A Compendium of Cochrane Reviews: Influenza

By Andrew W. Swartz, MD (12/30/2012)

Intro

Each topic below starts with the proper title of the respective Cochrane Systematic Review, which is also a link to the freely viewable page at the Cochrane Collaboration website. The italicized excerpt is the pertinent text of the lay description of the conclusions. Following the links to the respective pages allows access to the full lay description as well as the formal abstract, which provides a much more detailed description of the methods and results; each page also has a link (on the right) to the complete review at The Cochrane Library (requires institutional subscription (UW Access) or purchase price of $29.99 per review).

Cochrane Collaboration Cochrane Library

1. Vaccines

a. Vaccines for preventing influenza in healthy children (August 15, 2012)

The review authors found that in children aged from two years, nasal spray vaccines made from weakened influenza viruses were better at preventing illness caused by the influenza virus than injected vaccines made from the killed virus. Neither type was particularly good at preventing 'flu-like illness' caused by other types of viruses. In children under the age of two, the efficacy of inactivated vaccine was similar to placebo. It was not possible to analyse the safety of vaccines from the studies due to the lack of standardisation in the information given, but very little information was found on the safety of inactivated vaccines, the most commonly used vaccine in young children.

b. Vaccines to prevent influenza in healthy adults (June 28, 2011)

Authors of this review assessed all trials that compared vaccinated people with unvaccinated people. The combined results of these trials showed that under ideal conditions (vaccine completely matching circulating viral configuration) 33 healthy adults need to be vaccinated to avoid one set of influenza symptoms. In average conditions (partially matching vaccine) 100 people need to be vaccinated to avoid one set of influenza symptoms. Vaccine use did not affect the number of people hospitalised or working days lost but caused one case of Guillian-Barré syndrome (a major neurological condition leading to paralysis) for every one million vaccinations. Fifteen of the 36 trials were funded by vaccine companies and four had no funding declaration. Our results may be an optimistic estimate because company-sponsored influenza vaccines trials tend to produce results favorable to their products and some of the evidence comes from trials carried out in ideal viral circulation and matching conditions and because the harms evidence base is limited.

c. Influenza vaccination for healthcare workers who work with the elderly (Sept 8, 2010)

We conclude that there is no evidence that only vaccinating healthcare workers prevents laboratory-proven influenza, pneumonia, and death from pneumonia in elderly residents in long-term care facilities.

d. Vaccines for preventing seasonal influenza and its complications in people aged 65 or older (Feb 17, 2010)

Due to the poor quality of the available evidence, any conclusions regarding the effects of influenza vaccines for people aged 65 years or older cannot be drawn. The public health safety profile of the vaccines appears to be acceptable.

e. Vaccines for preventing influenza in people with asthma (Feb 18, 2008)

Few trials have been carried out in a way that tests whether asthma attacks following influenza infection (as opposed to following the vaccination) are significantly reduced by having influenza vaccination, so uncertainty remains in terms of how much difference vaccination makes to people with asthma. The included studies suggest that the vaccine against influenza is unlikely to precipitate asthma attacks immediately after the vaccine is used.

f. Vaccines for children and adults with cystic fibrosis (August 10, 2011)

There were a high number of adverse events, but none were serious or persistent. There is no evidence to show if regular influenza vaccine benefits people with cystic fibrosis.

g. Influenza vaccine for patients with chronic obstructive pulmonary disease (August 8, 2010)

… there is now some evidence from randomised trials that inactivated influenza vaccine indeed decreases "flare ups" of COPD, especially those that are related to the influenza virus itself. The inactivated influenza virus vaccine is given intramuscularly and is associated with an increase in local side effects such as pain at the site of injection. This is short-lived, not serious and is outweighed by the long term benefit of the vaccine. The inactivated virus vaccine does not cause influenza or any significant worsening of COPD.

h. Influenza vaccine for people with HIV/AIDS (September 12, 2012)

This Cochrane Review is at the protocol stage and there is no abstract or plain language summary.

i. Influenza vaccine for children and adults with bronchiectasis (September 8, 2010)

In this review however, our search for randomised control trials examining the effectiveness of influenza vaccines for people with bronchiectasis revealed no relevant studies. In the absence of evidence, patients' needs should be individualised and national guidelines be adhered to.

j. Influenza vaccination in children being treated with chemotherapy for cancer (January 19, 2011)

Based on this review it is not possible to recommend or discourage influenza vaccination in children with cancer being treated with chemotherapy.

k. Influenza vaccines for prevention of influenza-like illness and influenza in immunosuppressed cancer patients (Mar 16, 2011)

This Cochrane Review is at the protocol stage and there is no abstract or plain language summary.

2. Medications

a. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only) (April 18, 2012)

Oseltamivir and zanamivir appear to have modest benefit in reducing duration of illness in children with influenza. However, our analysis was limited by small sample sizes and an inability to pool data from different studies. In addition, the inclusion of data from published trials only may have resulted in significant publication bias. Based on published trial data, oseltamivir reduces the incidence of acute otitis media in children aged one to five years but is associated with a significantly increased risk of vomiting. One study demonstrated that laninamivir octanoate was more effective than oseltamivir in shortening duration of illness in children with oseltamivir-resistant influenza A/H1N1. The benefit of oseltamivir and zanamivir in preventing the transmission of influenza in households is modest and based on weak evidence. However, the clinical efficacy of neuraminidase inhibitors in 'at risk' children is still uncertain. Larger high-quality trials are needed with sufficient power to determine the efficacy of neuraminidase inhibitors in preventing serious complications of influenza (such as pneumonia or hospital admission), particularly in 'at risk' groups.

b. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (October 17, 2012)

We decided to update and amalgamate our reviews on the antiviral drugs zanamivir and oseltamivir for influenza on the basis of the manufacturers' reports to regulators (called clinical study reports) and regulators' comments (which we called regulatory information). Clinical study reports are extensive documents with exhaustive details of the trial protocol, methods and results. In view of the unresolved discrepancies in the data presented in published trial reports and of the substantial risk publication bias in this area, we elected not to use data from journal articles. Availability of documents generated by national and regional regulatory bodies during licensing processes in the UK, USA, continental Europe and Japan, partial trial reports from the manufacturers of oseltamivir and from the European regulator European Medicines Agency (EMA), enabled us to verify information from the trials. The authors have been unable to obtain the full set of clinical study reports or obtain verification of data from the manufacturer of oseltamivir (Roche) despite five requests between June 2010 and February 2011. No substantial comments were made by Roche on the protocol of our Cochrane Review which has been publicly available since December 2010. Based on our assessments of the documents we could obtain, we came to the conclusion that there were substantial problems with the design, conduct and availability of information from many of the trials. Due to these concerns we decided not to proceed with a meta-analysis of all the oseltamivir data as we had intended. Instead we carried out analyses of effects on symptoms (shortens them by 21 hours or so) and hospitalisations (no evidence of effect) of people with influenza-like illness ('flu') on data from all the people enrolled in treatment trials of oseltamivir. Other outcomes could not be assessed due to unavailability of data for all the people enrolled in treatment trials of oseltamivir. Our independent analysis concurs with the conservative conclusions regarding the effects of both drugs by the US Food and Drug Administration (FDA). The FDA only allowed claims of effectiveness of both drugs for the prevention and treatment of symptoms of influenza and not on other effects (such as interruption of person-to-person spread of the influenza virus or prevention of pneumonia). There is evidence to suggest that both drugs are associated with harms (oseltamivir: nausea, vomiting; zanamivir: probably asthma). The FDA described the overall performance of both drugs as "modest". We expect full clinical study reports containing study protocol, reporting analysis plan, statistical analysis plan and individual patient data to clarify outstanding issues. These full clinical study reports are at present unavailable to us.

c. Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis (October 26, 2011)

… the question of the safety and effectiveness of neuraminidase inhibitors for treating influenza in people with cystic fibrosis remains unanswered.

d. Amantadine and rimantadine for influenza A in children and the elderly (June 27, 2011)

AMT (amantadine) is effective in preventing influenza A in children but the NNTB is high (NNTB: 12 (95% CI 9 to 17). RMT (rimantadine) probably helps the abatement of fever on day three of treatment, but the quality of the evidence is poor. Due to the small number of available studies, we could not reach a definitive conclusion on the safety of AMT or the effectiveness of RMT in preventing influenza in children and the elderly.

e. Amantadine and rimantadine for influenza A in adults (April 26, 2008)

The review of trials found that both drugs are similarly helpful in relieving the symptoms of influenza A in adults, but only when there is a high probability that the cause of the flu is influenza A (a known epidemic, for example). It is likely that neither drug will interrupt the spread of influenza A and by treating symptoms may encourage viral spread in the community by people who are feeling better but are still infectious. Resistance of influenza viruses to amantadine is a serious worldwide problem as shown by recent surveys. Both drugs have adverse gastrointestinal (stomach and gut) effects, but amantadine can also have serious effects on the nervous system. They should only be used in an emergency when all other measures fail.

f. Antiviral treatment for influenza infection in people with cystic fibrosis (Dec 7, 2011)

We did not find any trials to support or refute the use of neuraminidase inhibitors for influenza in people with cystic fibrosis. However, 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, the question of the safety and effectiveness of neuraminidase inhibitors for treating influenza in people with cystic fibrosis remains unanswered.

g. Chinese medicinal herbs for patients with uncomplicated influenza (April 18, 2012)

This review assessed the prophylactic and therapeutic effects as well as safety of Chinese medicinal herbs as an alternative and adjunctive medicine to other commonly used drugs for uncomplicated influenza. Two studies involving 1012 participants were included in the review. The trial quality and evidence were poor and do not support or reject the use of any Chinese herbal preparations for influenza. Well-designed trials are required.

h. Homeopathic Oscillococcinum® for preventing and treating influenza and influenza-like illness (Dec 12, 2012)

Results from two poorly reported clinical trials (total of 327 participants) do not show that Oscillococcinum® can prevent the onset of flu. Although the results from four other clinical trials (total of 1196 participants) suggested that Oscillococcinum® relieved flu symptoms at 48 hours, this might be due to bias in the trial methods. One patient reported headache after taking Oscillococcinum®.

Addendum

For fans of medical controversies: the authors of the recent Cochrane reevaluation of the effectiveness of olsetamivir and zanamivir (*Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children*) have entered into somewhat non-cordial debate with the CDC and WHO. The BMJ has a web page dedicated to this issue. At the bottom of that page are links to pages with the actual email correspondences. Both CDC and WHO seem reluctant to discuss how they arrived at different conclusions than Cochrane or to answer specific questions about inconsistencies in the reviewed studies.