Prevention of influenza in the general population

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Abstract

Background: Although all jurisdictions in Canada offer annual influenza immunization to people at high risk of complications, only Ontario has provided universal annual immunization of healthy adults and children. Use of chemotherapy (amantidine, neuraminidase inhibitors) to prevent influenza varies among provinces. We sought to systematically review the evidence for the prevention of influenza infection in the general population.

Methods: The interventions reviewed were influenza vaccination and prophylactic use of neuraminidase inhibitors. The health outcomes of interest were rates of laboratory-confirmed influenza infection, clinical definitions of influenza-like illness and work absenteeism. MEDLINE and Cochrane databases were searched for relevant articles published between 1966 and March 2003. Only randomized controlled trials (RCTs) were selected. Evidence was appraised using the methodology of the Canadian Task Force on Preventive Health Care.

Results: Eighteen trials involving more than 33,000 healthy adults were identified that met the inclusion criteria; of these, 15 showed that influenza vaccination with either live-attenuated and inactivated vaccines was efficacious. Eleven trials were considered to be of “good” quality, and 7 were considered to be of “fair” quality. The relative risk reduction (RRR) associated with influenza immunization in adults ranged from 0% to 91%. Fifteen RCTs involving more than 45,000 healthy children aged 6 months to 19 years were identified, of which 9 were considered to contain “good” evidence and 6 “fair” evidence. Results from 12 of these trials showed protection against influenza. The RRR ranged from 0% to 93%. There were 6 RCTs of “good” quality showing that neuraminidase inhibitors are effective in preventing influenza infection. Side effects from both influenza vaccination and neuraminidase inhibitor administration were mild.

Interpretation: There are numerous RCTs of good quality in large populations that have consistently shown that influenza vaccination, using inactivated or live-attenuated vaccines, is moderately effective in preventing influenza in the general population (healthy adults and children over 6 months of age). There is good evidence that neuraminidase inhibitor prophylaxis in contacts given within 36 to 48 hours of symptom onset of the household index case is effective; appropriate use of this prevention method requires access to rapid diagnostic methods. Decisions about introduction of routine immunization programs must take into account the cost and cost-effectiveness of a universal program and the burden of illness associated with influenza in each jurisdiction.

Influenza virus causes yearly epidemics of respiratory illness of varying severity worldwide in people of all ages, and it may be the most important cause of medically attended acute respiratory illness.1 In Canada influenza and pneumonia are the leading cause of death from infection and the sixth cause of death overall.2 Rates of complications and death from influenza are high among adults over 65 years of age and people with cardiac or pulmonary disease or chronic medical conditions, and annual influenza immunization in this population is associated with lower frequency of hospital admissions because of respiratory disease, congestive heart failure and death from any cause.3,4 Previously healthy young children are increasingly recognized as having hospital admission rates comparable to those among elderly people during influenza epidemics5 and up to 12-fold greater than rates among older children.6 Because influenza occurs yearly and because re-infections occur throughout the lifespan and affect up to 20% of the population each year, considerable attention has been directed to the prevention of influenza in healthy people. Although annual immunization programs are routinely offered to high-risk groups, only the province of Ontario routinely offers influenza immunization to healthy adults and children.

We performed a systematic review of the literature to answer the following question: how effective are the influenza vaccine and prophylactic neuraminidase inhibitor antiviral agents for the prevention of influenza in healthy adults and children?

Methods

We searched MEDLINE for relevant articles published between 1966 and March 2003 using the following search strategy for influenza vaccination trials: (“influenza vaccine” [MeSH] and “clinical trial” [publication type]) and (“human” [MeSH] or “humans”).
minidae” (MeSH) or “human” (MeSH) and (“1996” [publication date]: “2003/03” [publication date]). The search strategy for trials on the effectiveness of neuraminidase inhibitor prophylaxis was as follows: (“neuraminidase/antagonists and inhibitors” [MeSH] and “clinical trial” [publication type]) and (“human” (MeSH) or “hominidae” (MeSH)) or “human” (MeSH) and (“1996” [publication date]: “2003/03” [publication date]) and (clinical trials or randomized clinical trials). The Cochrane Collaboration Library was also searched using the MeSH terms “influenza vaccine” and “neuraminidase” for these 2 searches respectively.

Our inclusion criteria for this review were (a) any randomized controlled trial (RCT) of influenza vaccines or neuraminidase inhibitors in humans and (b) an outcome measure of clinical efficacy against prevention of naturally occurring influenza in healthy people. A trial was considered randomized if the authors described the assignment of study drug or vaccine by random allocation or quasi-random allocation (e.g., alternation, case record number), and it was considered controlled if there was a concurrent comparison group. Clinical efficacy measurement had to be determined by either a clinical definition of influenza or laboratory diagnosis; studies that measured only vaccine immunogenicity were excluded. Studies were also excluded if they were not in English or French or if they were targeted at high-risk groups, since recommendations already exist for these groups.

The MEDLINE search for influenza vaccine trials yielded 533 studies and the Cochrane search identified 4 reviews (Fig. 1). All of the studies identified through the Cochrane search were also found through the MEDLINE search. Review of the 533 titles led to the exclusion of 3 of the Cochrane reviews (ineligible patient population) and of individual studies for the following reasons: high-risk populations (149 studies), language other than French or English (56) and interventions other than influenza vaccine (e.g., education, compliance, 

\[\text{Haemophilus influenzae} \text{ vaccination} \] (81). Review of the abstracts of the re-

Fig. 1: Methodological steps for systematic review of influenza vaccine trials and antiviral therapy trials.
mainly 247 titles led to the exclusion of 182 studies. The most common reason was that the study outcome was vaccine immunogenicity or that it was a review article. Review of the methods of the 65 remaining studies identified 33 that satisfied our inclusion criteria. The antiviral search identified 43 studies in MEDLINE and 2 reviews in the Cochrane database (Fig. 1). Review of these articles identified 6 that satisfied our inclusion criteria. Some of the eligible trials that were identified through the MEDLINE search were also found in 1 of the Cochrane reviews.

The methods of the Canadian Task Force on Preventive Health Care were used to critically appraise the evidence from the included studies (Appendix 1).7 Quality ratings of individual studies — good, fair and poor — were determined on the basis of a set of operational parameters specific to randomized controlled trials developed with the US Preventive Services Task Force.9

**Results**

**Immunization of healthy adults**

Eighteen trials involving more than 33 000 healthy adults were identified that met our criteria, and 15 of them demonstrated that influenza vaccination is efficacious (Table 1). Eleven trials with level I evidence were considered “good” quality. Seven trials with level I evidence were considered “fair” quality because of study characteristics that may have biased outcome ascertainment, including the presence16,25 or possibility of unblinding13,14,24 of treatment assignment, lack of reliable outcome measurement14,18,25 or high loss of participants to follow-up.19–21 Eight trials used laboratory-confirmed influenza as an outcome measure, 9 used a clinical definition of influenza-like illness, and 1 trial used both outcomes.

Reflecting the variable annual attack rate of influenza, the incidence of laboratory-confirmed influenza in the control groups varied from 1.3 to 20 per 100 control subjects. In trials demonstrating a statistically significant difference, the RRR associated with influenza immunization ranged from 0% to 91%. Both live-attenuated and inactivated vaccines were used with comparable efficacy; the results for these are combined where both were used within a trial.

The outcome measures used in these trials predominately captured acute influenza virus infection (e.g., laboratory-confirmed infection, influenza-like illness, febrile illness during peak influenza period, severe febrile illness, upper respiratory tract illness). Only 2 of 18 trials captured clinical outcomes related to influenza virus infections, such as hospital admissions and antibiotic use for respiratory infection.17,21 None of the trials evaluated secondary spread of influenza. Five studies used outcome measures related to work days lost that could potentially identify bacterial pneumonia as a complication of influenza virus infection.18–21,25,26 However, these studies did not use definitions for these outcomes that would allow the reader to accurately determine whether a bacterial pneumonia was present (e.g., chest radiograph, lower respiratory tract findings on examination). Event rates were higher in trials that used clinical definitions of influenza than in those that used laboratory confirmation. Event rates for laboratory-confirmed influenza ranged from 1.3 to 20 per 100 control subjects and from 0.3 to 5.3 per 100 vaccinees. In trials using a clinical outcome measure, event rates ranged from 1.6 to 26 per 100 control subjects and from 2 to 27.9 per 100 vaccinees.

Six trials used outcome measures that captured the economic burden associated with respiratory illnesses not confirmed by laboratory methods to be influenza: lost work days because of illness, visits to a health care provider and use of prescription antibiotics and over-the-counter medications. These trials showed no reduction17,24 to modest reductions18–21,24 in lost time because of respiratory illness. A cost–benefit analysis of one of these influenza vaccination trials25 involving healthy working adults that used days of work missed, days at work but at reduced effectiveness and days with a visit to a health care provider because of an influenza-like symptom showed that vaccination (live-attenuated intranasal vaccine) reduced costs associated with all of these outcomes.25 The mean break-even cost for the vaccine and its administration was US$43.07 using Monte Carlo analysis.

Adverse events were reported in all of but 5 trials.11,13,16,21,26 Among participants receiving injected vaccines, the most frequent side effects were local symptoms related to the injection site (e.g., pain, redness or induration). Statistically significant differences in these injection symptoms between vaccinees and placebo recipients were identified in several trials, with the highest incidence reported to be 64% among participants receiving inactivated injected vaccine, compared with 24% among placebo recipients.21 Various nonspecific complaints (e.g., tiredness, fever) were not more common among vaccine recipients than among control subjects. Recipients of live-attenuated vaccines were significantly more likely than placebo recipients to have a runny nose (44% v. 26.6%)20 and sore throat (15.6%–26.6% v. 6.6%–16.3%).16,22 Only 1 study related adverse events to subsequent medication use or lost work time; no difference between the vaccine and placebo groups was found.20

**Immunization of children**

Fifteen randomized controlled trials involving more than 45 000 healthy children aged 6 months to 19 years were identified (Table 2); 9 trials with level I evidence were considered to be “good.” Of the remaining 6 trials, 4 did not report blinded treatment assignment or outcome assessment10,11,13,18 and 4 did not have clear or uniform follow-up or application of outcome ascertainment.15,17,19,20 These 6 trials were therefore ranked as being of “fair” quality. Five trials used a clinical outcome mea-
| Study                  | Type of vaccine | Follow-up* | No. of subjects | Outcome                      | Rate per 100 vaccinees | Rate per 100 controls | RRR (95% CI), % | p value | NNT | Level of evidence† | Quality of evidence† |
|-----------------------|-----------------|------------|-----------------|------------------------------|------------------------|-----------------------|-----------------|---------|-----|-------------------|----------------------|
| Powers et al, 1995⁵    | TRI-IA v. placebo | 1         | 127             | LC influenza                 | 1.9                    | 20                    | 91 (55 to 98)   | 0.003   | 5.5 | 1                 | Good                 |
| Edwards et al, 1994¹⁰| BI-IA or TRI-IA or BI-LA (IN) v. placebo | 1–4       | 5 210 (809 were children) | LC influenza, yr 1          | 0.68                   | 3.2                   | 78 (58 to 89)   | < 0.001 | 52  | 1                 | Good                 |
|                        |                 |            |                 | LC influenza, yr 2          | 1.0                    | 2.7                   | 63 (36 to 79)   | 0.004   |     |                   |                      |
|                        |                 |            |                 | LC influenza, yr 3          | 0.49                   | 2.8                   | 83 (66 to 91)   | < 0.001 |     |                   |                      |
|                        |                 |            |                 | LC influenza, yr 4          | 0.59                   | 1.77                  | 66 (30 to 84)   | 0.03    |     |                   |                      |
| Kietel et al, 1988¹³  | TRI-IA v. placebo | 1–2       | 1 295           | LC influenza, yr 1          | 5.3                    | 9.3                   | 43 (~3 to 43)   | 0.06    | 25  | 1                 | Good                 |
|                        |                 |            |                 | LC influenza, yr 2          | 3.7                    | 7                     | 47 (~2 to 72)   | 0.05    |     |                   |                      |
| Monto et al, 1982¹⁵   | MONO-LA (IN) v. placebo | 1         | 284             | LC influenza                | 2.8                    | 10.7                  | 74 (24 to 91)   | 0.01    | 12.6| 1                 | Good                 |
| Hammond et al, 1978¹³ | TRI-IA v. diphtheria-tetanus | 1         | 225             | LC illness                  | 3.4                    | 12.8                  | 73 (21 to 91)   | 0.02    | 8.3 | 1                 | Fair                 |
| Rytel et al, 1977¹⁷   | BI-LA (IN) v. placebo | 1         | 143             | LC influenza or influenza-like illness | 3.6                    | 11.3                  | 68 (7 to 89)    | 0.04    | 25  | 1                 | Fair                 |
| Mair et al, 1974¹⁷    | MONO-influenza A(IA) v. MONO-influenza B(IA) | 1         | 507             | LC influenza                | 0.6                    | 1.3                   | 50 (~251 to 92)| 0.4     | 100 | 1                 | Good                 |
| Leibovitz et al, 1971¹¹| MONO v. control | 1         | 9 616           | LC influenza                | 0.3                    | 1.3                   | 77 (44 to 91)   | < 0.001 | 100 | 1                 | Fair                 |
| Bridges et al, 2000¹⁸ | TRI-IA v. placebo | 1–2       | 1 184           | LC influenza, yr 1          | 2.2                    | 4.4                   | 46 (~109 to 86) | 0.33    | NA  | 1                 | Good                 |
|                        |                 |            |                 | Hospital admissions        | 0.002                  | 0.000                 | NA             | 0.5     |     |                   |                      |
|                        |                 |            |                 | Antibiotic use             | 0.057                  | 0.070                 | 18             | 0.09    |     |                   |                      |
|                        |                 |            |                 | LC influenza, yr 2          | 1.4                    | 10.2                  | 86 (40 to 97)   | 0.01    | 11.4|                   |                      |
|                        |                 |            |                 | Hospital admissions        | 0.0                    | 0.0                   | NA             | NA      |     |                   |                      |
|                        |                 |            |                 | Antibiotic use             | 0.041                  | 0.055                 | 25             | 0.047   |     |                   |                      |
|                        |                 |            |                 | Influenza-like illness, yr 1| 27.9                   | 23.8                  | 42 (~43 to 4)   | NS      | NA  |                   |                      |
|                        |                 |            |                 | Influenza-like illness, yr 2| 14                    | 21                    | 34 (16 to 49)   | 0.001   | 14  |                   |                      |
| Tannock et al, 1984¹⁰ | TRI-IA v. placebo | 1         | 88              | Respiratory illness         | 1.6                    | 3.7                   | 42 (~782 to 96)| NA      | NA  | 1                 | Fair                 |
| Mixeu et al, 2002⁵     | TRI-IA v. placebo | 1         | 593             | Episodes of influenza-like illness | 203/299 people | 121/294 people   | 33             | < 0.001 |     |                   |                      |

**Table 1:** Efficacy of influenza vaccination in healthy adults, by outcome (laboratory-confirmed [LC] influenza and clinical influenza)
Table 1 continued

| Study                        | Type of vaccine   | Follow-up* | No. of subjects | Outcome                                      | Rate per 100 vaccinees | Rate per 100 controls | RRR (95% CI, %) | p value | NNT | Level of evidence‡ | Quality of evidence† |
|------------------------------|-------------------|------------|-----------------|----------------------------------------------|------------------------|----------------------|-------------------|----------|-----|-------------------|---------------------|
| Nichol et al, 1999\(^{11}\)  | TRI-LA (IN) v. placebo | 1          | 4 561           | Participants with at least 1 episode of severe influenza-like illness | 15                     | 9.8                  | 36 (19 to 59) | < 0.001  |     | Good              |                      |
|                              |                   |            |                 | Total work days lost because of influenza-like illness | 102 d                  | 75 d                 | < 0.05            |           |     |                   |                      |
|                              |                   |            |                 | Employees with work days lost because of influenza-like illness | 79 people              | 65 people            | NS                |           |     |                   |                      |
| Nichol et al, 1999\(^{11}\)  | TRI-IA v. placebo | 1          | 849             | Episodes of upper respiratory tract illness | 105\(^{\dagger}\)     | 140\(^{\dagger}\)   | NA               | 0.001   | 3   | Good              |                      |
|                              |                   |            |                 | Sick days because of upper respiratory tract illness | 70                     | 122                  | NA                | 0.001   | 2   |                   |                      |
|                              |                   |            |                 | Physician visits because of upper respiratory tract illness | 31                     | 55                   | NA                | 0.004   | 4   |                   |                      |
| Williams et al, 1973\(^{17}\)| MONO-IA, BI-IA v. placebo | 1          | 13 279          | Influenza-like illness | 6.5                    | 8                    | 20 (10 to 30)   | < 0.001  | 50 | Good              |                      |
| Waldman et al, 1972\(^{17}\)| MONO-IA (IN), BI-IA v. placebo | 1          | 846             | Influenza-like illness | 9                      | 20.4                 | 55 (31 to 72)   | < 0.001  | 8.7 | Good              |                      |
| Edmonson et al, 1970\(^{14}\)| BI-IA v. MONO-IA  | 1          | 1 983           | Work absence because of respiratory illness | 22                     | 26                   | 55 (31 to 72)   | 0.025   | 25 | Fair              |                      |
| Eddy et al, 1970\(^{10}\)   | MONO-IA v. placebo | 1          | 1 758           | Influenza-like illness | 2                      | 10                   | 80 (68 to 88)   | < 0.001  | 12.5 | Fair              |                      |
| Hobson et al, 1970\(^{13}\) | QUAD-IA v. MONO-IA | 1          | 1 601           | Respiratory illness causing work absence | 2.9                    | 1.6                  | –84 (–298 to 15) | NA      | NA | Good              |                      |

Note: RRR = relative risk reduction, CI = confidence interval, NNT = number needed to treat, TRI = trivalent, IA = inactivated, BI = bivalent, LA = live-attenuated, IN = intranasal, MONO = monovalent, QUAD = quadrivalent, NA = not applicable.

*Number of influenza seasons.

†See Appendix 1 for descriptions of the levels of evidence and quality ratings of trials.

‡Some of the rates exceed 100% of vaccinees, because many subjects had more than 1 URI or more than 1 day of absenteeism. Where possible, outcomes are reported by year in multiyear studies.

§Cochrane–Mantel–Haenszel.
Table 2: Efficacy of influenza vaccination in healthy children, by outcome (laboratory-confirmed [LC] influenza and clinical influenza)

| Study (age group studied) | Type of vaccine | Follow-up* | No. of subjects | Outcome | Rate per 100 vaccinees | Rate per 100 controls | RRR (95% CI), % | p value | NNT | Level of evidence† | Quality of evidence† |
|---------------------------|-----------------|------------|----------------|---------|------------------------|-----------------------|-----------------|---------|-----|-------------------|----------------------|
| Neuzil et al, 2001† (1–16 yr) | BI-IA, TRI-IA, TRI-IA, TRI-LA (IN) v. placebo or MONO-influenza B | 2–5 | 791 | LC illness | 0.88 | 5.75 | 85.9 (72 to 93) | < 0.001 | 20 | I | Good |
| Hurwitz et al, 2000† (24–60 mo) | TRI-IA v. hepatitis A | 1 | 145 | LC influenza | 28 | 51 | 45 (28 to 67) | NS | 4 | I | Fair |
| Belshe et al, 2000† (26–85 mo) | TRI-IA (IN) v. placebo | 1 | 135 | LC influenza | 1.63 | 14.5 | 87 (78 to 87) | < 0.001 | 24 | I | Good |
| Belshe et al, 1998† (15–71 mo) | TRI-IA (IN) v. placebo | 1 | 160 | LC influenza | 1.31 | 17.9 | 87 (88 to 96) | < 0.001 | 6 | I | Good |
| Gruber et al, 1996† (6–18 mo) | MONO-IA, BI-IA (IN) v. placebo | 1 | 182 | LC influenza | 6.45 | 24 | 65 (18 to 66) | 0.009 | 8 | I | Good |
| Clover et al, 1991† (3–18 yr) | LA (IN), TRI-IA v. placebo | 1 | 192 | LC illness | 19 | 43.9 | 56 (31 to 72) | < 0.001 | 40 | I | Good |
| Gruber et al, 1990† (3–19 yr) | BI-LA (IN), TRI-LA v. placebo | 1 | 189 | LC influenza | 18.5 | 48 | 61 (29 to 62) | < 0.001 | 3 | I | Good |
| Feldman et al, 1985† (1–7 yr) | LA (IN), BI-IA v. placebo | 1 | 111 | LC illness | 36 | 50 | –1 (–36 to 25) | 0.23 | 71 | I | Fair |
| Hoskins et al, 1973† (11–19 yr) | MONO-IA influenza A v. MONO-IA influenza B | 1–2 | 724 | LC influenza | 2.9 | 9.4 | 70 (41 to 70) | < 0.001 | 15 | I | Good |
| Wesselius-de Casparius et al, 1972† (<5 to >10 yr) | MONO-IA v. placebo | 1 | 374 | LC influenza | 9.8 | 16.2 | 43 (6 to 68) | 0.05 | 109 | I | Fair |
| Colombo et al, 2001† (1–6 yr) | TRI-IA v. no vaccine | 1 | 344 | Influenza-like illness; day-care absenteeism | 12.4 | 37.7 | 2.3 (49 to 79) | < 0.001 | 4 | I | Fair |
| Khan et al, 1996† (9–12 yr) | TRI-IA, TRI-LA v. placebo | 1 | 555 | School absence with doctor-diagnosed acute respiratory illness or influenza | 0 | 3 | 100 (NA) | < 0.05 | 333 | I | Fair |
| Rudenko et al, 1993† (7–14 yr) | TRI-IA, BI-IA (IN), BI-IA, TRI-IA v. placebo | 2 | 12 837 | Respiratory disease yr 1 | 16.77 | 17 | 2 (3 to 9) | < 0.001 | 333 | I | Good |
| | | | | Respiratory disease yr 2 | 22.9 | 33 | 20 (26 to 34) | < 0.001 | 10 | I | Good |
| Alexandrova et al, 1986† (3–16 yr) | BI-LA (IN) v. placebo | 1 | 30 000 | “Influenza” | 6 | 12 | 52 (48 to 56) | < 0.001 | 16 | I | Good |
| Maynard et al, 1968† (14–18 yr) | QUAD (IA) v. MONO (IA) | 1 | 488 | Influenza-like illness | 49 | 55 | 10 (9 to 25) | NS | 16 | I | Fair |

Note: See Table 1 for definitions of abbreviations. Where possible, outcomes are reported by year in multiyear studies.
*Number of influenza seasons.
†See Appendix 1 for descriptions of the levels of evidence and quality ratings of trials.
sure for influenza, and 10 used laboratory confirmation. Consistent differences in efficacy between the inactivated and live-attenuated vaccines were not observed, and therefore the treatment arms are combined for the purposes of this review.

Twelve trials involving children demonstrated protection against clinical influenza, whether laboratory-confirmed influenza or defined as influenza-like illness. In another 3 trials, benefit was not demonstrated.\textsuperscript{29,35,42} Influenza attack rates vary each influenza season, and this was reflected in disease incidence in the control groups of these studies, with laboratory-confirmed influenza in 5.75 to 51 per 100 control subjects and 0.88 to 36 per 100 vaccinees. Rates of influenza in studies using clinical outcome measures were 12 to 55 per 100 control subjects and 5.8 to 49 per 100 vaccinees. The highest efficacy rate (93%; 95% confidence interval 88%–96%) was reported among children 15 to 71 months old receiving 1 or 2 doses of a live-attenuated, trivalent, intranasal influenza virus vaccine. Immunization did not prevent non-influenza respiratory tract illness.

Adverse events were reported in 12 of the 15 trials involving children. Both inactivated and live-attenuated vaccines were well tolerated, and no severe adverse reactions attributable to vaccine were observed in the studies reviewed. Recipients of a live-attenuated vaccine were significantly more likely than placebo recipients to have a runny nose 2 days after administration (27% of children 26–85 months old v. 18% of control subjects),\textsuperscript{30} coryza and fever with live-attenuated vaccines occurred less frequently on reimmunization in subsequent seasons, with no difference observed between placebo and vaccine groups.\textsuperscript{30} Fever was more common among younger children than among older children regardless of vaccine type.\textsuperscript{28}

Neuraminidase inhibitor prophylaxis

The efficacy of the neuraminidase inhibitors oseltamivir and zanamavir for influenza prophylaxis during community outbreaks has been evaluated in 6 randomized controlled trials since 1999; all of these had level I evidence and were of “good” quality (Table 3). The RRR ranged from 32% to 84%, with influenza rates in the placebo groups ranging from 18% to 67% and in the prophylaxis groups from 3.6% to 38%. Oseltamivir was evaluated in people over 12 years of age. Zanamavir was evaluated in people over 5 years of age.

Adverse events were reported in all 6 trials. Gastrointestinal side effects were more common in recipients of oseltamivir in the 3 trials of that agent (9.3% v. 7.2% on placebo,\textsuperscript{45} and 13.1% [1 daily dose] and 14.6% [2 daily doses] on placebo,\textsuperscript{46} and 3.6% v. 0.1% on placebo,\textsuperscript{47} and 7.2% v. 0.1% on placebo). Zanamavir was associated with more common dry cough with both oral formulations, and more common headache with the oral formulation.

### Table 3: Efficacy of neuraminidase inhibitors compared with placebo for prophylaxis of laboratory-confirmed (LC) influenza

| Study                        | Neuraminidase inhibitor | Study population                                      | Incidence of LC influenza, % | RRR (95% CI), % | p value* | NNT | Level of evidence† | Quality of evidence† |
|------------------------------|-------------------------|-------------------------------------------------------|------------------------------|-----------------|----------|-----|--------------------|---------------------|
| Hayden et al, 1999\textsuperscript{43} | Oseltamivir (oral)      | 33 participants, aged 18–40 yr                           | 38                           | 67              | 43       | (12–71) | 0.11†  | 34                  | I                    | Good                |
| Hayden et al, 1999\textsuperscript{44} | Oseltamivir (oral)      | 1559 participants, aged 18–65 yr                         | 1.3                          | 4.8             | 74       | (53–88) | < 0.001 | 28                  | I                    | Good                |
| Welliver et al, 2001\textsuperscript{45} | Oseltamivir (oral)      | 377 households, participants aged > 12 yr                  | 3.6                          | 22.8            | 84       | (49–95) | < 0.001† | 5                   | I                    | Good                |
| Kaiser et al, 2000\textsuperscript{46}  | Zanamavir (inhaled or inhaled and intranasal) | 575 participants, aged 13–65 yr                           | 12.7                         | 18.7            | 32       | (7–32)  | NA                  | 16                  | I                    | Good                |
| Hayden et al, 2000\textsuperscript{47}  | Zanamavir (inhaled)     | 337 households, participants aged > 5 yr                   | 4                            | 19              | 78       | (52–78) | 0.001†  | 6                   | I                    | Good                |
| Monto et al, 2002\textsuperscript{48}   | Zanamavir (inhaled)     | 487 households, participants aged > 5 yr                   | 4.1                          | 19              | 78       | (58–78) | < 0.001† | 6                   | I                    | Good                |

*Statistical test for proportions.
†χ\textsuperscript{2} test.
‡Exact test.
known to decrease rates of hospital admission and death,3
age. Immunization programs for these target groups,
chronic medical conditions and in people over 65 years of
illness requiring hospital admission is most likely to occur
eral population each winter in nonpandemic years. Severe
sine efficacy.
exposure to vaccine or natural infection may increase vac-
mon gastrointestinal adverse event. Adverse events were
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Interpretation

This review indicates that effective influenza prevention
interventions are available for healthy adults and children. Protection with influenza vaccine varied from
moderate to high, with RRRs from 0% to 93%. We also
found that the neuraminidase inhibitors oseltamivir and
zanamivir were effective in people over 12 years and over
5 years of age respectively. These drugs have the advantage
of having fewer side effects than rimantadine and
amantadine and are effective against influenza A and B.49
In the studies included in this review, no serious adverse
events were reported as a result of either the influenza vaccine or antiviral therapy.

The apparent variation in efficacy of the influenza vac-
cine over time and between trials is likely due to a number of
factors, including vaccine immunogenicity and the de-
gree of match between the vaccine strain chosen before the
influenza season and the circulating virus strains. Influenza
A virus changes over time as it propagates in humans,
through an accumulation of point mutations and by genetic
reassortment between viral strains.50 The World Health
Organization recommends the composition of inactivated
vaccines each year based on the occurrence of strains caus-
ing outbreaks that are reported from 110 surveillance cen-
tres in 83 countries and the availability of strains for pro-
duction of vaccine. The “match” between predicted and
circulating strains was 88% in a 10-year period.51 Previous
exposure to vaccine or natural infection may increase vac-
ne efficacy.

Influenza viruses cause illness in up to 20% of the gen-
eral population each winter in nonpandemic years. Severe
illness requiring hospital admission is most likely to occur
in people with pre-existing lung or cardiac disease or
chronic medical conditions and in people over 65 years of
age. Immunization programs for these target groups,
known to decrease rates of hospital admission and death,3
are in place across Canada, although uptake is incom-
plete.52 Influenza also causes a significant health burden in
the general population in terms of hospital admissions,
outpatient visits, sick leave and antimicrobial use.53 In par-
icular, children under 2 years of age may have hospital ad-
mission rates of up to 112 per 100 000 population.54,55 In an
influenza pandemic, attack rates could exceed 30% of the
general population.55

Recommendations for influenza vaccination have be-
come more inclusive in recent years. The National Advi-
sory Committee on Immunization suggests that “any indi-
vidual who wishes to protect him/herself from influenza
should be encouraged to receive the vaccine.”56 The Amer-
ican Academy of Pediatrics57 and the Advisory Committee
on Immunization Practices of the US Centers for Disease
Control and Prevention58 recently revised its recommendations to include vaccination of children aged 6–23 months,
and contacts of infants aged 0–23 months. Whereas
Canada recommends immunization of people over 65
years of age, the US Centers for Disease Control and Pre-
vention recommends the inclusion of people over 50 years,
because of the increased incidence of high-risk conditions
in that age group.59 To date, Ontario is the only jurisdiction
in Canada to introduce a universal influenza immunization
program.59,60

The goal of our review was to determine the efficacy of
the influenza vaccine and neuraminidase inhibitors, not to
determine the efficacy of a universal immunization pro-
gram. With such a program, considerations that must be
weighed against the potential benefits (preventing illness
and death in high-risk groups, and decreasing economic
loss associated with absenteeism at work, visits to health
care providers and antibiotic use) include the economic
costs of vaccine and program delivery, vaccine procure-
ment for large populations, the need to immunize large
populations in a short period each year and public accept-
ability. There is some evidence that universal influenza
immunization of school children is associated with a re-
duction in excess winter deaths in the general population.61
Now in its fourth year, the universal influenza program in
Ontario may help to further clarify the efficacy of such a
program.

Although there is evidence to support the efficacy of
neuraminidase inhibitor prophylaxis, the treatment is ex-
pensive (at least $50 per day) and was used within 36–48
hours of diagnosis of the index case in the studies reviewed
here. Appropriate use during the winter respiratory illness
season, when many viruses may be circulating, would re-
quire access to rapid microbiologic diagnosis to evaluate
suspected exposures, or an active viral surveillance pro-
gram in the community to determine whether influenza is
epidemiologically the most likely cause of respiratory ill-
ness in the index case. Health Canada’s Fluwatch Program
(www.hc-sc.gc.ca/pphb-dgspsp/fluwatch/index.html) pro-
vides biweekly summaries of disease activity across
Canada, and local laboratories may also provide timely
information.

Limitations of our systematic review include the restric-
tion of reviewed publications to French or English and the
inability to provide an overall estimate of vaccine efficacy,
such as might be obtained through a meta-analysis. How-
ever, we concluded that the vaccines and outcome measures
of influenza were sufficiently different across trials to pre-
vent pooling of individual trial results.

Evaluation of new influenza vaccines is necessary. A live-
attenuated, nasally administered vaccine is now licensed for
use in the United States,62 and a nasally administered inacti-
vated product is being developed.63 Furthermore, determin-
ing the efficacy of universal vaccination and treatment pro-
grams will require ongoing scrutiny.
This article has been peer reviewed.

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Appendix 1: Canadian Task Force on Preventive Health Care levels of evidence used to rate research design and quality of individual studies*

| Research design rating | Quality (internal validity) rating† |
|------------------------|-----------------------------------|
| I                      | Evidence from at least 1 randomized controlled trial |
| II-1                   | Evidence from controlled trial(s) without randomization |
| II-2                   | Evidence from cohort or case-control analytic studies, preferably from more than 1 centre or research group |
| II-3                   | Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here |
| III                    | Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees |

*The task force’s methodology is described in Woolf et al. and is available from the task force’s Web site (www.ctfphc.org, click on History and Methods).
†General design-specific criteria by study type are outlined in Harris et al.*