Influenza 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 three days, but cough and malaise can persist for several weeks. The elderly and patients with chronic pulmonary and cardiac disease are at greatest risk for complications, including viral and bacterial pneumonia, otitis media, sinusitis and exacerbations of chronic respiratory disease. 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, and immunity wanes after a few months. **Evidence of effectiveness**

**Adults aged ≥ 60:** In the only large RCT, 1838 elderly patients were randomized to vaccine or placebo and followed over the winter of 1991-92. The incidence of clinical influenza was reduced by vaccine as defined by questionnaire, 9.8% placebo, 6.7% vaccine (ARR=3.1%, NNT=32) and as diagnosed by family physicians, 3.4% placebo, 1.8% vaccine (ARR=1.6% NNT=63). A meta-analysis of 20 cohort studies found vaccination associated with significant reductions in respiratory illness, pneumonia, hospitalizations, and mortality. However, in these cohort studies the population of vaccinated and non-vaccinated individuals differed at baseline; they, therefore, cannot be used to estimate the magnitude of the benefit provided by vaccination.

**Adults aged 14-60:** A meta-analysis of RCTs found an ARR of 5% (NNT=20) for clinically defined influenza following vaccination. Rates of influenza complications were too low to observe any reduction from vaccination.

**Repeated use:** A 1999 meta-analysis of cohort studies found similar vaccine efficacy when individuals with multiple annual vaccinations were compared with those with single vaccinations.

**Evidence of harm**

In the above large RCT in the elderly, vaccination caused more local reactions than placebo (17.5% vs 7.3%, ARI=10.2%, NNH=10), but no more systemic effects (11% vs 9.4%). In one cross-over RCT in asthma patients, more patients getting vaccine, 4.9%, than placebo, 1.2%, experienced asthma exacerbations (ARI=3.7%, NNH=27).

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

**Dose and cost**

0.5 ml IM injection for adults. Observe patient for about 15 minutes. $3.50 per dose. Approximate cost to prevent one case of clinical influenza based on the meta-analysis in healthy adults is $70.

### Prevention and treatment with drugs

**Amantadine**

Amantadine (Symmetrel®) is the only drug approved both for 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, or during influenza A outbreaks in nursing homes and other residential facilities.

**Evidence of efficacy**

**Prevention:** In a meta-analysis of 17 prevention RCTs, amantadine decreased clinical cases of influenza as compared to placebo (ARR=5.2%, NNT=19). An RCT of prevention regimens found 2 weeks of therapy to be as effective as 3 weeks.

**Treatment:** In 9 RCTs amantadine administered within 48 hours of onset shortened duration of fever compared to placebo by an average of 1.0±0.1 day. The effectiveness of amantadine in preventing hospitalisations and mortality is not known.

**Evidence of harm**

Withdrawals due to adverse effects were increased in prevention trials of amantadine as compared to placebo (ARI=3.5%, NNH=29).
The commonest adverse effects are nausea, dizziness, confusion, dry mouth, constipation and seizures.

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

Neuraminidase inhibitors
Two drugs were approved in Canada last year for treatments of influenza A and B. Both selectively inhibit neuraminidase, a surface enzyme of the influenza virus. Oral oseltamivir (Tamiflu®) is indicated for patients aged 18 and over and inhaled zanamivir (Relenza®) for patients aged 12 and over. Begin treatment within 36 hours of first symptoms. Both drugs are indicated for influenza A and B, but clinical evidence of efficacy for B is limited.

Evidence of efficacy
Zanamivir and oseltamivir have not been compared to each other or to amantadine. In placebo-controlled trials, the primary outcome was defined as the time to the first 24 hours with absent or mild symptoms. This outcome measure does not necessarily reflect a patient’s full experience of the flu; 32% of participants had moderate to severe symptom recurrence after this endpoint. Only 50–60% of patients in clinical trials were influenza positive and in regular clinical care that proportion will likely be lower. Since there is no practical way to detect influenza positive patients prior to treatment, the assessment of efficacy is based on all trial participants. In pooled data from 2 RCTs zanamivir reduced the primary outcome by a median of 0.9 days10,11 and oseltamivir by 0.8 days.12,13 Symptom severity was not significantly different between zanamivir and placebo.10 Symptom severity was not adequately reported apart from duration for oseltamivir.12,13 No significant difference was seen in use of acetaminophen, cough syrup or antibiotics with either drug versus placebo. Serious complications leading to hospitalization or mortality were rare and not different. Minor complications were not adequately defined and were not consistent 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 pre-existing lung disease. As a result of these reports the manufacturer has changed the drug’s labelling and sent a warning letter to physicians in both Canada and the US.

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Abbreviations
ARI=Absolute Risk Increase; NNH=Number Needed to cause one Harmful event

Conclusions
Prevention: Vaccination in cohort studies lowered rates of hospitalization, serious morbidity and mortality in patients over 60. Amantadine is a second-line preventive agent.

Treatment: Antiviral treatment at the onset of symptoms shows that amantadine reduces fever by one day and oseltamivir and zanamivir reduce duration of flu symptoms by 0.8 – 0.9 day.

RCTs are needed to determine whether any prevention or treatment of influenza reduces complications leading to hospitalization or mortality.

References