.52, 2.78]
Test of θi = θj: Q(3) = 0.77, p = 0.86
Test of θ = 0: z = 0.43, p = 0.67
Rapid Antigen
Beigel 4 273 2 277 2.01 [ 0.37, 10.91] 6.32
Roberts 0 7 0 7 1.00 [ 0.02, 44.50] 1.25
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 1.79 [ 0.38, 8.40]
Test of θi = θj: Q(1) = 0.11, p = 0.74
Test of θ = 0: z = 0.74, p = 0.46
Viral Culture
Lin 2 56 5 55 0.41 [ 0.08, 2.05] 7.05
Dorkings (WV15670) 1 241 1 235 0.98 [ 0.06, 15.50] 2.36
Dorkings (WV15671) 1 210 1 209 1.00 [ 0.06, 15.81] 2.36
McGarty (MV76001) 7 965 4 482 0.88 [ 0.26, 2.97] 12.05
Grosse (WV15707) 2 17 1 9 1.05 [ 0.11, 10.24] 3.48
McCarvil (WV15812) 6 199 8 203 0.77 [ 0.27, 2.19] 16.65
WV15819 / WV15876 / WV15978 6 360 10 376 0.63 [ 0.23, 1.72] 17.97
WV16277 1 226 4 225 0.25 [ 0.03, 2.24] 3.78
Dorkings (WV15730) 0 31 0 27 0.88 [ 0.02, 42.67] 1.19
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.68 [ 0.41, 1.15]
Test of θi = θj: Q(8) = 1.70, p = 0.99
Test of θ = 0: z = -1.45, p = 0.15
Overall 0.85 [ 0.55, 1.30]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(14) = 4.83, p = 0.99
Test of θ = 0: z = -0.76, p = 0.45
Test of group differences: Qb(2) = 2.24, p = 0.33
1/8
1/2
2
8

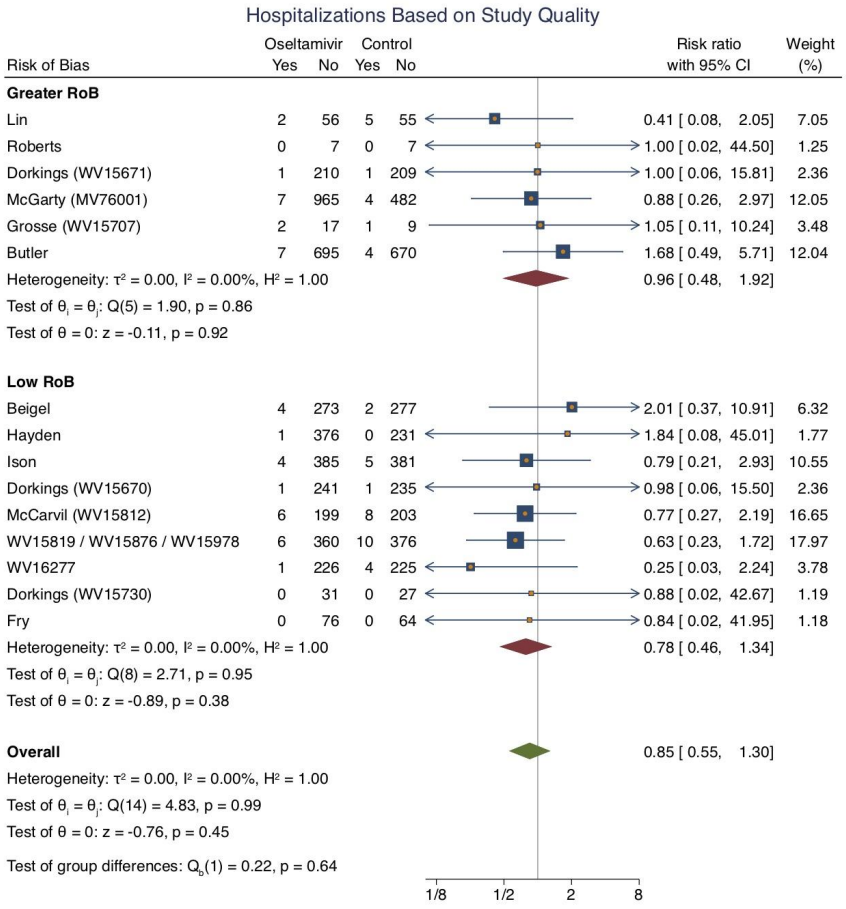
B)


Hospitalizations Based on Mean Population Age
Mean Population Age
Oseltamivir Yes No
Control Yes No
Risk ratio with 95% CI
Weight (%)
65 and Older
Grosse (WV15707) 2 17 1 9 1.05 [ 0.11, 10.24] 3.87
WV15819 / WV15876 / WV15978 6 360 10 376 0.63 [ 0.23, 1.72] 19.94
Butler 4 61 0 57 7.91 [ 0.44, 143.79] 2.38
Heterogeneity: τ² = 0.23, I² = 18.58%, H² = 1.23 0.99 [ 0.32, 3.02]
Test of θi = θj: Q(2) = 2.64, p = 0.27
Test of θ = 0: z = -0.02, p = 0.98
Younger than 65
Beigel 4 273 2 277 2.01 [ 0.37, 10.91] 7.02
Hayden 1 376 0 231 1.84 [ 0.08, 45.01] 1.96
Ison 4 385 5 381 0.79 [ 0.21, 2.93] 11.71
Lin 2 56 5 55 0.41 [ 0.08, 2.05] 7.82
Roberts 0 7 0 7 1.00 [ 0.02, 44.50] 1.39
Dorkings (WV15670) 1 241 1 235 0.98 [ 0.06, 15.50] 2.62
Dorkings (WV15671) 1 210 1 209 1.00 [ 0.06, 15.81] 2.62
McGarty (MV76001) 7 965 4 482 0.88 [ 0.26, 2.97] 13.37
McCarvil (WV15812) 6 199 8 203 0.77 [ 0.27, 2.19] 18.47
WV16277 1 226 4 225 0.25 [ 0.03, 2.24] 4.20
Dorkings (WV15730) 0 31 0 27 0.88 [ 0.02, 42.67] 1.32
Fry 0 76 0 64 0.84 [ 0.02, 41.95] 1.31
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.80 [ 0.48, 1.35]
Test of θi = θj: Q(11) = 3.22, p = 0.99
Test of θ = 0: z = -0.83, p = 0.41
Overall 0.82 [ 0.52, 1.28]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(14) = 5.88, p = 0.97
Test of θ = 0: z = -0.89, p = 0.37
Test of group differences: Qb(1) = 0.11, p = 0.74
1/8
1/2
2
8

C)

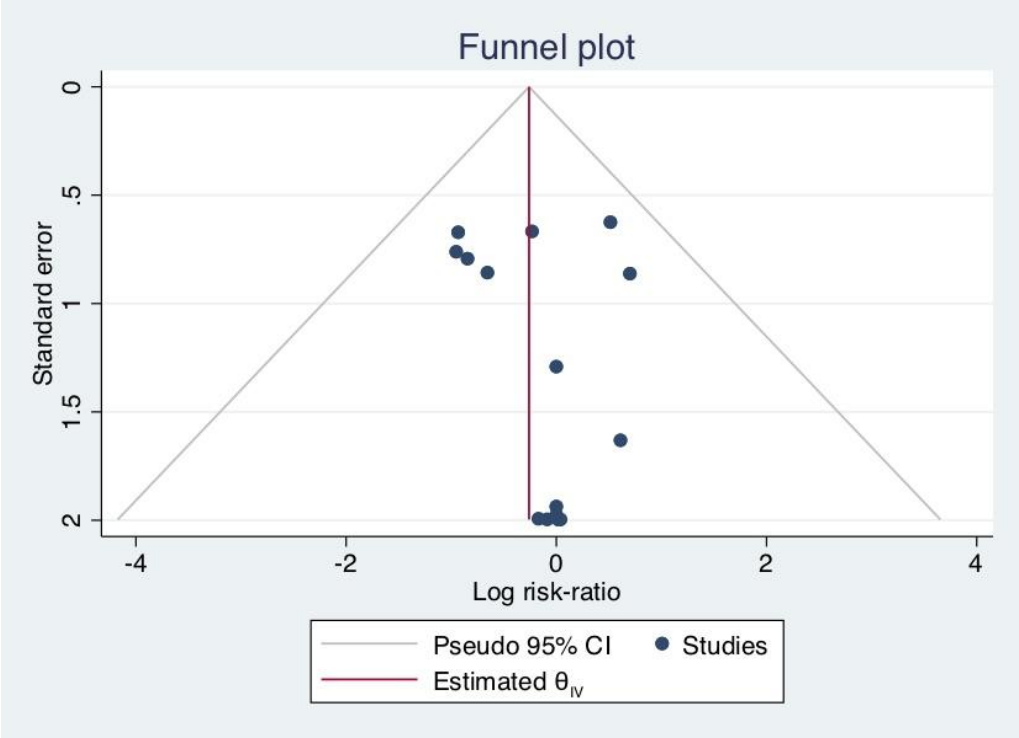

Hospitalizations Based on Population Risk Level
Risk Level
Oseltamivir Yes No
Control Yes No
Risk ratio with 95% CI
Weight (%)
Low Risk
Beigel 4 273 2 277 2.01 [ 0.37, 10.91] 7.02
Hayden 1 376 0 231 1.84 [ 0.08, 45.01] 1.96
Roberts 0 7 0 7 1.00 [ 0.02, 44.50] 1.39
Dorkings (WV15670) 1 241 1 235 0.98 [ 0.06, 15.50] 2.62
Dorkings (WV15671) 1 210 1 209 1.00 [ 0.06, 15.81] 2.62
McGarty (MV76001) 7 965 4 482 0.88 [ 0.26, 2.97] 13.37
WV16277 1 226 4 225 0.25 [ 0.03, 2.24] 4.20
Dorkings (WV15730) 0 31 0 27 0.88 [ 0.02, 42.67] 1.32
Fry 0 76 0 64 0.84 [ 0.02, 41.95] 1.31
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.95 [ 0.45, 2.00]
Test of θi = θj: Q(8) = 2.37, p = 0.97
Test of θ = 0: z = -0.14, p = 0.89
High Risk
Ison 4 385 5 381 0.79 [ 0.21, 2.93] 11.71
Lin 2 56 5 55 0.41 [ 0.08, 2.05] 7.82
Grosse (WV15707) 2 17 1 9 1.05 [ 0.11, 10.24] 3.87
McCarvil (WV15812) 6 199 8 203 0.77 [ 0.27, 2.19] 18.47
WV15819 / WV15876 / WV15978 6 360 10 376 0.63 [ 0.23, 1.72] 19.94
Butler 4 61 0 57 7.91 [ 0.44, 143.79] 2.38
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.75 [ 0.43, 1.31]
Test of θi = θj: Q(5) = 3.27, p = 0.66
Test of θ = 0: z = -1.01, p = 0.31
Overall 0.82 [ 0.52, 1.28]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(14) = 5.88, p = 0.97
Test of θ = 0: z = -0.89, p = 0.37
Test of group differences: Qb(1) = 0.24, p = 0.63
1/8
1/2
2
8

D)




**E)**

**Supplemental Figure 6.** Random effects sensitivity subgroup analyses. Hospitalization outcome data was based on theITT populations for Roche-sponsored studies and ITTi populations for non-industry studies. Studies were stratified according to A) Study Sponsor, B) Method of Confirming Influenza Infections, C) Mean Study Population Age, D) Population Risk Level, and E) Study Quality. Yes = number of individuals hospitalized, No = number of individuals who were not. Note: Butler's (2020) data was utilized the same as in eFigure 2.




**Supplemental Figure 7.** Publication bias funnel plot. Based on the outcome of hospitalizations within the 12+ ITTi population.