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NEWS

Cochrane review questions effectiveness of neuraminidase inhibitors

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The Department of Health for England has wasted more than £500m (€600m; $830m) on stockpiling neuraminidase inhibitors to use in the event of a flu pandemic, and it should not replace them when they expire, concludes the first complete systematic review of the drugs by the Cochrane Collaboration.[1-3]

For the first time the collaboration was able to look at complete data from all trials conducted on oseltamivir (marketed as Tamiflu) and zanamivir (Relenza) by their respective manufacturers, Roche and GlaxoSmithKline, after a four and a half year battle by the reviewers and *The BMJ* to gain access to the full data. GSK was the first to provide the information, doing so early last year, and by September 2013 Roche had also complied.[4]

The review looked at 46 trials (20 on oseltamivir and 26 on zanamivir), involving more than 24 000 people and reported in more than 160 000 pages of regulatory documents. Previous Cochrane reviews and appraisals by most regulatory authorities, including the European Medicines Agency, have had access to only a limited amount of the data made available by the drug manufacturers.

Recommendations based on these limited data have prompted governments around the world to stockpile oseltamivir in the belief the drug would reduce the length and severity of infection and the numbers of serious complications, hospitalisations, and deaths. However, the Cochrane Collaboration's latest findings show that although treating flu with oseltamivir can shorten the duration of symptoms by around half a day, the evidence did not support its use to reduce hospitalisations or the risk of serious complications, such as pneumonia.

The reviewers found that oseltamivir shortened the duration of symptoms in adults by 16.8 hours (95% confidence interval 8.4 to 25.1 hours; P<0.0001). There was no effect on the duration of symptoms in children with asthma; and in otherwise healthy children symptom duration was reduced by 29 hours (12 to 47 hours; P=0.001).

The reviewers found no good evidence to support claims that oseltamivir reduced the number of people admitted to hospital or that it reduced serious complications of flu, including confirmed pneumonia, bronchitis, sinusitis, or ear infection in either adults or children. Such claims by Roche about complications were a key factor in decisions of governments around the world to stockpile the drugs for use in a future pandemic.[5]

As prophylaxis, oseltamivir did reduce the risk of symptomatic flu in people who had been treated (risk difference 3.05% (95% confidence interval 1.83% to 3.88%), but there was no significant effect on the risk of asymptomatic flu. From this second result the researchers concluded that there was no evidence to support the idea that the drug stopped people carrying the flu virus and spreading it to others.

When oseltamivir was used to prevent flu, there was a 1% increase in the risk of psychiatric events (risk difference 1.06% (0.07% to 2.76%), and it increased the risk of renal complications when patients were taking the drug (risk difference 0.67% (−0.01% to 2.93%)) and of headaches (risk difference 3.15% (0.88% to 5.78%)).

Use of oseltamivir increased the risk of nausea and vomiting in adults by around 4% and in children by 5%.

In a statement Daniel Thurley, UK medical director of Roche, said, "We disagree with the overall conclusions of this report. Roche stands behind the wealth of data for Tamiflu and the decisions of public health agencies worldwide, including the US and European Centres for Disease Control and Prevention and the World Health Organization.

"The report's methodology is often unclear and inappropriate, and their conclusions could potentially have serious public health implications. Neuraminidase inhibitors are a vital treatment option for patients with influenza."

Between 2006-07 and 2012-13 the Department of Health for England spent £560m on stockpiling antivirals for use in an influenza pandemic: £424m on oseltamivir and £136m on zanamivir. It is due to spend another £49m in 2013-14 to maintain a stockpile of neuraminidase inhibitors at 50% population coverage.

Carl Heneghan, a member of the Cochrane review team and professor of evidence based medicine at the University of Oxford, told a press conference on Monday 7 April that this money "has been thrown down the drain." The Cochrane reviewers and *The BMJ* have called on governments and health policy decision makers throughout the world to review their guidance on use of oseltamivir in light of the new findings.

In January the House of Commons Committee of Public Accounts recommended, "Once the Cochrane Collaboration has completed its review of Tamiflu using all clinical study report information, the Department, MHRA [Medicines and Healthcare Products Regulatory Agency] and NICE [National Institute for Health and Care Excellence] should consider

whether it is necessary to revisit previous judgements about the efficacy of Tamiflu.”[6]

A health department spokesman said, “The UK is recognised by the World Health Organization as being one of the best prepared countries in the world for a potential flu pandemic. Our stockpile of antivirals is a key part of this.”

However, as *The BMJ* went to press the department announced that it would publish its response to the Public Accounts Committee report imminently.

The department has already written off £74m worth of oseltamivir as a result of poor record keeping by the NHS on how the drug had been stored during the 2009 flu pandemic.[7]

Another Cochrane reviewer, Tom Jefferson, a clinical epidemiologist and former GP, emphasised the rigid and transparent methods of Cochrane reviews. “I cannot find a single line on the methods the regulators use either on the Food and Drug Administration [website] or on the European Medicines Agency website,” he said. “Should they not be public? Should we not know how the drugs that we use are assessed and evaluated?”

He called on the World Health Organization to review its guidance on use of neuraminidase inhibitors and the inclusion of oseltamivir in its list of essential medicines.[8 9]

The BMJ asked the World Health Organization and the European Medicines Agency for comment, but they had not responded by the time the journal went to press.

For all the latest articles from *The BMJ* on neuraminidase inhibitors see bmj.com/tamiflu.

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