

## Prevention and treatment of influenza A and B

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**I**nfluenza is a common and usually self-limiting acute respiratory infection. Onset is rapid, and the main symptoms are fever, myalgia, headache, general malaise, and cough. Acute illness lasts on average 3 days, but cough and malaise can persist for several weeks. Elderly people and patients with chronic pulmonary and cardiac disease are at greatest risk of complications, such as viral and bacterial pneumonia, otitis media, sinusitis, and exacerbations of chronic respiratory disease.<sup>1</sup> Two subtypes cause serious infection in humans, influenza A and B. Influenza A is more common and more severe.

### Prevention with vaccines

Inactivated parenteral influenza vaccines are updated annually to match newly evolved viral strains. Optimal timing for vaccination is mid-October to November. Adequate immune response takes about 2 weeks to develop; immunity wanes after a few months.

### Evidence of effectiveness

**Adults aged 60 and older:** In the only large randomized controlled trial (RCT),<sup>2</sup> 1838 elderly patients were given vaccine or placebo and followed during the winter of 1991-1992. Incidence of clinical influenza (as defined by responses to a questionnaire) was 9.8% with placebo and 6.7% with vaccine and, therefore, reduced by vaccine (absolute risk reduction [ARR] 3.1%, number needed to treat to prevent one event [NNT] 32). Incidence of clinical influenza as diagnosed by family physicians was 3.4% with placebo and 1.8% with vaccine (ARR 1.6%, NNT 63).<sup>2</sup>

A meta-analysis of 20 cohort studies found vaccination was associated with significant reductions in respiratory illness, pneumonia, hospitalizations, and mortality.<sup>3</sup> In these cohort studies, however, the populations of vaccinated and unvaccinated people differed at baseline. Therefore, they cannot be used to estimate the magnitude of benefit provided by vaccination.

**Adults aged 14 to 60:** A meta-analysis of RCTs found an ARR of 5% (NNT 20) for clinically defined influenza following vaccination.<sup>1</sup> Rates of complications of influenza were too low to observe any reductions due to vaccination.

**Repeated use:** A 1999 meta-analysis of cohort studies<sup>4</sup> found the vaccine had similar efficacy whether it was administered many times during the year or only once.

**Evidence of harm.** In the large RCT mentioned above, vaccination caused more local reactions than placebo did (17.5% vs 7.3%, absolute risk increase [ARI] 10.2%, number needed to cause one harmful event [NNH] 10), but no more systemic effects (11% vs 9.4%).<sup>5</sup> In one crossover RCT in asthma patients, more patients receiving vaccine (4.9%) than placebo (1.2%) experienced exacerbations of their asthma (ARI 3.7%, NNH 27).<sup>6</sup>

**Contraindications.** Allergy to eggs or other vaccine components.

**Dose and cost.** Adult dose is 0.5 mL by intramuscular injection. Patients should be observed for about 15 minutes. Cost is \$3.50 per dose. Approximate cost to prevent one case of clinical influenza based on results of the meta-analysis in healthy adults is \$70.<sup>1</sup>

### Prevention and treatment with drugs

**Amantadine.** Amantadine (eg, Symmetrel) is the only drug approved for both prevention and treatment in Canada. It is effective against influenza A, targeting a membrane protein essential to virus replication. Amantadine is used for prevention in exposed high-risk patients who were not vaccinated and during influenza A outbreaks in nursing homes and other residential facilities.

**Evidence of efficacy:** In a meta-analysis of 17 RCTs on prevention, amantadine decreased clinical cases of



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influenza as compared with placebo (ARR 5.2%, NNT 19).<sup>7</sup> An RCT of prevention regimens found 2 weeks of therapy as effective as 3 weeks.<sup>8</sup>

In nine RCTs of treatment, amantadine administered within 48 hours of onset of influenza shortened duration of fever compared with placebo by an average of  $1.0 \pm 0.1$  day. The effectiveness of amantadine in preventing hospitalizations and death is unknown.<sup>8</sup>

**Evidence of harm:** In prevention trials, withdrawals due to adverse effects were more frequent among treated patients than among those given placebo (ARI 3.5%, NNH 29).<sup>8</sup> The most common adverse effects were nausea, dizziness, confusion, dry mouth, constipation, and seizures.

**Dose and cost:** Adult dose is 100 mg twice daily or 100 mg once daily for those 65 years or older (reduce dose for renal dysfunction). For prevention, 2 weeks of therapy is recommended at a cost of \$8 to \$16. Cost to prevent one clinical influenza case is \$150 to \$300. For treatment, amantadine should be initiated within 48 hours of first symptoms and continued for 5 days. Cost for a 5-day course is \$6 to \$12.

**Sialidase inhibitors.** Two drugs were approved in Canada in 1999 for treatment of influenza A and B. Both selectively inhibit sialidase, a surface enzyme of the influenza virus. Oral oseltamivir (Tamiflu) is indicated for patients aged 18 and older and inhaled zanamivir (Relenza) for patients aged 12 and older. Treatment should begin within 36 hours of first symptoms. Both drugs are indicated for influenza A and B, but clinical evidence of efficacy for influenza B is limited.

**Evidence of efficacy:** Zanamivir and oseltamivir have not been compared with each other or with amantadine. In placebo-controlled trials, the primary outcome was defined as time to the first 24 hours with no or mild symptoms. This outcome measure does not necessarily reflect patients' full experience of influenza; 32% of participants had moderate-to-severe symptoms after this end point.<sup>9</sup> Only 50% to 60% of patients in clinical trials tested positive for the influenza virus, and that proportion would likely be lower in regular clinical care.

Because there is no practical way to detect influenza-positive patients before treatment, assessment of efficacy is based on all participants. In pooled data from two RCTs, zanamivir reduced the primary end point by a median of 0.9 days,<sup>10,11</sup> and oseltamivir reduced it by a

median of 0.8 days.<sup>12,13</sup> Symptom severity was not significantly different between those receiving zanamivir and those receiving placebo.<sup>10</sup> Symptom severity was not adequately reported, apart from duration, for oseltamivir.<sup>12,13</sup>


No significant difference was seen with use of acetaminophen, cough syrup, or antibiotics with either drug compared with placebo. Serious complications leading to hospitalization or death were rare and similar for treated and untreated participants. Minor complications were inadequately defined and were inconsistent across trials. Neither oseltamivir nor zanamivir have been specifically tested in high-risk groups, such as immunocompromised patients.

**Evidence of harm:** Zanamivir has been associated with bronchospasm in patients with and without existing lung disease. As a result of this, the manufacturer changed the drug's labeling and sent a warning letter to physicians in both Canada and the United States.

Oseltamivir's most common adverse effects are nausea and vomiting. Pooling the two trials showed that nausea was experienced by 14% in the oseltamivir groups and 5% in the placebo groups (ARI 9%, NNH 11), and vomiting was experienced by 11% in the oseltamivir groups and 3% in the placebo groups (ARI 8%, NNH 13).<sup>12,13</sup>

**Dose and cost:** Both drugs should be started within 36 hours of first onset of symptoms. Zanamivir is supplied as a powder for inhalation at a dose of 10 mg twice daily for 5 days. Cost for a 5-day course is \$38. Oseltamivir is in tablet form; dose is 75 mg twice daily for 5 days. Cost for a 5-day course is \$45.

## Conclusion

For prevention, cohort studies showed that vaccination lowered rates of hospitalization, serious morbidity, and death among patients older than 60. Amantadine is a second-line preventive agent. Antiviral treatment at onset of symptoms shows that amantadine reduces fever by 1 day and oseltamivir and zanamivir reduce duration of symptoms by 0.8 to 0.9 day. Trials are needed to determine whether any prevention or treatment of influenza reduces complications leading to hospitalization or death. 

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