

## **QUESTION AND ANSWER BRIEFING PAPER**

Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. *Lancet* 2006; 367 (19 January 2006). [www.thelancet.com/journals/eop](http://www.thelancet.com/journals/eop)

### **WHAT IS THE AIM OF THE PAPER?**

The paper reports two Cochrane reviews (see below) on the effects of licensed antiviral drugs against influenza. These reviews bring together the current evidence from clinical trials of these drugs to provide an estimate of their effects. The paper includes information from more than 50 trials published during forty years on two classes of drugs, the so called M2 ion channel blockers (amantadine – *Lysovir* and rimantadine - *Fluvirin*, 34 trials) and the newer neuraminidase inhibitors (zanamivir – *Relenza* and oseltamivir - *Tamiflu*, 19 trials). Eleven of the amantadine trials took place during the 1968-69 “Hong Kong” influenza pandemic.

### **WHAT ARE THE EFFECTS WERE INVESTIGATED?**

The clinical trials assessed the effects of the drugs on cases of influenza and its complications (e.g. pneumonia), as well as cases of influenza-like illness and its complications. Some of the trials also assessed adverse effects caused by the drugs and measures of viral infection, such as the body’s antibody response and shedding of viruses from the nose. Shedding of viruses in this way is important in considering the spreading of influenza.

### **WHAT IS THE DIFFERENCE BETWEEN INFLUENZA AND INFLUENZA-LIKE ILLNESS?**

Influenza (“real influenza”) is caused by influenza A or B viruses, whereas influenza-like illness is caused by scores of different viruses, not all of which are influenza. As the symptoms of influenza and influenza-like illness are the same, a doctor cannot identify what has caused the infection without further tests. These are impractical in a busy surgery. So, in practice, “influenza-like illness” is the diagnosis made by the doctor when he/she has not tested for influenza or is still awaiting the results of the test.

### **DOES THIS DIFFERENCE MATTER?**

If the doctor cannot readily identify why the patient in front of him is ill, he or she cannot prescribe a specific therapy, such as antivirals, which are only registered for use against influenza, not other viruses. The doctor is “flying blind” and has to make a decision based on this incomplete knowledge

### **MIGHT THE EFFECTS OF THESE DRUGS BE DIFFERENT IF SOMEONE HAS “REAL INFLUENZA” OR HAS “INFLUENZA-LIKE ILLNESS”?**

The ability of antivirals to prevent or treat “real” influenza is known as their “efficacy”. This is high only when most of the patients being treated have real influenza. We call the ability of antivirals to prevent or treat influenza-like illness their “effectiveness”. This is what we need to know for most real life settings, when the doctor isn’t able to identify the virus causing the illness. This is a crucial and practical difference and is apparent from the trials of each antiviral assessed in the review.

### **WHAT DID THE REVIEW FIND?**

Despite the fact that this is the most up-to-date and comprehensive review of antivirals for influenza, the Cochrane reviewers did not find any evidence that either class of antiviral drugs was effective at treating influenza-like illness. They did find evidence that both classes of antivirals prevented or eased the symptoms of “real influenza” but did not prevent infection. However, while M2 ion channel blockers had no effect on the shedding of the virus from the patient’s nose or the persistence of the influenza viruses in their upper airways, neuraminidase inhibitors did diminish the body’s viral load and viral shedding. This effect lasted while the patient was taking the treatment. The effect on viral shedding could explain the apparent ability of oseltamivir to interrupt household spread of seasonal influenza but the finding on the inability to prevent infection is consistent with the non-interruption of viral shedding. The use of amantadine quickly led to the selection of resistant viral strains, and both amantadine and rimantadine caused unpleasant adverse effects, such as hallucinations and agitation. Neuraminidase inhibitors are better tolerated, although some people feel nauseous after taking oseltamivir.

#### WHAT DO THESE RESULTS MEAN?

- The lack of effect on influenza-like illness means routine use of these drugs during the usual 'influenza season' is impractical.
- Because amantadine rapidly induces viral resistance and has unpleasant adverse effects, the Cochrane reviewers do not recommend further use of either it or the other M2 ion channel blocker, rimantadine.
- Because neuraminidase inhibitors do not stop the virus being shed by an infected person, people can still catch influenza from someone who is being treated. This is especially so in a pandemic when the concentration of virus in the upper airways (so-called viral load) will be much higher than that found with seasonal influenza.
- Therefore, if neuraminidase inhibitors are used to control a serious epidemic or a pandemic, other control measures must be used as well.
- Public health measures such as barriers (masks, gowns, gloves), distance (quarantine, buffer zones) and personal hygiene measures (hand washing) should also be used.
- Overreliance on drugs to control a serious epidemic or pandemic may lull recipients of the drugs into a false sense of security, encourage risk-taking and viral spread, which will make the public health consequences worse.

#### WHAT ABOUT AVIAN INFLUENZA ("BIRD FLU")?

The reviewers found information about the use of oseltamivir (Tamiflu) by people affected by three separate outbreaks (Far East, the Netherlands and Canada), each caused by different types of avian-derived influenza viruses. This information did not come from trials but simply described what happened to people who had been treated. The reports did not show efficacy of the drug. This is possibly because it was either used too late or because it has no effect against avian influenza. Either way, the experiences to date do not allow firm conclusions to be drawn.

#### IS THERE ANYTHING ELSE OF PARTICULAR INTEREST?

The evidence base supporting the use of neuraminidase inhibitors is small and mainly reflects the need of the manufacturers of these drugs to fulfil the regulatory requirements to get the drugs registered. For example, only five trials, based on a total of 1661 patients, reported viral nasal concentration. Yet, reliable information on this is possibly critical to controlling a pandemic. Furthermore, the relatively small amount of trial research makes it difficult to interpret some apparently contradictory findings, such as the inability of neuraminidase inhibitors to prevent infection but their apparent effectiveness in preventing some complications requiring admission to hospital.

#### WHO FUNDED THE REVIEW?

The Piemonte Region of Italy and the Department of Health in England. The review was carried out under the auspices of the Cochrane Acute Respiratory Infections Group (based at Bond University, Australia) which received a grant from the Cochrane Collaboration Steering Group.

#### WHAT IS THE COCHRANE COLLABORATION?

The Cochrane Collaboration is an international, non-profit, independent organisation, established to ensure that up-to-date, accurate information about the effects of healthcare interventions is readily available worldwide. It produces and disseminates systematic reviews of healthcare interventions, and promotes the search for evidence in the form of clinical trials and other studies of the effects of interventions.

#### WHAT DOES THE ORGANISATION DO?

The Cochrane Collaboration prepares Cochrane Reviews and aims to update them regularly with the latest scientific evidence. Members of the organisation (mostly volunteers) work together to provide evidence to help people make decisions about health care. Some people read the healthcare literature to find reports of randomised controlled trials; others find such reports by searching electronic databases; others prepare and update Cochrane Reviews based on the evidence found in these trials; others work to improve the methods used in Cochrane Reviews; others provide a vitally important consumer perspective; and others support the people doing these tasks. The Cochrane Collaboration website provides information on a variety of ways of registering interest or becoming directly involved.

#### HOW BIG IS THE COCHRANE COLLABORATION?

Data from The Cochrane Library in 2005 show that there are more than 13,000 people working within The Cochrane Collaboration in nearly 100 countries, half of whom are authors of Cochrane Reviews. The number of people has increased by 10-20% every year for the last five years. The increase in the number of contributors from low, lower-middle and upper-middle income countries has been even greater, to nearly 1300 (9.9%) in 2005 - a more than four fold increase since 2000.

#### HOW IS IT ORGANISED?

The members of The Cochrane Collaboration are organised into groups, known as 'entities', of which the Cochrane Review Groups (such as the Acute Respiratory Infections Group) are responsible for Cochrane reviews. These Groups are made up of people who prepare, maintain and update Cochrane Reviews, and people who support them in this process. Each Group has an 'editorial base' where a small team of people supports the production of Cochrane Reviews.

#### WHAT ARE COCHRANE REVIEWS?

Cochrane Reviews are systematic assessments of evidence of the effects of healthcare interventions, intended to help people to make informed decisions about health care, their own or someone else's. Cochrane Reviews are needed to help ensure that healthcare decisions throughout the world can be informed by high quality, timely research evidence. Cochrane Reviews are published in full in The Cochrane Database of Systematic Reviews, one of several databases in The Cochrane Library, and versions of these reviews are also sometimes published in other health journals.

#### WHO FUNDS THE COCHRANE COLLABORATION?

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