Methodological Considerations for Controlled Influenza Treatment Studies in CAM

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Authors:

Ryan Kirkby, MSAOM (Corresponding Author)
Herscu Laboratory, Research Division
356 Middle St.
Amherst, MA 01002
Phone: (206) 660 – 9040
Email: ryankirkby@hotmail.com

Liz Kaltman, MPH
Helfgott Research Institute
Portland, OR

Janet Monnier, MD
Adventist Health Clinic
Portland, OR

Paul Herscu, ND
Herscu Laboratory, Research Division
Amherst, MA

Abstract

Background: The growing threat of influenza pandemic, as well as the ongoing costs to human life and health care systems from yearly epidemics, create a continual need for progress in this area of public health. The diversity of available CAM treatment options are well known to the CAM profession, but poorly understood and accepted in mainstream medicine. This situation comes as no surprise given conventional medicine's reliance on repeated, large-scale RCTs of standardized design to support evidence-based clinical usage of influenza antiviral drugs. The relatively low volume of well-conducted clinical trials on the treatment of influenza with CAM therapies magnifies this problem.

Objectives: The aim of this article is to provide structured guidelines for future CAM influenza studies based on a thorough review of consistent and standard design elements present in the controlled-trial design of conventional antiviral influenza therapies.

Results: A selection of high-quality, influenza antiviral controlled trials is reviewed, and important design elements are extracted and summarized to show both consistency and acceptable range within study design.

Conclusions: The standardized elements form influenza antiviral trials can be considered and mirrored in future CAM studies. In this way, CAM therapies might be looked at on similar grounds as conventional medicines in terms of potential usefulness and benefit in the treatment of influenza.

Introduction

Viral epidemics are a recurrent and growing threat in the globalized environment. Seasonal influenza epidemics affect 5-20% of the population and cause an estimated 36,000 deaths in the US each year, most of which occur among the elderly.[1, 2] This is further compounded by over 200,000 hospitalizations from influenza complications yearly[2] as well as the growing concern over avian influenza A (H5N1). Of the three pandemics that have occurred during the 20th century, the 1918 H1N1 influenza pandemic (also an avian influenza A virus) was the most devastating, causing an estimated 50-100 million deaths.[3] As of April 2009, the clinically documented mortality rate of H5N1 infection since its emergence in Hong Kong in 1997 has been 62% (257 deaths out of 417 laboratory-confirmed cases).[4]

Public health systems may respond to seasonal epidemics and pandemics through vaccination and antiviral drugs, but many barriers to effectiveness exist. Vaccines are limited by the rapid and unpredictable evolution of viral pathogens, and there remain uncertainties regarding effectiveness. Each year a new influenza vaccine is created composed of multiple strains of virus. This year, for example, the 2007-08 influenza vaccine had a poor match on the influenza A (H3N2) and influenza B viruses, despite a good match on influenza A (H1N1).[5] Progress is needed in the ability to dynamically and accurately identify prevalent influenza strains and prevent misses. Antiviral drugs are limited by the quantity that can be quickly and effectively manufactured and distributed. Limitations to treatment are compounded by the challenge of a growing global population that is increasingly mobile through rapid intercontinental travel. New approaches are currently in development, and are greatly needed for both prevention and treatment of this potential global health emergency. Finally, the potential

overwhelming economic burden of a large scale pandemic necessitates exploration of new strategies. In a 1999 study[6], Meltzer et al. estimated an economic impact of \$71.3 to \$166.5 billion for the next influenza pandemic, which excludes disruptions to commerce and society.

According to a 2006 review by Whitley et al.[7], current funding provided by Congress for pandemic preparedness is far below the yearly costs associated with seasonal influenza. The review continues goes on to list critical aspects of preparedness that are underfunded or not funded at all, including state, local, and hospital preparedness; public communication and education; essential medical supplies (antivirals, antibiotics, respirators, other medical supplies); expedition of vaccine development; resources for hospital/health care system planning; plans for surge capacity in the healthcare system; and even the development of novel antiviral medications. They suggest a need for a minimum of \$30 billion in additional funding to address these areas of influenza preparedness.

There is a clear and pressing need for the development of efficient and effective means to aid in a concerted effort to prepare for future influenza epidemics and pandemics, and some complementary and alternative medicine (CAM) approaches may have the potential to offer critical prevention, treatment, and preparedness measures. This includes nutritional and vitamin supplementation, botanical medicine, homeopathy, acupuncture, hydrotherapy, and other modalities. The general mechanisms of action in these therapies are via stimulating or boosting natural immunity and response, driving fever through hyperthermia, decreasing the effects of stress on the body, or antiviral, anti-inflammatory, and anti-catarrhal approaches using natural medicines. With some exceptions in herbal therapy, these approaches are more directly targeted

at enhancing effective bodily response to the pathogen, rather than aimed directly at combating the offending organism. If positive outcomes from testing CAM therapies with the same rigor as conventional therapies occur, this helps promote understanding and usage of such potentially effective means. With the possibility of a severe influenza pandemic in the near future, it will become critical to know the efficacy of CAM treatment methods with regards to a particular pathogen, such as a specific strain of influenza. To this end, it will be beneficial to pursue narrowly focused CAM clinical research in order to better understand specific action of a particular therapy against an identifiable pathogen and be able to state unequivocally that the treatment will be of benefit in that situation. In designing future CAM studies, researchers may benefit from a thorough understanding of current design standards within primary clinical trials testing the efficacy of various therapies in influenza treatment or prevention. High quality CAM studies which adhere to standards of accepted public health measures and indices will allow more accurate comparisons among different influenza treatment options.

Currently published CAM studies on the treatment of influenza have a relatively low prevalence compared to conventional antiviral trials. A search of the Cochrane Database of Systematic Reviews, for the term "influenza" in all fields, returns 114 results, of which 2 relate to the treatment and/or prophylaxis of influenza with CAM therapies. One is a review of homeopathic *Oscillococcinum*[8] consisting of 7 RCTs (4 treatment, 3 prevention), the other a review of Chinese herbal medicines in treating influenza[9], consisting of 2 RCTs. By way of comparison, a 2006 systematic review[10] of antiviral influenza treatment includes nineteen randomized controlled trials on a single class of antiviral drugs, the neuraminidase inhibitors (NAIs). Other reviews also support this trend, such as the 2007 systematic review by Guo et al.[11]

on CAM treatment and prophylaxis of influenza, in which no single type of treatment is represented by more than two RCTs published in peer-reviewed journals. In this review, a total of 29 randomized controlled trials (either placebo-controlled or controlled against antiviral treatment) were identified. Of these 29, 15 were subsequently excluded for either not reporting randomization (2 studies), not having a subgroup analysis of influenza patients in trials including common cold and other upper respiratory tract infection (4 studies), and only measuring objective immune response to influenza vaccination (9 studies). The authors assessed the quality of the 14 accepted studies based on various methodological design elements. A common observation related to the lack of a predefined primary outcome measure for the trial, of which only 7 out of 14 had. Only 6 of the 14 trials confirmed influenza virus infection by laboratory test, and 2 of these only did a random sampling of patients for confirmation. Because of these shortcomings, and despite the fact that some studies reported statistically significant results, the authors questioned the methodological quality, and thus the applicability, of these trials. Overall, the authors reported finding no compelling evidence from randomized controlled trials (RCT) to support the use of any CAM therapy in influenza treatment or prophylaxis. Similar conclusions are made in a 2006 review[12] on CAM treatment of upper respiratory tract infections, in which the authors cite "poor study design, small sample size, and inadequate or unknown power within a majority of the trials" and are therefore unable to make conclusions on the efficacy of those treatments.

The focus in the rest of the review is on making recommendations for future CAM study design by closely reviewing the clinical trials of the most commonly used conventional influenza treatment; influenza antiviral drugs. To this end, this review specifies both the range between

different study designs on influenza antiviral drug therapy and the consistent elements among them so that CAM researchers may use the commonly accepted and standard design elements in future studies on the treatment of influenza with CAM modalities.

Methods and Materials

A selection of RCTs examining antiviral treatment efficacy in naturally occurring influenza A and B in healthy adult populations were evaluated for this review. Current drugs used and studied for their antiviral activity in influenza include the earlier M2 ion channel-blocking drugs, amantadine and rimantadine, and the newer neuraminidase inhibitors (NAIs), of which the most common are nebulised zanamivir and oral oseltamivir. According to Monto et al.[13], early studies on the antivirals amantadine and rimantadine lacked consistency in design, whereas the newer assessments of the NAIs have been more similar in study design and outcome measures. For this reason, the focus of review in this paper is on highlighting the consistencies and common elements in RCTs of zanamivir and oseltamivir, in order that future CAM studies may mirror these accepted criteria.

A general PubMed search (to December 2008) on influenza antiviral treatment was completed, limited to English-language clinical trials and RCTs. The search term used was "influenza treatment OR neuraminidase inhibitor", in the title or abstract text, which resulted in 291 returned references. Of these, 32 were relevant primary studies examining treatment of influenza with NAIs. Seventeen of these 32 were excluded because they either a)only examined a high-risk subgroup of patients (e.g. children, elderly, or patients with preexisting respiratory disease), b) did not use a placebo-controlled or randomized design, or c) were meta-analyses and

not original studies. Out of the remaining 15 studies, 4 were RCTs on the treatment of experimental influenza infection, with treatment given to volunteers after inoculation regardless of influenza status. These studies were excluded because the difference in design made them difficult to compare to the other studies in areas such as inclusion criteria. Similar searches, for the term "neuraminidase inhibitor", were carried out in EMBASE and the Cochrane Central Registry of Controlled Trials, returning 410 and 56 results respectively, but no additional sources meeting the selection criteria were found. Finally, two recent systematic reviews on antiviral treatment[10, 14] were also examined to make sure that relevant studies were not being left out. As a result, we selected 11 primary clinical studies that met the criteria of being an RCT examining the efficacy of NAI drugs in treating naturally occurring influenza or ILI in non-high risk, healthy adult populations.[13, 15-24] This subset was chosen in order to establish the common, reproducible design elements in the most recent, and most frequently cited and reviewed influenza clinical or antiviral trial reports. Although we excluded trials on high-risk groups or prophylaxis, as well as studies lacking a control arm, these trials are other important avenues of research for CAM therapies, and should be followed up on once a firm foundation for primary clinical treatment trials has been established. Table 1 shows basic designs and demographics, including incidence of laboratory confirmed influenza as a percentage of ILI patients, for the 11 studies examined.

We address the study designs on four characteristics: Inclusion and exclusion criteria for entry into study, clinical methods for obtaining data, primary and secondary outcome measures, and basic data analysis. We reviewed these categories one by one to show the ranges and also the consensus within these components, in order to identify important design criteria for

comparable CAM study design. We purposefully left out of the review categories where conventional antiviral trials have questionable methodological design according to previous reviews. Jefferson et al.[25] rates less than half (5) of the eleven trials included in this review as having adequate allocation concealment/blinding procedures. Other commonly cited problems with antiviral trials were poor or unclear reporting.[10] These elements are also important to consider in future CAM trials, but here the conventional study design is less helpful to examine.

Results

Inclusion and Exclusion Criteria

Inclusion Criteria

Selecting clinical criteria for identifying influenza based on subjective and objective signs and symptoms is complicated by the similar presentation of other bacterial and viral acute illnesses, collectively referred to as influenza-like illness (ILI). These include respiratory syncytial virus, adenoviruses, and mycoplasmas, among other infections.[26] As can be seen from the demographics of the influenza studies listed in Table 1, the percentage of patients presenting with ILI who are confirmed by laboratory diagnosis as influenza positive ranges from 57% to 78%, and larger reviews show a typical range of 60-70%.[26] These ranges are dependent on multiple factors, one of which is the clinical symptom-based inclusion criteria used. The most predictive symptoms of influenza are reported to be cough and fever.[27] In another review of data from 1,918 patients with influenza, headache and fever (>37.8° C) were the two most common presenting symptoms, seen in 97 and 98 percent of patients respectively.[28] The same study demonstrated that 96% of patients presented with a minimum of four common influenza

symptoms (including fever, headache, malaise, myalgia, cough, sore throat), and 98% were diagnosed for treatment on the basis of clinical symptoms. While it is common clinical practice to base influenza diagnosis solely on symptoms, the clinical and antiviral studies show substantial misdiagnosis of what are actually other respiratory illnesses. Therefore in any influenza study, it is critical to identify the subpopulation of laboratory-diagnosed influenza patients if treatment efficacy is to be attached to a single diagnosable disease.

In the 11 primary clinical studies reviewed herein, inclusion into the study group of intention to treat (ITT) patients is made on the basis of both objective and subjective symptoms and signs. In all cases, laboratory confirmation of influenza is done, but, because of the lag time in obtaining results, this factors into the analysis rather than the initial inclusion and exclusion criteria. The individual inclusion criteria for the studies are listed in Table 2. The basic inclusion categories and criteria are quite similar between studies, with some range in the details.

Because all of the studies were designed primarily to test the efficacy of antiviral medication in a relatively healthy (i.e., low-risk) population, the age criteria exclude children and in some cases seniors. In the studies that allow for patients over the age of 65, some define a separate sub-group in the analysis in order to differentiate efficacy in a high-risk group. Eight of the eleven studies require a measurable fever greater than 37.8° C while three of the studies include patients who may only have a subjective sensation of feverishness. As referenced above, the majority (~98% in the given study) of patients presenting with influenza have a fever greater than 37.8° C, but there is a small percentage who do not. Allowing participants into the study that have either a measurable fever *or* subjective sensations of feverishness could create an

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opportunity to analyze an interesting sub-group of influenza sufferers, and seems reasonable on the basis of the precedence set by these studies. For subjective symptoms the inclusion parameters are consistent among studies. All studies require at least two common influenza symptoms, and the only differences are in the range of symptoms considered, and in the case of two studies, the parsing of influenza symptoms into two categories, 'respiratory' and 'constitutional', and requiring one symptom from each for inclusion.

Overall, the three criteria of age, fever, and subjective symptoms are consistent design elements that should be included in any influenza treatment study. The time from onset of symptoms to beginning of treatment as in inclusion criteria is a consistent parameter in influenza antiviral drug trials, set to less than 36 or 48 hours in all studies reviewed. One reason for this is data on NAIs showing that treatment started within the first 12 hours after onset of fever significantly shortened the length of illness compared to treatment started at 48 hours, and initiation times within that range had a proportional effect as well.[29] The importance of this inclusion criteria thus depends on the therapy being tested, but at least in the case of antiviral drugs for influenza this inclusion criteria has significant effect on the efficacy outcomes of the trial. In general, the natural length of an acute disease varies depending on the disease entity and the health of the patient. In the influenza studies examined, the median number of days until resolution of the illness in the placebo groups was 4 to 8 days after the beginning of the study period.[13, 15-24, 26] If patients are being treated around the end of the disease course, the data may therefore be inconclusive.

Exclusion Criteria

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Exclusion criteria are more variable amongst studies than inclusion criteria. Only pregnancy is specified as an exclusion criterion in almost all studies. Other exclusionary criteria are mostly meant to eliminate certain high-risk groups such as immunocompromised patients or influenza sufferers who have a concomitant bacterial infection. Also excluded are those who have made recent use of antiviral or antimicrobial drugs, as this could interfere with, or obscure the results of the test treatment. Four out of eleven studies exclude patients who had been vaccinated within the previous year. Overall the main use of the exclusionary criteria is to limit the study population to an apparently healthy group, while also eliminating participants in whom there may be interference with the test drug. Table 3 includes a more detailed breakdown of exclusion criteria among studies.

Clinical Methods for Data Gathering

Another variable aspect of study design is the specification of parameters followed and recorded in patients during and after treatment. Common to almost all studies reviewed is the tracking of individual symptoms, though there is some difference in specific symptoms recorded as can be seen in Table 4. Symptom recording in the studies reviewed is predominantly done on a zero to three numerical scale, representing symptom severity from none to severe. Most symptom recording is done two times daily, though during the first three to five days of drug treatment many studies have participants recording symptoms and temperature four times daily. Temperature recording is common to almost all the studies, either oral, or in some cases axillary or aural. About half the studies follow sleep disturbance and overall health perception of participants, and a majority of the studies measure the patients' ability to do normal daily

activity, though the scales for these measures vary considerably among studies. Also common to the majority of studies, but not listed in Table 4, are recording of adverse events (such as drug side effects like GI events, headache, etc.), additional drug usage (i.e. acetaminophen, cough suppressants) during the study period, and development of secondary complications or the need for antibiotic treatment.

Of the eleven studies reviewed, five included viral load determination throughout some portion of the study period. In these studies, viral loads were looked at in the efficacy analysis, whereas all studies did initial laboratory testing simply to confirm influenza. Three of the studies in this review showed a positive reduction in viral load compared to placebo[22-24], but did not definitively show a reduction in viral shedding duration. A more recent study on viral shedding during antiviral treatment of influenza treatment in children has shown that the NAIs do not have a positive effect on reducing viral shedding duration.[30] This aspect is an important consideration for study design because tracking of viral load and viral shedding adds great expense to the study. However, the efficacy in terms of viral shedding is an important aspect of the preventive aspect of influenza treatment, and should be considered if the primary focus of the trial is to be on transmission of disease and prophylaxis.

Influenza laboratory confirmation methods

All of the studies reviewed used laboratory testing to confirm influenza, with the following common methods: 1) viral culture, 2) polymerase chain reaction (PCR), or 3) seroconversion with at least a 4-fold increase in serum antibody titers over the course of the study (generally 21-28 days). Table 4 lists which studies utilized which specific methods. None

of the studies relied solely on the available rapid detection assays for confirmation of influenza. Influenza diagnostic confirmation through laboratory study is a basic requirement for any treatment efficacy study, and is used not so much in the process of excluding non-influenza positive participants (because of the lag time) but in the efficacy analysis.

Outcome measures

Study design methods for determining efficacy and safety of drugs are generally divided into two categories: primary and secondary outcome measures.

Primary Outcome Measures

The primary outcome measure, which is the main endpoint for analysis of efficacy compared to placebo, is almost identical in ten of the eleven studies reviewed and is the total elapsed time from drug treatment initiation until the alleviation of influenza symptoms. The differences among studies mainly come in relation to the inclusion criteria, i.e., what are the most clinically important symptoms to monitor. In the majority of these studies, the measurable fever is required to be less than 37.8° C (37° C in Matsumoto et al.[20]), and the subjective symptoms of feverishness must be recorded as 'none' for a 24 hour period. The other defining influenza symptoms (most commonly headache, cough, myalgia, and sore throat) must be recorded as none or mild (a score of 0 or 1 on a 4 point scale) for 24 hours. These are the criteria for 'alleviation of influenza'. Thus the symptoms may still be present at a low level in illness that is considered to be alleviated for purposes of efficacy analysis. One of the eleven studies, focused more on subjective outcomes of productivity and economic impacts, looked at overall

mean scores of broad health measures versus placebo; this study also did not track individual symptoms.[15] Table 5 lists the four distinctive primary outcome measures used in the reviewed studies.

Secondary outcome measures

There is a wider distribution of secondary outcome measures utilized by different studies compared with primary outcome measures. Table 6 provides a brief summary of secondary outcome measures by study. Some measures not included in the table that are common to the majority of studies are: reporting of adverse events and safety measures (like nausea worsening or respiratory symptoms.)

One issue worthy of close inspection in study design is the recording and analyzing of concomitant illness and the use of other medications, either for symptom relief or to address complications. Schmidt et al. found that, of over 1,900 patients treated for influenza, 38% had concomitant conditions, and approximately 48% of the study population received concomitant therapy during the influenza treatment.[28] The use of relief medication during the study for influenza symptoms can be quite high. Li, et al.[18] reported acetaminophen usage ranging from 60-62% of all patients in both the treatment and placebo groups. The high usage of relief medication generally found and allowed for in influenza treatment studies is worth considering for the design of trials with other therapies, especially if any interaction with the study therapy is possible. It is possible that some CAM therapies may become less efficacious or even ineffective due to these interactions, and given that the majority of patients may be using relief medication in influenza trials, it is critical to control for those uses or create guidelines that

would limit detrimental interactions. In many cases of antiviral trials, some relief medication is actually provided at the onset (such as cough medicines), and patients are asked to use it only when necessary and to record the usage. To this end, some studies define a secondary outcome measure of time to alleviation of illness without the use of relief medication in order to examine the efficacy of the trial drug in those not using any relief medication (see Puhakka et al.[23] for an example).

Data Analysis

The statistical methods vary among the studies, but the grouping of sub-populations for efficacy analysis is quite consistent, and fits within the CAM perspective of looking at conventional disease diagnoses as a compilation of clinically unique sub-populations. Nine of the eleven studies define the primary population for efficacy as the subset of the ITT population who also show laboratory confirmed influenza. Two of the studies use the entire ITT population (all randomized, treated patients) as the primary population for efficacy analysis; these use the confirmed influenza participants in secondary analysis. Six of the eleven studies do a secondary analysis for efficacy on all the ITT patients, that is, all patients presenting with influenza-like illness. Finally, three of the eleven studies retrospectively define a high-risk subgroup for separate analysis, either based on age (for those studies allowing participants over 65) or other risk factors for influenza complications. The primary endpoint for analysis in most studies, as mentioned above, is reduction in total days of illness as compared to placebo. For analysis of the secondary outcome measures there is a wide variety of methods, due to the differences in secondary endpoints and methods of measurement.

Conclusions and Discussion

Our review of clinical influenza research suggests that a relatively consistent standard of specific study design elements has emerged in antiviral treatment trials, and it is one that can be mirrored in CAM influenza research where appropriate. A summary of the main design elements, and the one or two most common specifications for each element, is given in Table 7. The goal in understanding influenza study design is twofold; it is both an important step towards generating internal consistency and legitimacy for CAM studies, and it will also be beneficial in creating a standard basis for comparison to pharmaceutical treatment for influenza. The design methodology presented is aimed primarily at understanding the efficacy of a therapy in reducing the length of influenza and ILIs, while also allowing comparison of symptom severity, viral loads, complications, and other subjective health measures like ability to do normal activity and overall health perception. In this way, it can easily cover a wide array of endpoints that are appropriate to any CAM therapy, and there is enough built in flexibility, as seen in the ranges of the studies reviewed, for further specification, especially of exclusion criteria, secondary endpoints, and data-analysis on different sub-groups. Overall, this review is meant to provide a useful base to build from in future study design of CAM approaches to the treatment of influenza.

One question brought up by this review, in terms of making recommendations for CAM studies, is some uncertainty over the utility and necessity of measuring ongoing viral loads and shedding during the study course (in addition to testing for laboratory confirmation of influenza).

This is a large limiting factor in terms of overall cost of a study, but it is something which a significant number of pharmaceutical studies track, especially because of its potential relevance to prevention in influenza spread. Another serious consideration of any future CAM study should be the effects of symptom relief medication taken during the trial period. With the possibility of a majority of the study participants taking cough medication, aspirin, or other OTC or CAM products among other drugs, it is critical that the potential interactions with the study therapy are well understood and controlled for.

Study design issues not covered in this review include different methods for appraising influenza treatment within certain subgroups like chronically ill patients or children, and techniques for blinding, allocation concealment, and effective reporting of results. Also ignored in this study is design for establishing efficacy of prophylaxis of treatment therapies. These are issues that deserve further attention.

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Disclosure Statement

There are no conflicts of interest, and no competing financial interests exist.

Table 1: Characteristics of Reviewed Influenza Antiviral RCTs					
Study Source	# of Participants*	% Participants with Lab-confirmed** Influenza	Study Length	Year(s) of Study	Location(s) of Study
Hayden 1997 [17]	417	63%	28 days	1994-95	North America, Europe
MIST 1998 [21]	455	71%	28 days	1997-98	Australia, New Zealand, South Africa
Matsumoto 1999 [20]	116	63%	28 days	1995	Japan
Monto 1999 [13]	1256	57%	21 days	1995-96	North America, Europe
Aoki 2000 [15]	1256	57%	21 days	1995-96	North America, Europe
Boivin 2000 [16]	35	77%	14 days	1997-98	Canada
Makela 2000 [19]	356	78%	28 days	1997-98	Europe
Nicholson 2000 [22]	726	66%	21 days	1998	Europe, Canada, China
Treanor 2000 [24]	629	60%	21 days	1998	United States
Li 2003 [18]	451	61%	21 days	2001	China
Puhakka 2003 [23]	588	74%	28 days	2000-01	Finland

*Number of participants includes all participants entering into the study with influenza like illness (ILI); this group is the Intention to Treat population (ITT).

**Laboratory-confirmed presence of influenza A or B virus; through culture, PCR, or seroconversion.

Table 2: Inclusion Criteria Details		
Criteria	**Specific parameters**	**Studies using**
Age	Greater than 12-14 years of age	6 [13, 15-17, 19, 21]
	Between 16-65 years of age*	3 [20, 22, 24]
Time from symptom onset to treatment	Within the first 36 hours	5 [18, 20-22, 24]
	Within the first 48 hours	6 [13, 15-17, 19, 23]
Temperature	Fever greater than 37.8° C**	5 [16-19, 23]
	Fever greater than 38° C	2 [22, 24]
	Fever greater than 37.8° C, feverishness (subjective), or both	1 [21]
	Axillary temp greater than 37.5° C	1 [20]
	Feverishness (subjective)	2 [13, 15]
Subjective symptoms	Two or more of: headache, myalgia, cough, sore throat	8 [13, 15-17, 19-21, 23]
	Two or more of: Coryza/nasal congestion, sore throat, cough, myalgia, fatigue, headache, chills/sweats	1 [18]
	One or more respiratory symptom (cough, sore throat, nasal symptoms) AND one or more constitutional symptom (headache, malaise, myalgia, sweats/chills, fatigue)	2 [22, 24]

*18-65 years of age [22, 24]

**Greater than 37.2° C for participants over 65 years of age [16, 19]

Table 3: Exclusion Criteria Details		
Category	**Specific parameter**	**Studies using**
Chronic Illness	Unstable/clinically significant chronic illness	4 [13, 15, 22, 24]
	Known HIV infection, immunocompromised	3 [22-24]
Drug Use	Recent/current use of antiviral or antimicrobial drugs	4 [13, 17, 21, 23]
	Currently taking steroids or other immunosuppressants	3 [18, 22, 24]
	History of alcohol or drug abuse	3 [21, 22, 24]
Sensitivity	Known or suspected hypersensitivity to study medication	2 [13, 23]
Pregnancy	Pregnancy, lactating, at risk of pregnancy	9 [13, 15, 17, 19-24]
Concurrent Infection	Suspected bacterial infection concurrently	3 [17, 18, 21]
Vaccination	Received influenza vaccination within last 12 months	4 [17, 18, 22, 24]

^Based on *reported* exclusion criteria in the literature, as with other aspects of study design it is possible that some elements of design are not adequately reported and thus don't appear here.

Table 4: Data Gathering During Study		
Category	Specific parameters	Studies using
Symptoms recorded	Headache, myalgia, cough, sore throat	3 [13, 16, 20]
	Headache, myalgia, cough, sore throat, nasal symptoms, fatigue, feverishness	3 [18, 22, 24]
	Headache, myalgia, cough, sore throat, nasal symptoms, fatigue, feverishness, loss of appetite	4 [17, 19, 21, 23]
Scale and timing for symptom recording	4-point scale (none, mild, moderate, severe), 2-4x/day	9 [16-24]
	6-point scale, 2x/day	1 [13]
Temperature, type and timing	Oral, 2-4x/day	7 [13, 16-18, 21, 23, 24]
	Axillary 4x/day	1 [20]
	Ear, daily	1 [19]
Sleep disturbance	On various scales	5 [13, 15-17, 20]
Level of ability to perform normal daily activity	On various scales	9 [13, 15, 17, 19-24]
Overall health status	Assessed on various scales	6 [13, 15, 21-24]
Viral detection method	Viral culture, antibody titre, or PCR	5 [13, 15, 19, 20, 23]
	Viral culture or antibody titre	5 [17, 18, 21, 22, 24]
	Viral culture or PCR	1 [16]
Viral sampling (for viral load/shedding)	Collected at various time scales	5 [16, 17, 22-24]

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Table 5: Primary Outcome Measures		
Category	**Specific Criteria**	**Studies using**
Time to alleviation of influenza symptoms	Temp less than 37.8° C, score of 0 (none) on feverishness, score of 0-1 (none to mild) for headache, cough, myalgia, sore throat; maintained for 24 hours	6 [13, 16, 17, 19, 21, 23]
	Score of 0-1 (none to mild) for all influenza symptoms (cough, sore throat, nasal symptoms, headache, malaise, myalgia, feverishness, fatigue; maintained for 24 hours	2 [22, 24]
	Temp less than 37° C and score of 0-1 (none to mild) on feverishness, headache, myalgia	1 [20]
Comparison of mean scores for particular categories	Health status, sleep status, productivity, additional healthcare utilization, treatment satisfaction	1 [15]

Table 6: Secondary Outcome Measures		
Category	**Specific Criteria**	**Studies using**
Individual symptoms	Symptom scores, time to alleviation	9 [13, 15-17, 19, 21-24]
Overall health, quality of life measures	Sleep disturbance scores, time to reach mild to none	4 [13, 20-22]
	Time to return to normal activities, level of ability to perform normal activity scores	7 [13, 17, 19-22, 24]
	Overall symptom severity, general health perception	4 [13, 21-23]

Viral Shedding	Loss of detectable virus		1 [17]
	Viral load, quantity of viral shedding		4 [16, 22-24]
Use of relief medication	Time to alleviation of symptoms with no use of relief medication		1 [23]
	Use of symptom relief medication		5 [13, 15, 17, 19, 21]
Complications	Secondary complications and antibiotic usage		5 [15, 21-24]
Other	Time to alleviation of five influenza symptoms: feverishness, headache, myalgia, cough, sore throat; and temp less than 37° C maintained 24 hours		1 [20]

Table 7: Design Elements Summary		
Category	**Design Consideration**	**Most Common**
Demographics	Study size	350-650 ITT population
	Study length	21 days
		28 days
	Study design	Multicenter RCT
Inclusion Criteria	Age	12+ years old
		16-65 years old
	Time from onset of symptoms to treatment	36 hours
		48 hours
	Fever	Fever greater than 37.8º C
		Feverishness
	Subjective symptoms	2 or more of headache, myalgia, cough, sore throat
		1 respiratory symptom (cough, sore throat, nasal symptom) and 1 constitutional symptom (headache, malaise, myalgia, sweats/chills, fatigue)
Exclusion Criteria	Chronic Illness	Immunocompromised
		Unstable chronic disease
	Drug Use	Antiviral drug use (recent/current)
		Immunosuppresant medications
		Drug/alcohol abuse history
	Pregnancy	Pregnant or risk of pregnancy

	Vaccination	Vaccinated this year
	Bacterial infection	Suspected concurrent bacterial infection
Primary Outcome Measures	Time to alleviation of influenza	Temperature < 37.8⁰ C, score of 0 on feverishness, score of 0-1 on other influenza inclusion symptoms maintained for 24 hours
Secondary Outcome Measures	Individual symptom scores	Headache, myalgia, cough, sore throat, nasal symptoms, fatigue, feverishness, loss of appetite
	Quality of life scores	Sleep disturbance
		Time until return to normal activities
		Overall symptoms severity
	Viral load	Viral shedding/viral load
	Relief medication use	Use of relief medications for influenza symptoms
	Complications	Secondary complications of influenza
		Use of antibiotics
		Effects of study drug (safety measures)

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