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Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis (Review)

Jagannath VA, Govindaraj Vaithinathan AV, Fedorowicz Z, Lee TWR

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[Intervention Review]

Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis

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ABSTRACT

Background

Cystic fibrosis is the most common, life-threatening, recessively inherited disease of Caucasian populations. It is a multisystem disorder caused by a mutation in the gene encoding the cystic fibrosis transmembrane conductance regulator protein which is important in producing sweat, digestive juices and mucus.The impaired or absent function of this protein results in the production of viscous mucus within the lungs and an environment that is susceptible to chronic airway obstruction and pulmonary colonization by a range of pathogenic bacteria. Morbidity and mortality of cystic fibrosis is related to chronic pulmonary sepsis and its complications by these bacteria.

Influenza can worsen the course of the disease in cystic fibrosis by increasing the risk of pneumonia and secondary respiratory complications. Antiviral agents form an important part of influenza management and include the neuraminidase inhibitors zanamivir and oseltamivir. These inhibitors can limit the infection and prevent the spread of the virus.

Objectives

To assess the effects of neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

Most recent search: 02 November 2015.

Selection criteria

Randomised controlled trials and quasi-randomised controlled trials comparing neuraminidase inhibitors with placebo or other antiviral drugs.

Data collection and analysis

Two review authors had planned to independently screen studies, extract data and assess risk of bias using standard Cochrane methodologies. No studies were identified for inclusion.

Main results

No relevant studies were retrieved after a comprehensive search of the literature.

Authors' conclusions

We were unable to identify any randomised controlled studies or quasi-randomised controlled studies on the efficacy of neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis. The absence of high level evidence for the effectiveness of these interventions emphasises the need for well-designed, adequately powered, randomised controlled clinical studies.

PLAIN LANGUAGE SUMMARY

Antiviral treatment for influenza infection in people with cystic fibrosis

Review question

We looked for evidence for the use of antiviral treatment against influenza infection in people with cystic fibrosis.

Background

Cystic fibrosis is a genetic, life-threatening disorder which affects many organs in the body. and people with cystic fibrosis have a higher risk of chronic lung disease. Influenza can worsen the course of the disease in cystic fibrosis by increasing the risk of pneumonia and secondary respiratory complications. During a pandemic (an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people), flu symptoms may be more severe and complications more frequent. Severe cases of pandemic flu have occurred in people with underlying chronic conditions including people with cystic fibrosis. Although there is no evidence that people with cystic fibrosis are more likely to contract this infection than healthy people, the impact for them could be greater and the outcome worse as the lower airways are more often affected. Antiviral agents are important in managing influenza and include the neuraminidase inhibitors zanamivir and oseltamivir. These drugs can limit the infection and prevent the spread of the virus.

Search date

The evidence is current to: 02 November 2015.

Study characteristics

We did not find any studies looking at the use of neuraminidase inhibitors for influenza in people with cystic fibrosis.

Key results

Limited data from previous studies have shown that these drugs can be effective in healthy people and may be useful in high-risk populations if used rationally. However, we are not able to answer the question of the safety and effectiveness of neuraminidase inhibitors for treating influenza in people with cystic fibrosis.

BACKGROUND

Neuraminidase inhibitors (NIs) are thought to help reduce the symptoms of influenza in adults and children (Jefferson 2006; Matheson 2007). Although the proposed influenza virus-specific mechanism of action by NIs and worldwide usage and stockpiling of these agents to tackle pandemics have been recommended by public health agencies, it does not seem to fit the clinical evidence of effectiveness in the treatment of influenza as explored by the subsequent updates of the original Cochrane systematic review on this topic (Jefferson 2012; Jefferson 2014). Furthermore, little is known specific to the effectiveness and safety of NIs in treating influenza in people with cystic fibrosis (CF).

Description of the condition

Cystic fibrosis is the most common, life-threatening, recessively inherited disease of Caucasian populations, with a carrier rate of 1 in 25 and an incidence of 1 in 2500 live births (Ratjen 2003). It is a multisystem disorder caused by a mutation in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. The CFTR protein is a chloride ion channel, important in producing sweat, digestive juices and mucus. The impaired or absent function of this protein results in the production of viscous mucus within the lungs and an environment that is susceptible to chronic airway obstruction and pulmonary colonization by pathogenic bacteria. Most of the morbidity and more than 90% of the mortality of CF is related to chronic pulmonary sepsis and its complications (Høiby 2000). Initial infections are caused by *Staphylococcus aureus* (*S. aureus*) and *Haemophilus influenzae* and chronic infections are caused by *Pseudomonas aeruginosa* (*P. aeruginosa*) which is one of the important prognosis-determining factors in CF. Viral respiratory infections in people with CF are also associated with an increase in morbidity (van Ewijk 2008). Some studies suggested that 40% of acute pulmonary exacerbations in CF are associated with respiratory viruses (Smyth 1995); these viruses also lead to pulmonary function abnormalities and disease progression (Wat 2008). In another study 52% of all infants with CF admitted to the hospital with respiratory symptoms were caused by respiratory viruses, 35% of these hospitalised infants acquired *P. aeruginosa* at follow up compared with 6% of those who were not hospitalised for respiratory symptoms (Armstrong 1998).

Influenza is an acute, usually self-limiting, viral respiratory infection in the general population and can worsen the course of the disease in CF by increasing the risk of complications, like pneumonia and secondary respiratory complications (Conway 1992). Whereas seasonal influenza occurs regularly and usually during the winter months, pandemic influenza occurs rarely (only three times in the previous century). Populations have little or no immunity to pandemic flu and healthy people may find themselves at risk for serious complications, which is not the case for seasonal flu. During a pandemic, flu symptoms may be more severe and complications more frequent, which in turn leads to an increase in the mortality rate. Severe cases of pandemic flu have occurred in people with underlying chronic conditions including people with CF; though there is no evidence of increased susceptibility to this infection in people with CF than in healthy people, the impact could be greater and the outcome worse as the lower respiratory tract is affected more often.

Description of the intervention

The two main measures for the treatment and prophylaxis of influenza are immunisation using influenza vaccines directly isolated from influenza A and B viruses and antiviral agents (Demicheli 2007). Annual flu vaccines are developed from known flu strains and therefore vaccines may not be available in the early stages of a pandemic flu outbreak. Antiviral agents form an important part of influenza management (Moscona 2005) and currently include two classes each with two approved drugs: M2 ion channel inhibitors (amantadine and rimantadine) and NIs (zanamivir (also known as Relenza®) and oseltamivir (also known as Tamiflu®)) (Moscona 2005).

In 2005/6, increasing incidence of drug resistance by strain H3N2 to amantadine and rimantadine led the Centers for Disease Control and Prevention to recommend the use of either oseltamivir or zanamivir as treatment (Hayden 2004). Zanamivir and oseltamivir have significantly different formulations. Zanamivir is a dry powder for inhalation that requires manual dexterity to assemble and cannot be used in children under seven years of age. Oseltamivir is a liquid or capsule, used for the treatment in adults and children (one year and older) within two days of the beginning of symptoms. It also is approved for emergency use in children less than one year old and requires dose adjustment in cases of renal failure. The dosages vary with the medication, age group and medical condition, as indicated in the Advisory Committee on Immunization Practices guidelines (MMWR 2008).

How the intervention might work

The core ribonucleic acid component of influenza virus is surrounded by a protein, the nucleoprotein antigen, which determines the type of virus (A, B or C). The outer surface of the virus consists of a lipid membrane with two attached glycoprotein antigens, neuraminidase and haemagglutinin antigens. Haemagglutinin, is the glycoprotein which assists the virus entry into host cells, whereas neuraminidase is an enzyme that helps the virus to bud and release virions from the infected cell, during both viral entry and exit from the target host cell, to infect other cells leading to spread of the virus. Neuraminidase also facilitates virus spread within the respiratory tract by dissolving mucus surrounding the airway epithelial cells (Matrosovich 2004). Without neuraminidase, infection would be limited to one round of replication, rarely enough to cause disease or spread of the virus. Hence, NIs limit the infection and prevent the spread of the virus; NIs are effective against all neuraminidase subtypes and, therefore, against all known strains of influenza. Influenza A resistance to oseltamivir has been increasing since 2004, but remains relatively rare (oseltamivir-resistant strains of influenza were found in 0.4% to 4% of patients, with higher resistance rates in children) (Schirmer 2009).

Why it is important to do this review

This Cochrane review is an update of previous versions (Jagannath 2009; Jagannath 2010; Jagannath 2011; Jagannath 2014); while no new studies have been found for this review there has been further research in the area. An earlier Cochrane review on the use of NIs for preventing and treating influenza in healthy adults concluded that zanamivir and oseltamivir can be effective in prophylaxis (Jefferson 2006). A second Cochrane review from around the same time concluded that NIs used in healthy children with influenza

may be effective in shortening illness duration, but efficacy in 'high-risk' children remains to be proven (Matheson 2007). In the meantime, the review on adults has been withdrawn and replaced by one looking at the use of NIs for preventing and treating influenza in both healthy adults and children (Jefferson 2012). The authors conclude that the evidence available supports the use of oseltamivir for symptoms of influenza, but there is insufficient evidence to draw conclusions about its effect on complications or transmission (Jefferson 2012). A Health Technology Assessment investigating the effectiveness of zanamivir concluded that it may prove useful when used judiciously in at-risk patients (Burls 2002). Although there have been several systematic reviews of the effects of NIs, none have evaluated the potential role of NIs in a high-risk population such as people with CF (Burls 2002; Cooper 2003; Jefferson 2006; Turner 2003).

Although vaccination is the primary strategy for the prevention of influenza in people with CF (Wat 2008), as discussed in another Cochrane review, the vaccine can be less protective during the influenza season due to mutations (Dharmaraj 2000). Effective antiviral agents would be of utmost importance to reduce complications which may necessitate adjunctive antiviral therapy, especially in more vulnerable populations such as people with CF. Currently available antiviral drugs need to be rationally used to prevent resistance, as there are very limited therapeutic alternatives.

It has been shown that NIs are effective against influenza in a healthy population, but evidence is now required to illustrate their effectiveness in treating influenza attacks in people with CF.

OBJECTIVES

To assess the effects of NIs for treating influenza infection in people with CF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled studies and quasi-randomised controlled studies.

Types of participants

Children and adults with confirmed diagnosis of CF by the presence of two disease causing mutations, or by a combination of positive sweat test and recognised clinical features of CF. Participants should also have either or both (*post hoc* change - see Differences between protocol and review) of the following:

- a clinical diagnosis of influenza (temperature above 37.8 °C; at least two of the following symptoms: cough, headache, myalgia, sore throat or fatigue; and no clinical evidence of bacterial infection) made by a healthcare professional in a community in which there was an influenza outbreak;
- laboratory or near-patient test confirmation of influenza.

Types of interventions

Interventions comparing NIs to placebo or other antiviral drugs for treating influenza in people with CF at any dose or regimen and each NI agent to be considered separately.

Types of outcome measures

Primary outcomes

1. Need for hospitalisation (directly related to influenza illness)
2. Time to alleviation of constitutional symptoms (fever and associated symptoms) (*post hoc* change - see Differences between protocol and review)
3. Respiratory function
   a. forced expiratory volume in one second (FEV_1) as per cent of predicted for age, sex and height
   b. forced vital capacity (FVC) as per cent of predicted for age, sex and height

Secondary outcomes

1. Quality of life (as measured by a validated tool)
2. Acquistion of characteristic CF pathogens
   a. *Pseudomonas aeruginosa*
   b. other pathogens
3. Pulmonary exacerbation (protocol defined) or need for additional antibiotic treatment (oral or intravenous)
4. Need for ventilator support (hospital admission)
5. Development of flu-related complications
6. Death
7. Clinical score (e.g. Schwachman score)
8. Treatment burden (using a validated measure such as Challenges of Living with Cystic Fibrosis (CLCF))
9. Time off school or work
10. Nutritional parameters
    a. weight
    b. body mass index (BMI)
    c. height
11. Adverse events (relating to treatment)
    a. mild (not needing additional treatment)
    b. moderate (needing treatment or admission to hospital)
    c. severe (life-threatening)

Search methods for identification of studies

Although there were no language restrictions on included studies we did not retrieve any relevant non-English papers. We will not apply any language restrictions on any studies identified for future updates of the review.

Electronic searches

We searched the Group's Cystic Fibrosis Trials Register using the search terms: neuraminidase inhibitors AND cystic fibrosis.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the

register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of last search of the Cystic Fibrosis Trials Register: 02 November 2105.

Searching other resources

We did not identify any relevant studies and were therefore unable to do any searching of the reference lists of relevant articles. We have contacted Roche UK (manufacturers of Tamiflu®) (last email sent September 2013) and GlaxoSmithKline (manufacturers of Relenza®) to request any unpublished information on any relevant ongoing or completed studies of their products. To date we have not received any response.

Data collection and analysis

Although no studies were identified for inclusion in this review the following methods of selection of studies, data extraction, assessment of risk of bias and data management will apply for subsequent updates, and when future studies are identified.

Selection of studies

Two review authors Vanitha Jagannath (VJ) and Zbys Fedorowicz (ZF) will independently assess the abstracts of studies resulting from the searches. We will obtain full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, and those for which there are insufficient data in the title and abstract to make a clear decision.The two review authors will independently assess the full text papers and resolve any disagreement on the eligibility of included studies through discussion and consensus, or through a third party Jai Shanthini Singaram (JS). We will exclude all irrelevant records and note the details of the studies and the reasons for their exclusion in the 'Characteristics of excluded studies' table in the Review Manager software (RevMan 2014).

Data extraction and management

The authors will enter extracted study details into the 'Characteristics of included studies' table in the Review Manager software and will collect outcome data using a pre-determined form designed for this purpose. Both authors will compare extracted data to reach a consensus and one author (ZF) will enter the data into the Review Manager software.

We will extract the following details.

1. Trial methods
   a. method of allocation
   b. masking of participants, trial investigators and outcome assessors
   c. exclusion of participants after randomisation and proportion and reasons for losses at follow up
2. Participants
   a. country of origin and location: private clinic or academic institute
   b. sample size
   c. age
   d. sex
   e. inclusion and exclusion criteria
3. Intervention
   a. type, dosage, route of administration
   b. length of time in follow up.
4. Control
   a. type, dosage, route of administration
   b. length of time in follow up.
5. Outcomes
   a. primary outcomes mentioned in the 'Types of outcome measures' section of this review
   b. secondary outcomes mentioned in the 'Types of outcome measures' section of this review

If stated, we will record the sources of funding of any of the included studies.

The review authors will use this information to help them assess heterogeneity and the external validity of the studies.

We plan to report outcomes at up to one week, between one and two weeks, more than two weeks to three weeks, more than three weeks to four weeks. We will also consider additional follow-up data recorded at other time periods. The above time points were chosen to comprehensively evaluate the effect of intervention:

1. on the viral influenza infection in CF which would be immediate;
2. on the secondary complications of Influenza like bacterial infections pneumonia or acute suppurative otis media (ASOM), which would last for a few days to weeks; and
3. the impact of flu and its secondary complications on the CF disease course which could last for weeks to months.

Assessment of risk of bias in included studies

Each review author will grade the risk of bias in the selected studies using a simple contingency form following the domain-based evaluation described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). They will compare the evaluations and any disagreements between the review authors will be discussed and resolved.

The following domains will be assessed as 'Yes' (i.e. low risk of bias), 'Unclear' (uncertain risk of bias) or 'No' (i.e. high risk of bias):

1. sequence generation;
2. allocation concealment;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data;
5. selective outcome reporting.

These assessments will be reported for each individual study in the 'Risk of bias in included studies' table.

Measures of treatment effect

We will report risk ratios (RR) and their associated 95% confidence intervals (CIs) for dichotomous outcomes, and odds ratios (OR) with 95% CIs for adverse events.

For continuous outcomes, we will report the mean relative change from baseline or the mean post-intervention value as well as the difference in means between treatment groups and their associated 95% CIs. We will also record the standard deviations

(SDs); if standard errors (SEs) are provided, these will be converted to SDs.

Time-to-resolution data will be reported as hazard ratio (HR) with 95% CIs.

Unit of analysis issues

We expect to include studies in which the individual participants were the units of randomisation and subsequent analysis. If cluster-randomised studies are included in the analyses, we will adjust their sample sizes using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial or another source (Higgins 2011).

We do not plan to include any cross-over studies as the interventions are not appropriate for this review.

Dealing with missing data

We will make attempts to retrieve missing data from the investigators for any of the included studies, and if unsuccessful or the discrepancies are significant, we will provide a narrative synthesis of the data as reported. We have contacted the manufacturers of the two currently commercially available drugs (Tamiflu® and Relenza®) for any unpublished trial information.

Assessment of heterogeneity

We will assess clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions and the outcomes as specified in the criteria for included studies. We will assess statistical heterogeneity using a Chi^2 test and the I^2 statistic (Higgins 2003). Using Chi^2, we will consider a P value of less than 0.10 as evidence of heterogeneity. We will evaluate the I^2 statistic as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

To assess publication bias, we will follow the recommendations on testing for funnel plot asymmetry (with at least 10 studies) as described in section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we will explore these in the Discussion section if appropriate. We will also attempt to assess outcome reporting bias as stated above by comparing the protocols of included studies to the final published papers to establish that all outcomes measured are reported. If the protocols of studies are not available, we will compare the 'Methods' and the 'Results' sections of the final published papers. We will also use clinical knowledge to identify the measures usually reported for specific outcomes.

Data synthesis

We will seek statistical support from the Cochrane Cystic Fibrosis and Genetic Disorders Group. Two review authors Zbys Fedorowicz (ZF) and Vanitha Jagannath (VJ) will analyse the data and report them as specified in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* Version (Higgins 2011). We will report the different types of NIs separately. In view of the expectation of a degree of clinical heterogeneity between the studies we intend using the random-effects model with studies grouped together by mode of drug activity. In the event that there are insufficient clinically homogeneous studies for any specific intervention or insufficient trial data that can be pooled, we will present a narrative synthesis.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses if we identify moderate, substantial or considerable heterogeneity (as defined above) and if we are able to include at least 10 studies:

1. age (under 16 years; 16 years and older);
2. severity of CF (Schwachman score: severe - under 40; moderate - 41 to 55; mild - 56 to 70; good - 71 to 85; excellent - over 85);
3. influenza immunisation status (influenza immunisation within last 12 months).

Sensitivity analysis

If there are sufficient included studies (n = 10) we plan to conduct sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments: exclusion of quasi-randomised studies; of studies with unclear or inadequate allocation concealment; of studies with unclear or inadequate blinding of outcomes assessment and completeness of follow up; exclusion of cluster-randomised studies.

RESULTS

Description of studies

Results of the search

No studies were identified in the comprehensive searches undertaken for this review.

Risk of bias in included studies

No studies were included in this review.

Effects of interventions

No studies were included in this review.

DISCUSSION

The comprehensive search used in this review provided no references to studies. Thus, the lack of relevant randomised controlled studies as well as any robust evidence to support or refute the effectiveness of NIs for the treatment of influenza in people with CF proved to be somewhat disappointing. Over the last 10 years there have been several studies on the effectiveness of NIs. These comprehensive studies have also provided some limited data on at-risk individuals (Burls 2002), but questions still remain unanswered as to whether treatment options based on this intervention can be considered both effective and safe in people with CF.

AUTHORS' CONCLUSIONS

Implications for practice

Whilst there is no evidence to either support or refute the effectiveness of NIs for treating influenza in people with CF,

clinicians should continue to base their treatment decisions on clinical experience and the individual circumstances and preferences of well-informed patients. These should include a full risk assessment of the potential harms and benefits of withholding NIs, while balancing the possible sequelae of severe infection against the risk of any potential adverse events; more especially as the benefits of administration may outweigh these risks. The World Health Organisation (WHO) recommendations, based on the available evidence of effectiveness of these medications in the general population and in some at-risk populations, stipulate that oseltamivir should be considered the first line of treatment for influenza and, in circumstances where oseltamivir is unavailable or cannot be used, zanamivir may be given; furthermore, the treatment decisions should not wait for laboratory confirmation during a pandemic (WHO 2009). These recommendations apply to all patient groups, including pregnant women, and all age groups, including young children and infants. However, in people with CF, there are some specific safety concerns in using zanamivir because of possible poor bioavailability and some adverse effects like bronchospasm that can worsen the intrinsic pathology in this population.

Implications for research

The effects of NIs for influenza in people with CF are unclear. There are some ongoing studies in the general population, though none specifically in people with CF, which may provide insight into some of the issues. Contemporary concerns about the adverse consequences of NI overuse and concerns about averting the severity of influenza illness in vulnerable populations highlight a need for randomised controlled trials to address the issues of appropriate indication, timing of initiation and duration of NI therapy for seasonal as well as pandemic influenza in people with CF. A recent umbrella review of NIs concludes that there is no evidence to show a benefit for treatment in elderly and at-risk individuals, vaccinated or not, on outcomes such as hospitalization and mortality (Michiels 2013). Large multi-centred trials which focus on this specific population group are now required.

New randomised controlled studies need to focus on people with CF and measure severe influenza complications as an outcome, which must be powered accordingly. This should include recently developed NIs, peramivir and laninamivir, head-to-head studies between existing NIs and with the newer NIs in prophylaxis and treatment scenarios (Michiels 2013).

Any future studies will also need to be rigorous in design and delivery, with subsequent reporting to include high quality descriptions of all aspects of methodology to enable appraisal and interpretation of results, and conform with the Consolidated Standards of Reporting Trials (CONSORT) statement. We agree with the recommendation by Michiels in the recent paper, "In the future, a new policy should be established regarding the ownership of trial results. All of the stakeholders should acquire full access to clinical data reports and individual study results to avoid publication bias and selective reporting afterwards" (Michiels 2013).

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REFERENCES

Additional references

Armstrong 1998

Armstrong D, Grimwood K, Carlin JB, Carzino R, Hull J, Olinsky A, et al. Severe viral respiratory infections in infants with cystic fibrosis. *Pediatric Pulmonology* 1998;**26**(6):371-9. [PMID: 9888211]

Burls 2002

Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, et al. Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation. *Health Technology Assessment* 2002;**6**(9):1-87.

Conway 1992

Conway SP, Simmonds EJ, Littlewood JM. Acute severe deterioration in cystic fibrosis associated with influenza A virus infection. *Thorax* 1992;**47**(2):112-4.

Cooper 2003

Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner D, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2003;**326**(7401):1235.

Demicheli 2007

Demicheli V, Di Pietrantonj C, Jefferson T, Rivetti A, Rivetti D. Vaccines for preventing influenza in healthy adults. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No: CD001269. [DOI: 10.1002/14651858.CD001269.pub3]

Dharmaraj 2000

Dharmaraj P, Tan AA, Smyth RL. Vaccines for preventing influenza in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2000, Issue 1. Art. No: CD001753. [DOI: 10.1002/14651858.CD001753]

Hayden 2004

Hayden FG, Belshe R, Villanueva C, Lanno R, Hughes C, Small I, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. *Journal of Infectious Diseases* 2004;**189**(3):440-9.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Høiby 2000

Høiby N, Frederiksen B. Microbiology of cystic fibrosis. In: Hodson ME, Geddes DM, editors(s). Cystic Fibrosis. London: Arnold, 2000:83-107.

Jefferson 2006

Jefferson T, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No: CD001265. [DOI: 10.1002/14651858.CD001265.pub2]

Jefferson 2012

Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *The Cochrane database of systematic reviews* 2012;**1**:CD008965. [PMID: 22258996]

Jefferson 2014

Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *The Cochrane database of systematic reviews* 2014;**4**:CD008965. [PMID: 24718923]

Matheson 2007

Matheson NJ, Harnden A, Perera R, Sheikh A, Symmonds-Abrahams M. Neuraminidase inhibitors for preventing and treating influenza in children. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No: CD002744. [DOI: 10.1002/14651858.CD002744.pub2]

Matrosovich 2004

Matrosovich MN, Matrosovich TY, Gray T, Roberts NA, Klenk HD. Neuraminidase is important for the initiation of influenza virus infection in human airway epithelium. *Journal of Virology* 2004;**78**(22):12665-7.

Michiels 2013

Michiels B, Van Puyenbroeck K, Verhoeven V, Vermeire E, Coenen S. The value of neuraminidase inhibitors for the prevention and treatment of seasonal influenza: a systematic review of systematic reviews. *PloS one* 2013;**8**(4):e60348. [PMID: 23565231]

MMWR 2008

Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, Mootrey G, et al. Prevention & Control of Influenza - Recommendations of the Advisory Committee on Immunization Practices (ACIP) 2008. MMWR. Morbidity and Mortality Weekly Report 2008;**57**(No. RR-7):1-60.

Moscona 2005

Moscona A. Neuraminidase inhibitors for influenza. *New England Journal of Medicine* 2005;**353**(13):1363-73.

Ratjen 2003

Ratjen F, Döring G. Cystic fibrosis. *Lancet* 2003;**361**(9358):681-9.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schirmer 2009

Schirmer P, Holodniy M. Oseltamivir for treatment and prophylaxis of influenza infection. *Expert Opinion Drug Safety* 2009;**8**(3):357-71.

Smyth 1995

Smyth AR, Smyth RL, Tong CY, Hart CA, Heaf DP. Effect of respiratory virus infections including rhinovirus on clinical status in cystic fibrosis. *Archives of disease in childhood* 1995;**73**(2):117-20. [PMID: 7574853]

Turner 2003

Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. *Health Technology Assessment* 2003;**7**(35):iii-iv, xi-xiii, 1-170.

van Ewijk 2008

van Ewijk BE, van der Zalm MM, Wolfs TF, Fleer A, Kimpen JL, Wilbrink B, et al. Prevalence and impact of respiratory viral infections in young children with cystic fibrosis: Prospective cohort study. *Pediatrics* 2008;**122**(6):1171-6.

Wat 2008

Wat D, Gelder C, Hibbitts S, Bowler I, Pierrepoint M, Evans R, et al. Is there a role for influenza vaccination in cystic fibrosis? *Journal of Cystic Fibrosis* 2008;**7**(4):85-8.

WHO 2009

WHO Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and other Influenza Viruses. www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html (accessed 20 August 2009).

References to other published versions of this review

Jagannath 2009

Jagannath VA, Asokan GV, Fedorowicz Z, Singaram JS, Lee TWR. Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No: CD008139. [DOI: 10.1002/14651858.CD008139]

Jagannath 2010

Jagannath VA, Asokan GV, Fedorowicz Z, Singaram JS, Lee TWR. Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2010, Issue 3. Art. No: CD008139. [DOI: 10.1002/14651858.CD008139.pub2]

Jagannath 2011

Jagannath VA, Asokan GV, Fedorowicz Z, Singaram JS, Lee TWR. Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2011, Issue 12. Art. No: CD008139. [DOI: 10.1002/14651858.CD008139.pub2]

Jagannath 2014

Jagannath VA, Asokan GV, Fedorowicz Z, Lee TWR. Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2014, Issue 2. Art. No: CD008139. [DOI: 10.1002/14651858.CD008139.pub3]

WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	Due to a lack of research in this area the Editorial Board of the Cystic Fibrosis and Genetic Disorders Review Group have decided to no longer update this review.

HISTORY

Protocol first published: Issue 4, 2009
Review first published: Issue 3, 2010

Date	Event	Description
15 February 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group did not identify any new references potentially eligible for inclusion in this review.
15 February 2016	New citation required but conclusions have not changed	Since no new studies have been included in this updated review, our conclusions remain the same.

Date	Event	Description
10 February 2014	New search has been performed	A search of the Cystic Fibrosis & Genetic Disorders Group's Cystic Fibrosis Trials Register did not identify any potentially eligible studies for inclusion in this review.
10 February 2014	New citation required but conclusions have not changed	No new studies were included in this update of the review, therefore our conclusions remain the same. Jai Shanthini Singaram has stepped down from the author team for this update.
26 October 2011	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for inclusion in the update of this review.
26 April 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
Draft the protocol	VJ/AG/ZF/JS/TL
Develop and run the search strategy	Trial Search Co-ordinator at the CFGD Group
Obtain copies of studies	AG/ZF
Select which studies to include	VJ/AG/ZF/JS
Extract data from studies	VJ/AG/ZF/JS
Enter data into RevMan	AG/ZF
Carry out the analysis	AG/ZF
Interpret the analysis	AG/ZF/TL
Draft the final review	VJ/AG/ZF/JS/TL
Update the review	VJ/AG/ZF/JS/TL

DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

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- No sources of support supplied

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- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In line with the WHO recommendations of antiviral treatment in the ongoing H1N1 pandemic which recommends initial treatment decisions to be based on clinical assessment and knowledge about the presence of the virus in the community without waiting for laboratory confirmation (WHO 2009), the definition of Types of participants has been changed in the review to also include the people with CF with only clinical diagnosis of influenza (without laboratory confirmation) .

There is an additional primary outcome listed in the review compared to the protocol 'Time to alleviation of constitutional symptoms'. This outcome will allow us to study the effect of NIs on uncomplicated influenza as well, in people with CF.

INDEX TERMS

Medical Subject Headings (MeSH)

Cystic Fibrosis [*complications]; Enzyme Inhibitors [*therapeutic use]; Influenza, Human [*drug therapy]; Neuraminidase [*antagonists & inhibitors]

MeSH check words

Humans