CRD summary
This well-conducted review concluded that extended-duration zanamivir and oseltamivir chemoprophylaxis appeared highly effective in preventing symptomatic influenza among immunocompetent white and Japanese adults. Extended-duration oseltamivir was associated with increased nausea and vomiting. Although these conclusions accurately reflect the results of the review, their clinical significance is unclear.

Authors' objectives
To assess the efficacy and safety of extended-duration (more than four weeks) neuraminidase inhibitor chemoprophylaxis against influenza.

Searching
The following databases were searched from 1926 to June 2009 without language restrictions: MEDLINE, EMBASE, BIOSIS Previews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Cochrane Database of Systematic Reviews, NHS EED, HTA, ACP Journal Club and DARE. Search terms were reported. Trial registries of the US Food and Drug Administration, GlaxoSmithKline and Roche were also searched. References of identified studies were checked.

Study selection
Randomised controlled trials (RCTs) that assessed neuraminidase inhibitors (oseltamivir, zanamivir or peramivir), administered for at least four weeks, for the prophylaxis of naturally occurring influenza A virus infection were eligible for inclusion. Trials were required to report one of the following outcomes: laboratory-confirmed symptomatic influenza illness, laboratory-confirmed asymptomatic influenza virus infection, or adverse events.

Included trials assessed zanamivir or oseltamivir in predominantly white or Japanese populations. Most of the trials were carried out in healthy adults; mean ages ranged from 28.8 to 81.2. One trial assessed the intervention in elderly nursing home residents. Women were a majority in all except one trial population. Trial duration was four or six weeks. Oseltamivir was given orally at a dose of 75 or 150 mg/day. Zanamivir was given by inhalation at a dose of 10 mg/daily.

Two reviewers independently assessed the studies for inclusion in the review; differences were resolved through discussion.

Assessment of study quality
Two reviewers independently assessed the trials for validity, except in the case of one foreign language trial which was assessed by one reviewer; differences were resolved by discussion or consultation with a third reviewer. Trials were assessed using the Jadad scale which awards up to 5 points for the criteria of randomisation, blinding and treatment of withdrawals and dropouts. The following additional criteria were also used in the assessment: withdrawal frequencies; adherence to at least 80% of medication doses; and use of intention-to-treat analysis. Data on funding, conflicts of interest and recruitment and compensation methods were also extracted. Authors were contacted for additional data where necessary. It was planned that only trials with a Jadad score of at least 3 points would be included in the review.

Data extraction
Data were extracted to permit the construction of 2x2 tables for each outcome. Risk differences (RD) and relative risks (RR) with 95% confidence intervals (CI) were calculated.

Two reviewers independently performed the data extraction, except in the case of one foreign language trial which was extracted by one reviewer.
**Methods of synthesis**

Random-effects model analyses were used to calculate pooled RRs and RDs with 95% CIs. Statistical heterogeneity was assessed using the $I^2$ statistic. A priori subgroup analyses were conducted based on the following criteria: age, influenza risk status, vaccination status, inpatient or outpatient setting, neuraminidase inhibitor and dose used. Sensitivity analyses were used to investigate the impact of omitting each trial from the analyses. Publication bias was assessed using funnel-plot testing and Begg and Mazumdar's test.

**Results of the review**

Seven RCTs (n=7,021 patients) were included in the review. Six trials used an intention-to-treat analysis. The mean Jadad score was 4 points; no trials were excluded on this basis. Adherence to at least 80% of medication doses ranged from 87.1% to 98.1%. Withdrawal rates ranged from 1 to 10%. Three RCTs assessed zanamivir chemoprophylaxis and four assessed oseltamivir.

**Symptomatic influenza**: Extended-duration neuraminidase inhibitor treatment decreased the risk of symptomatic influenza (RR 0.26, 95% CI: 0.18 to 0.37; RD -3.9%, 95% CI: -5.8% to -1.9%; six RCTs, n=6,335 patients). There was no evidence of statistically significant heterogeneity ($I^2 = 0\%$), and there was no statistically significant difference between zanamivir and oseltamivir.

**Asymptomatic influenza virus infection**: There was no statistically significant difference between intervention and control groups in asymptomatic influenza virus infection (six RCTs) or in serious adverse events or all adverse events (both seven RCTs). Again there was no evidence of statistically significant heterogeneity and no difference between zanamivir and oseltamivir.

**Adverse events**: Four trials of oseltamivir reported nausea and vomiting; there was an increased risk of this compared to control groups in these studies (RR 1.48, 95% CI: 1.86 to 2.33; four RCTs, n=1,867). None of the trials was powered to detect rare adverse events. Apart from an increased incidence of nausea and vomiting in a trial of higher dose oseltamivir, there were no significant differences found in any of the subgroup analyses. None of the sensitivity analyses significantly affected the findings.

There was evidence of publication bias on both the funnel plot analysis and the Begg test, although analysis was limited by the small trial numbers.

**Authors’ conclusions**

Extended-duration zanamivir and oseltamivir chemoprophylaxis appeared highly effective in preventing symptomatic influenza among immunocompetent white and Japanese adults. Extended-duration oseltamivir was associated with increased nausea and vomiting. Safety and efficacy in several sub-populations which might receive extended duration influenza chemoprophylaxis were not known.

**CRD commentary**

The review question and inclusion criteria were clear. The search was comprehensive and included systematic attempts to identify unpublished studies and studies in any language. This reduced the chances of relevant studies being omitted and made language and publication bias less likely. However, an assessment of publication bias did indicate some evidence of this, despite being hampered by small trial numbers. Rigorous methodology was used at all stages of the review process. The validity assessment used a number of appropriate criteria, and was used to inform the synthesis. The decision to use meta-analyses was appropriate. A thorough evaluation and exploration of statistical heterogeneity was conducted. The authors’ conclusions accurately reflect the results of this well-conducted review and are likely to be reliable, although the clinical significance of the decrease in the rate of symptomatic influenza may be overstated.

**Implications of the review for practice and research**

**Practice**: The authors stated that zanamivir can be used in immunocompetent adults without obstructive lung disease when extended-duration chemoprophylaxis against seasonal influenza is needed. It can be stockpiled for distribution to these individuals as chemoprophylaxis against pandemic influenza.
Research: The authors stated that research in the safety of extended-duration chemoprophylaxis with zanamivir or oseltamivir in children, and the development of zanamivir formulations that can be delivered safely and effectively to young children, patients with obstructive lung diseases and the elderly, should be encouraged.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.