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CADTH
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Canadian Agency for Drugs and Technologies in Health

**Effectiveness of Neuraminidase Inhibitors
for Prevention of Influenza**

Ray Deonandan, PhD¹
Shaila Mensinkai, MLIS²
Amanda Hodgson, MLIS²

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¹ Provincial Centre of Excellence for Child & Youth Mental Health and University of Ottawa, Ottawa ON

² Canadian Agency for Drugs and Technologies in Health, Ottawa ON



Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure they were addressed appropriately.

Reviewers

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Reviewers who agreed to be acknowledged include:

Tom Jefferson, MD MSc MRCGP FFPHM
Editor, Cochrane Acute Respiratory Infections Group
Cochrane Collaboration

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ABBREVIATIONS

FDA	Food and Drug Administration
HCW	health care workers
ILA	influenza A
ILB	influenza B
ILI	influenza-like illness
LCI	laboratory-confirmed influenza
LTCF	long-term care facility
NI	neuraminidase inhibitors
NR	not reported
NS	not significant
O75	oseltamivir 75 mg
O150	oseltamivir 150 mg
PB	placebo
RCT	randomized controlled trial
RIM	rimantadine
SLCI	symptomatic laboratory-confirmed influenza
URI	upper respiratory infection
WHO	World Health Organization
ZAN	zanamivir

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1 CONTEXT AND POLICY ISSUES

In a given influenza season, affected individuals exhibit symptoms that are laboratory-confirmed influenza (LCI) or influenza-like illness (ILI). A subset of patients who have ILI are truly infected with the influenza virus, because the same symptoms may result from other seasonal pathogens. LCI and ILI are characterized by respiratory discomfort, fatigue, aches, headache, and fever. While yearly vaccine formulations are generally well tolerated for seasonal influenza, in a pandemic setting, it is unlikely that a vaccine would be available immediately. Thus, antiviral agents may be a viable option for preventing influenza.

This report investigates the evidence about the use of two neuraminidase inhibitors (NIs), zanamivir (Relenza™) and oseltamivir (Tamiflu™), for the prophylaxis of influenza. Oseltamivir is available as a tablet and powder for oral suspension, and zanamivir is administered through a diskhaler inhalation device.

2 POLICY QUESTIONS

This report investigates the evidence of benefit from oseltamivir and zanamivir for the prophylaxis of influenza, and the harm and tolerability of the drugs when used for prophylaxis. The evidence presented here will provide guidance to decision makers on questions related to the role of these and other drugs in influenza pandemic planning.

3 RESEARCH QUESTION

What is the evidence for effectiveness in terms of demonstrated harm (side effects and drug

resistance) and benefit from oseltamivir and zanamivir prophylaxis (post-exposure, outbreak, seasonal or prolonged) versus other medical care or no prophylaxis against influenza, including avian influenza, for people with or without underlying health conditions, long-term care residents, health care workers with or without close patient contact, household contacts, and public health responders?

4 METHOD

4.1 Search Strategy

We obtained published literature by searching Ovid's multi-file databases including MEDLINE®, EMBASE® and BIOSIS Previews® from 1990 to the present. There were no language restrictions. Search results were restricted to human studies. The search strategy included appropriate descriptors and keywords, with a filter to restrict results to controlled trials, observational studies, meta-analyses, and systematic reviews. We ran parallel searches on PubMed and The Cochrane Library.

We performed the search in July 2006 and established regular alerts on MEDLINE®, BIOSIS Previews®, and EMBASE® databases to capture new studies in August 2006. We obtained grey literature by searching the web sites of regulatory agencies, and health technology assessment and related agencies. Specialized databases from the University of York NHS Centre for Reviews and Dissemination and World Health Organization (WHO) were searched. The web sites of professional associations such as the International Society of Infectious Diseases, American Society for Microbiology, European Scientific Group on Influenza, International Conference on Options for Control of Influenza, and Infectious Diseases Society of America were searched for additional information and conference abstracts.

4.2 Eligibility Criteria

Patient groups investigated

- healthy people
- people with underlying health conditions

- long-term care residents
- health care workers with close patient contact
- health care workers without close patient contact
- household contacts
- public health responders.

Interventions investigated

Oseltamivir or zanamivir at any dose given as any of the following four types of prophylaxis:

- post-exposure prophylaxis (five to 14 days)
- outbreak control (10 to 14 days)
- seasonal prophylaxis (six to eight weeks)
- prolonged prophylaxis (>2 months).

Comparison groups investigated

- placebo
- active comparator.

Outcomes investigated to assess efficacy

- cases of symptomatic or asymptomatic LCI
- cases of ILI
- cases of pneumonia or other complications
- cases of LCI or ILI admitted to hospital
- deaths due to LCI or ILI
- all-cause mortality
- duration and concentration of nasal shedding of viruses, or evidence of transmission.

Outcomes investigated to assess safety

- reported adverse events (e.g., incidence of nausea)
- rates of drug discontinuation for adverse events or other reasons
- evidence of resistance and fitness or transmissibility of the resistant virus.

4.3 Study Design

All types of clinical studies were included in our search, regardless of design, as long as the studies described original data on the use of NIs as prophylaxis (as opposed to treatment only) against influenza in human subjects. All relevant identified systematic reviews were examined, and their cited studies screened. This report considered evidence from randomized controlled trials (RCTs) and observational studies for outbreak and prolonged prophylaxis. Only

evidence from RCTs was considered for post-exposure and seasonal prophylaxis. Although evidence from observational studies is considered to be less interpretable than that derived from RCTs, such studies were included at the originator's request to capture available evidence relating to the research question (i.e., effectiveness, not just efficacy) and because observational studies often report harm data. Thus, this report complements existing systematic reviews of randomized trials, most of which did not consider observational studies.

4.4 Quality Assessment

The reporting quality of RCTs was assessed using the criteria in a document by Jadad *et al.*¹ Jadad scores can range from zero to five, with higher scores associated with better quality. Low-quality trials (≤ 2) are associated with exaggerated estimates of treatment efficacy.² The ratings are based on the reporting of randomization, double-blinding, and withdrawals and drop-outs. Allocation concealment reported in RCTs was not assessed. Non-RCTs were not assessed for quality.

5 SUMMARY OF FINDINGS

Seventeen studies met the eligibility criteria and were included in this report.³⁻¹⁹ Information about the individual trials can be found in Tables 1 to 8. Most of the evidence involved seasonal influenza. One study⁴ involved the use of NIs in avian influenza prophylaxis (Table 8).

5.1 Seasonal Influenza

Healthy People (Table 1): One RCT evaluated post-exposure prophylaxis with zanamivir.³ It was deemed to be of low quality according to the Jadad criteria (score=2). No significant differences were found in the rates of LCI and adverse events (AEs) between those who received zanamivir and those who received placebo.

Two RCTs of varying quality evaluated oseltamivir for seasonal prophylaxis in adult patients.^{5,6} An RCT of zanamavir²⁰ was

identified, but was judged inadmissible as a result of the requisite minimum treatment duration of six weeks, which had been established a priori for this review.

Both studies were of six weeks' duration. The first trial⁵ is of high quality (score=4), while the other trial⁶ scored poorly according to the Jadad criteria because only its abstract was available, so pertinent information could not be extracted. Both studies compared oseltamivir with placebo over six weeks, and both found that the NIs significantly reduced LCI rates. In both trials, the rates of AEs were similar between the oseltamivir and placebo groups. Only the trial by Hayden *et al.*⁵ examined ILI. It found a statistically significant lower rate of culture-proven ILI among the groups who received oseltamivir prophylaxis compared with those who received placebo. No evidence was available for the outbreak control and prolonged prophylaxis scenarios in this population.

People with Underlying Health

Conditions (Table 2): Only evidence for seasonal prophylaxis was available. The sole RCT⁷ evaluated high-risk adults (n=3,363) in the community (the old and chronically ill) and found a significant protective effect with zanamivir. The prevalence of symptomatic LCI during prophylaxis was significantly lower among the zanamivir group, relative to placebo. The rates of AEs and rates of withdrawals due to AEs were similar in the zanamivir and placebo groups, but no statistical tests were performed to determine if there were any significant differences. There was no evidence available for the post-exposure, outbreak control, or prolonged prophylaxis scenarios.

Long-term Care Residents (Table 3): For the post-exposure prophylaxis and the prolonged prophylaxis of long-term care facility (LTCF) residents, no evidence fulfilled the eligibility criteria that had been established a priori.

Eight studies evaluated NIs for outbreak prophylaxis, including, three RCTs^{8,9,14} of varying quality and five case series reports.^{10-13,17} The RCT of the highest quality⁸ (Jadad score=4), failed to find a protective effect provided by

zanamivir for nursing-home residents. There were no significant differences in AEs between the zanamivir and the placebo groups. The vaccination rate in this trial was low (9%). The RCT of the lowest quality⁹ (Jadad score=2) compared zanamivir with rimantadine and concluded that zanamivir is safe and well tolerated in this population of rural nursing home residents. Because of the small sample size, the absence of LCI among those treated with zanamivir, and the presence of only one case of LCI among the group treated with rimantadine, no statistical analysis was performed. Thus, the results are inconclusive with regards to comparative benefit. The third trial¹⁴ (Jadad score=3) evaluated 482 residents (in nine nursing homes), >90% of whom were vaccinated. The trial found that, compared with rimantadine, zanamivir significantly reduced symptomatic LCI at days one to 15, but not at days one to 28. Among the patients included in this trial, >90% were vaccinated.

Three case series reports examined oseltamivir^{10,11,13} while the other two examined zanamivir.^{12,17} All suggested that the NIs could be useful for outbreak control in LTCF. The conclusions of these five studies should be viewed with the limitations of a case series design in mind (even when historical controls are used for comparison).

For seasonal prophylaxis, one RCT of high quality¹⁵ (Jadad score=4) that compared oseltamivir with placebo found no significant difference in the incidence of LCI for the study population, but a significant reduction in LCI was noted among vaccinated seniors. This study noted a statistically significant lower incidence of laboratory-confirmed clinical influenza (i.e., symptomatic LCI) among those who received oseltamivir prophylaxis. The same was true for flu-related complications.

Health Care Workers with Close Patient Contact (Table 4): No evidence was found for this population in any type of prophylaxis.

Health Care Workers without Close Patient Contact (Table 5): No evidence was found for this population in any type of prophylaxis.

Household Contacts (Table 6): By definition, studies of the household contact population involve the post-exposure prophylaxis scenario. Three RCTs^{16,18,19} met the eligibility criteria and were included in this review. Two high-quality RCTs (Jadad score=4) showed that zanamivir significantly reduced LCI compared with placebo.^{16,19} There were no significant differences in the incidence of AEs. One RCT¹⁸ showed that oseltamivir had significant protective effects compared to placebo, with statistically significant reductions in LCI among groups receiving active treatment. There were no significant differences in AEs or withdrawals due to AEs in these two trials.

Public Health Responders (Table 7): No evidence was found for this population in any of the pre-determined scenarios of interest.

5.2 Avian Flu

Healthy People (Table 8): One case series report⁴ evaluated oseltamivir as a prophylaxis for poultry workers and their families during an outbreak of the H7N7 strain of avian influenza in the Netherlands. H7N7 infection was found in five of 52 (9.6%) untreated subjects compared with one of 38 (2.4%) who took the drug,⁴ resulting in a protective efficacy of 75%, which was not statistically significant. AEs were not reported. This study was not a controlled trial, but a description of incidental data collected during an emergency outbreak containment scenario. H7N7 is not as virulent, as deadly, or as preponderant as H5N1.

6 DISCUSSION

Existing systematic reviews have addressed, at least partly, the issue of oseltamivir's and zanamivir's efficacy in influenza prevention. Relevant studies cited in those reviews have been included in this report, so those reviews do not represent additional evidence. The most relevant and up-to-date of those reviews²¹ included RCTs and analyzed the efficacy of NIs for treatment and prophylaxis of influenza, whereas this report includes all relevant study

types associated with prophylaxis alone, with attention to specific patient populations.

All the included RCTs examined LCI, thus ensuring that their findings reflect the drugs' effect on influenza and not on infections with similar symptoms. It could be argued, however, that ILI is the clinically important outcome of seasonal influenza A (ILA) and influenza B (ILB), and that functional definitions of an influenza epidemic have more to do with symptomatic characteristics than with which virus is responsible. Most studies examined LCI and ILI, providing a more complete picture of these drugs' real-world effectiveness.

Many of the included RCTs found that NIs significantly reduced LCI.^{5-7,14-16,18,19} This is reinforced by case series reports that demonstrated low LCI with zanamivir prophylaxis^{12,17} and few or no cases of LCI with oseltamivir prophylaxis.^{10,11,13} These findings are in line with those from another review²² that looked only at good quality RCTs.

Both trials that examined ILI found non-significant results.^{5,7} The authors of a high-quality systematic review²¹ on the efficacy of NIs concluded that this class of drug is "ineffective" against ILI, and that NIs should not be used routinely for seasonal influenza, but only with "associated public health measures in a pandemic situation."²¹

Oseltamivir and zanamivir were generally well tolerated. Gastrointestinal symptoms, such as nausea, abdominal pain, and diarrhea, were the most commonly reported AEs for both drugs. None of the included studies reported decreased mortality or morbidity rates due to influenza. No significant differences in AEs or withdrawals due to AEs were reported in any of the RCTs. Among the case series reports, zanamivir¹⁷ and oseltamivir^{10,13} resulted in patients withdrawing from the study because of discomfort that may have been related to the drug.

Five RCTs reported evidence on the resistance to NIs.^{5,8,14,16,19} Four RCTs involved zanamivir,^{8,14,16,19} while one involved oseltamivir.⁵ All five RCTs found no evidence

of resistance to NIs. There was no evidence of sequence changes due to NIs reported in three trials.^{14,16,19}

The elderly and LTCF residents are the most commonly examined patient populations, when NIs are used as an influenza prophylaxis. Three other patient types [children, health care workers (HCWs), and pregnant women] were identified before this review as being of interest, because of their vulnerability to influenza or in the case of HCWs, their close contact with vulnerable individuals.

No RCTs focused solely on children, though several looked at families that included children. These showed significant benefit for both drugs with a significantly reduced incidence of LCI among NI-treated household contacts of an ILI or LCI index case. Influenza in a neonate or a young child (i.e., ≤ 1 year old) is associated with morbidity.²³ All the studies that included children excluded the very young, so no conclusions can be made about the NIs' efficacy and tolerability in this group. The product monographs advise against prescribing these drugs to children < 1 year (oseltamivir)²⁴ and < 7 years (zanamivir).²⁵

The Food and Drug Administration (FDA) and Roche, the manufacturer of oseltamivir (Tamiflu), have notified health care professionals of neuropsychiatric events resulting from the use of this drug.²⁶ There are post-marketing reports (mostly from Japan) of self-injury and delirium after the use of Tamiflu in patients with influenza. The FDA notes that people with the flu, particularly children, may be at an increased risk of self-injury and confusion shortly after taking Tamiflu, and they should be monitored for signs of unusual behaviour.

There was a lack of evidence about the usefulness of these antiviral agents in protecting HCWs. Schilling⁹ included HCWs in their study of zanamivir's efficacy in outbreak control, but the HCW data were not reported separately from those of patients and volunteers. There is no reason to expect uncompromised health care workers to respond differently from otherwise healthy individuals.

Data from the influenza pandemics of 1918 and 1957 illustrate the potential harm from influenza for pregnant women and fetuses.²³ None of the studies examined included pregnant women in their study populations. Both product monographs indicated that these drugs should only be used if the potential benefits outweigh the possible risk to the fetus.^{24,25}

Because ILB is less common than ILA, it is not surprising that all the included studies focused on ILA in isolation or on a mixed outbreak of ILA and ILB. While this is representative of the types of outbreaks experienced in Canada, the lack of a study that focused on the efficacy of NIs in preventing ILB restricts any comment on the usefulness of the drugs as full-spectrum influenza prophylaxes.

There was a lack of evidence on the use of NIs to prevent the acquisition or spread of H5N1 influenza. This review identified one case series report evaluating the effectiveness of oseltamivir for post-exposure prophylaxis against H7N7. This is not surprising because neither strain exists with a high enough frequency in human populations. Also, it would be unethical to intentionally expose human subjects to the virus in a laboratory environment, given the associated high mortality rate. Our literature search was restricted to clinical studies involving humans and excluded animal or tissue studies.

Lye²⁷ reports that oseltamivir may have been used as a prophylaxis (at 75 mg twice daily) in several hospitals in Asia where cases of H5N1 infection were feared. No data from these experiences have been published. Despite this absence of evidence, WHO recommends²⁸ that oseltamivir be used for post-exposure prophylaxis, at a dosage of 75 mg per day for seven days.

While the NIs are the newest antivirals to be used for the prevention and treatment of influenza, other antiviral drugs are available. Amantadine is approved in Canada for the prevention of ILA virus respiratory infections.²⁹ It has been available in Canada for > 30 years in the less expensive, generic form. Also in the

same class as amantadine is rimantadine, which is unavailable in Canada. These drugs should also be considered from a policy making standpoint, but were not examined in this review.

Economic issues were beyond the scope of this study. Given the choice of drugs, types of prophylaxes, and ranges of efficacy, any approach to planning must be based on the potential economic impact of available options.

The definition of prolonged use prophylaxis (i.e., >2 months) that was established a priori may have been, in retrospect, too restrictive. Studies self-described as exploring a prolonged or long-term prophylaxis, such as Peters *et al.*,¹⁵ considered six weeks of antiviral use to be long-term. No studies explored extended use beyond this timeframe for any of the patient groups of interest.

A summary estimate of drug effectiveness, which could be obtained through a meta-analysis, was beyond this project's scope. Issues of between-study heterogeneity may have precluded the pooling of results even if resources were available. Only an abstract was available for one RCT.⁶ Because of time constraints, this review was conducted by one researcher. Although eligibility criteria and data extraction forms were created a priori, the use of one reviewer could limit the objectivity and comprehensiveness of the systematic review.

The effectiveness of prophylaxis at the population level will depend on the prevalence of influenza. The efficient use of these drugs requires accurate epidemic forecasts to determine the optimal timing for maximum benefit from short-term use, or the use of these agents for extended periods beyond those observed in the examined studies.³⁰ The appropriate use of NIs is confounded by uncertainty about the level of circulation of influenza viruses. Given that there are uncertainties about these drugs' ability to treat ILI²¹ and a lack of unequivocal evidence showing their effectiveness in the prevention of ILI, correct diagnosis and identification of the viral strain are important to consider when formulating policy about large-scale use of Canada's antiviral stockpiles.

7 CONCLUSIONS

There is enough evidence to conclude that the antiviral drugs zanamivir and oseltamivir are effective in preventing the acquisition of common LCI, and are well tolerated by healthy humans and those whose health is compromised (the elderly and those living in LTCF). There is no evidence about prophylaxis among very young children, pregnant women, or HCWs, though there is no reason to expect that HCWs would respond differently from other healthy people. There is no strong evidence that these drugs provide protection against ILIs. These agents are most effective in providing seasonal prevention, though there is a dearth of evidence on the safety of prophylactic use after a few weeks. The evidence in this report reflects data from seasonal influenza and isolated outbreak situations; it may be impossible to generalize to a pandemic scenario. There is no evidence on the use of these drugs for public health responders and HCWs, and no evidence about the drugs' performance in post-exposure prophylaxis for people with underlying health conditions.

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APPENDIX 1: Evidence Tables

Table 1: Evidence for effectiveness of zanamivir and oseltamivir in prophylaxis of influenza in healthy people

Study	Study Design and Quality	Participants	Intervention	Outcome Measures	Results	AEs	Comments
Post-Exposure Prophylaxis							
Kaiser ³	double-blinded RCT, Jadad score=2	N=575, healthy, aged 13 to 77 years old, after close contact with ILI subjects	ZAN intranasal (n=141) 16 mg/mL; ZAN inhaled (n=144) 5 mg; ZAN intranasal+inhaled (n=146); PB (n=144); all groups self-administered for 5 days	LCI	LCI (symptomatic or asymptomatic) during 21 days after initiation: PB 27 (19%), ZAN intranasal 28 (20%), ZAN inhaled 16 (11%), ZAN intranasal+inhaled 21 (14%); SLCI during 10 days after initiation: placebo 11 (8%), ZAN intranasal 9 (6%), ZAN inhaled 4 (3%), ZAN intranasal +inhaled 6 (4%); SLCI during 5 days of prophylaxis: PB 9 (6%), ZAN intranasal 8 (6%), ZAN inhaled 3 (2%), ZAN intranasal+inhaled 5 (3%); intranasal (p=0.855 versus PB); inhaled (p=0.058 versus PB); intranasal+inhaled 3.4% (p=0.247 versus PB)	possibly drug-related AEs: PB 25 (17%), ZAN intranasal 23 (16%), ZAN inhaled 27 (19%), ZAN intranasal+inhaled 20 (14%); primarily headaches, nasal signs, fatigue, throat discomfort; AEs did not differ across groups	virus types ILA and ILB; ILA subtype H3N2 predominant circulating strain; November 1995 to March 1996 flu season; LCI defined as 4-fold increase in antibody level or documentation of influenza by culture or direct antigen detection
Outbreak Control							
no evidence							
Seasonal Prophylaxis							
Hayden <i>et al.</i> ⁵	double-blinded RCT, Jadad score=4	N=1,559, healthy non-immunized adults (18 to 65 years old), 8 to 12 weeks before anticipated start of flu season	O75=75 mg orally, once daily (n=520); O150=75 mg twice daily (n=520); PB (n=519); duration of 6 weeks	LCI during 6-week period; culture-proved ILI; LCI with fever; LCI symptomatic or asymptomatic; ILI without laboratory evidence; resistance	LCI during 6-week period: O75 6 (1.2%); O150 7 (1.3%); PB 25 (4.8%); p<0.001 for both groups versus PB; culture-proved ILI O75 0; O150 4 (0.8%); PB 15 (2.9%); p<0.01 for both groups versus PB; LCI with fever: O75 2 (0.4%); O150 5 (1%); PB 19 (3.7%); p<0.005	withdrawals due to AEs or intercurrent illness, O75 8 (1.5%); O150 7 (1.3%); PB 10 (1.9%); withdrawals due to transient increases in aminotransferase values, 1 patient in O group, 1 patient in PB group; most common AE is	large sample size (n=1,559) and rigorous make this a significant study; virus types ILA and ILB; winter 1997 to 1998 in Virginia, Texas, and Kansas; no evidence of new drug resistance as assessed by neuraminidase

					for both groups versus PB; LCI (symptomatic or asymptomatic): O75 28 (5.4%); O150 27 (5.2%); PB 55 (10.6%); p<0.005 for both groups versus PB; ILI without laboratory evidence: O75 5 (1%); O150 5 (1.2%); PB 7 (1.3%); p=NS	headache, equally distributed across 3 groups; upper GI disturbances (nausea): O75 12.1%; O150 14.6%; PB 7.1%; vomiting, O75 2.5%; O150 2.7%; PB 0.8%; discontinuation due to GI AEs, O75 3; O150 3; PB 0	susceptibility in 2 viral isolates available for study from these episodes
Kashiwagi ⁶	RCT Jadad score=1	N=308 Japanese adults ≥16 years old	O75 mg (n=155); PB (n=153); for 6 weeks	LCI, AEs	LCI, O75 2 (1.3%); PB 13 (8.5%); p=0.003	treatment-related AEs, O75 21.9%; PB 26.1%; diarrhea, O75 4.5%; PB 8.5%; abdominal pain, O75 5.3%; PB 7.2%; nausea, O75 3.9%; PB 2.6%; vomiting, O75 1.3%; PB 1.3%	only abstract available in English; 1998 to 1999 and 1999 to 2000 flu seasons
Prolonged Prophylaxis							
no evidence							

AE=adverse event; ILA=influenza A; ILB=influenza B; ILI=influenza like illness; LCI=laboratory-confirmed influenza; NR=not reported; NS=not significant; O75=oseltamivir (75 mg); O150=oseltamivir (150 mg); PB=placebo; RCT=randomized controlled trial; RIM=rimantadine; SLCI=symptomatic laboratory-confirmed influenza; URI=upper respiratory infection; ZAN=zanamivir.

Table 2: People with underlying health conditions

Study	Study Design and Quality	Participants	Intervention	Outcome Measures	Results	AEs	Comments
Post-Exposure Prophylaxis							
no evidence							
Outbreak Control							
no evidence							
Campbell ⁷	double-blinded RCT Jadad score=4	N=3,363 community-dwelling, high risk adults (≥12 years old), e.g., elderly (≥65 years) and chronic pulmonary, or cardiovascular disease, or diabetes; trial began within 5 days of outbreak being declared in area; vaccinated 67% of ZAN group, 68% of PB group	inhaled ZAN (n=1,678) 10 mg; PB (n=1,685); self-administered daily for 28 days	LCI (ILA or ILB) symptomatic, during prophylaxis; LCI symptomatic days 2 to 28; LCI symptomatic days 3 to 28; LCI symptomatic or asymptomatic; ILI ; febrile illness and LCI; any febrile illness; LCI with complication; LCI with complication requiring antibiotics; ILI with complication; ILI with complication requiring antibiotics; ILI with use of relief medication	LCI (ILA or ILB) symptomatic, during prophylaxis, ZAN 4 (<1%); PB 23 (1%); p<0.001; LCI symptomatic days 2 to 28, ZAN 4 (<1%); PB 21 (1%); p<0.05; LCI symptomatic days 3 to 28, ZAN 4 (<1%); PB 20 (1%); p<0.05; LCI symptomatic or asymptomatic, ZAN 39 (2%); PB 52 (3%); p=NS; ILI, ZAN 151 (9%); PB 169 (10%); p=NS; febrile illness and LCI, ZAN 6 (<1%); PB 16 (<1%); p<0.05; any febrile illness, ZAN 81 (5%); PB 109 (6%); p<0.05; LCI with complication, ZAN 1 (<1%); PB 8 (<1%); p<0.05; LCI with complication requiring antibiotics, ZAN 1 (<1%); PB 6 (<1%); p=NS; ILI with complication, ZAN 26 (2%); PB 36 (2%); p=NS; ILI with complication requiring antibiotics, ZAN 23 (1%); PB 28 (1%); p=NS; ILI with use of relief medication, ZAN 87 of 151 (58%); PB 102 of 169 (60%); p=NR	patients with AEs, ZAN 850 (51%); PB 851 (51%); withdrawals due to AEs, ZAN 32 (2%); PB 36 (2%); headache, ZAN 284 (17%); PB 296 (18%); cough, ZAN 243 (14%); PB 248 (15%); throat and tonsil discomfort and pain, ZAN 225 (13%); PB 236 (14%); temperature regulation disturbances, ZAN 122 (7%); PB 111 (7%); muscle pain, ZAN 114 (7%); PB 108 (6%); viral and respiratory infections, ZAN 77 (5%); PB 80 (5%); nasal signs and symptoms, ZAN 3 (4%); PB 63 (4%); musculoskeletal pain, ZAN 62 (4%); PB 47 (3%); ear, nose, and throat infections, ZAN 20 (2%); PB 39 (2%); diarrhea, ZAN 39 (2%); PB 39 (2%); nausea and vomiting, ZAN 33 (2%); PB 40 (2%); patients with non-fatal SAEs, ZAN 16 (1%); PB 16 (1%)	virus type ILA and ILB; safety analysis included events occurring up to 1 day after end of treatment
Prolonged Prophylaxis							
no evidence							

AE=adverse event; ILA=influenza A; ILB=influenza B; ILI=influenza like illness; LCI=laboratory-confirmed influenza; NR=not reported; NS=not significant; O75=oseltamivir (75 mg); O150=oseltamivir (150 mg); PB=placebo; RCT=randomized controlled trial; RIM=rimantadine; SLCI=symptomatic laboratory-confirmed influenza; URI=upper respiratory infection; ZAN=zanamivir.

Table 3: Long-term care residents

Study	Study Design and Quality	Participants	Intervention	Outcome Measures	Results	AEs	Comments
Post-Exposure Prophylaxis							
no evidence							
Outbreak Control							
Hirji <i>et al.</i> ¹⁷	case series (non-randomized trial using historic controls)	51 chronic care adult patients (mean age of 70.6 years); with unstable chronic illness or multi-system disease, dependent on technology-based continuing or intermittent care (3 to 12 hours daily); 63% (n=32) had flu vaccines; 82% (n=42) had received amantadine 10 days before study began	oral inhalations of ZAN 10 mg, once daily for 14 days for prophylaxis; index patients treated with 10 mg ZAN twice daily for 5 days for treatment	ILI	92.7% efficacy, based on observed attack rate of 2.3% (compared with historic attack rate of 43%); 93% completed course of ZAN	drug discontinuation due to AE: 1 patient (sore throat)	virus types ILA and ILB; February to March, 1999 flu season; index cases from 547-bed facility providing complex continuing care and rehabilitation through inpatient and day treatment; 48 (94%) patients had ≥ 2 comorbid illnesses
Ambrozaitis <i>et al.</i> ⁸	double-blinded RCT Jadad score=4	N=494 adult residents; 12 nursing homes in Lithuania, the Netherlands, and Israel; 9% had received flu vaccine	inhaled ZAN 10 mg (n=242); PB (n=252); commencing immediately after outbreak declaration in facility and lasting 14 days	SLCI as result of twice weekly naso-pharyngeal swabs; febrile illness; symptomatic culture-confirmed influenza; SLCI with complications; AEs; resistance	SLCI, ZAN 15 (6%); PB 23 (9%); p=0.355; LCI with febrile illness, ZAN 4 (2%); PB 14 (6%); p=0.043; symptomatic culture-confirmed influenza, ZAN 5 (2%); PB 15 (6%); p=0.052; SLCI with complications, ZAN 12 (5%); PB 16 (6%); p=0.653	AE, ZAN 78 (32.2%); PB 92 (36.5%); p=0.365; no SAEs related to drug; high-risk respiratory event, ZAN 30 (12.4%); PB 32 (12.7%); p=0.972; drug-related AE, ZAN 16 (6.6%); PB 14 (5.6%); p=0.762; SAE, ZAN 6 (2.5%); PB 6 (2.4%); p=0.824; deaths, ZAN 1 (0.4%); PB 2 (0.8%); p=0.971; drug discontinuation due to AEs, ZAN 6 (2.5%); PB 2 (0.8%); p=0.259	vaccination rate low (9% of all subjects); virus types ILA and ILB; 1% of participants failed to take study medication on ≥ 2 consecutive days; 3 flu seasons from November 1997 to March 2000; 5 participants randomized twice because of multiple seasons; 107 influenza isolates obtained over 3 seasons; no evidence for resistance to ZAN in 98 isolates; remaining 9

							isolates had viral titres too low for susceptibility determination
Schilling <i>et al.</i> ⁹	non-blinded RCT Jadad score=2	N=141 rural American nursing home residents, plus staff population; characteristics NR	ILA outbreak, inhaled ZAN (10 mg twice daily)+4.4 mg intra-nasally twice daily (n=65); RIM 100 mg, once daily (n=23); duration of 14 days; ILB outbreak, inhaled ZAN (10 mg twice daily)+4.4 mg intranasally twice daily (n=35); standard care (n=18)	ILI; RI; LCI; AE	ILA outbreak, RI, ZAN 8 (12.3%), RIM 1 (4.3%); ILI, ZAN 1 (1.5%); RIM 0; LCI, ZAN 0; RIM 1 (4.3%); ILB outbreak, RI, ZAN 1 (2.9%); RIM 3 (17.6%); ILI, ZAN 0; SC, 0; LCI, ZAN 0; SC, 1 (5.9%); no statistical tests provided	ZAN-related AEs, nasal symptoms, 16%; GI symptoms, 8%; throat irritation, 7%; fever, 4%; cough, 4%; 1 drug discontinuation due to mild AE; drug-related SAE, 0	virus types ILA and ILB; dates and duration of outbreaks NR; numbers of staff versus residents treated NR; LCI defined as viral isolation by culture of throat or nasal swab or 4-fold rise in HI titer to circulating strain
Bowles <i>et al.</i> ¹⁰	case series (with historical controls); 11 outbreaks	N=993 Ontario long-term care residents requiring 1.5 to 3 hours of care per day; N=730 (received O prophylaxis for median 9 days); median age=84 years; 94% of residents and 86% of staff vaccinated; 21% estimated vaccine efficacy	after ≥6 residents had LCI, O given to residents; dosage NR; duration varied over 11 outbreaks (7 to 12 days)	control of outbreak; pneumonia (after acute influenza); hospitalization (due to acute influenza); death (due to acute influenza)	use of O associated with termination of outbreak in 8 evaluable outbreaks; 178 of 185 (96%) of case-residents met case definition of influenza; antibiotics, 63 of 178 (35%); pneumonia, 37 of 178 (21%); hospitalized, 19 of 178 (11%); died, 16 of 178 (9%)	30 of 730 (4.1%) patients experienced AEs; most common were diarrhea, cough, confusion, nausea; discontinuation of drug due to AE, 21 patients (14 due to illness symptoms within 28 hours, 5 where prophylaxis started in error, 1 due to nausea and vomiting, 1 refusal after 3 rd day of treatment); deaths, 16 patients	virus type ILA; strain was A/H3N2/Sydney/05/97; 61% had diagnoses of heart disease, lung disease, diabetes mellitus, active malignancy, or cerebrovascular disease
Parker ¹¹	case series	N=263 extended care nursing home; 77% vaccinated	O for average 15 days duration (range 11 to 23 days); 75 mg once daily (those who exhibited ILI, n=5, given treatment	ILI	ILI, 5 (2%) patients; 4 ILI within 48 hours of prophylaxis; 1 ILI within 96 hours of prophylaxis (10% overall attack rate in facility)	2 subjects experienced nausea; neither discontinued use	virus type ILB; outbreak began December 2000, duration NR

			regimen of O75 mg twice daily for 5 days)				
Lee <i>et al.</i> ¹²	case series	N=176 elderly residents of LTCF; 90% vaccinated	inhaled ZAN 10 mg once daily for those without ILI symptoms (inhaled ZAN 10 mg, twice daily given as treatment to those with symptoms)	LCI	N=129 attempted prophylaxis; N=100 succeeded in inhaling ZAN; 2 of 176 (1.1%) LCI cases in 2 weeks after prophylaxis	no AE could be attributed to drug	unclear whether 2 LCI were among subjects who received drug or among all patients at centre; virus type ILA similar to A/Sidney/05/97; outbreak declared March 8, 1999; surveillance ended April 16, 1999
Monto <i>et al.</i> ¹³	case series	residents of 59 American nursing homes, 2000 to 2001; 28 homes, mean size 134 residents (range 23 to 705), mean vaccination rate 79% (0 to 96), 2001 to 2002; 31 homes, mean size 136 residents (range 30 to 711), mean vaccination rate 76% (0 to 98)	O given to residents when outbreak identified in home (defined as 2 cases within 5 days), 2000 to 2001; 194 residents (in 3 homes) received O; 25 for treatment, 169 for prophylaxis, 2001 to 2002; 432 residents (in 5 homes) rapidly received O, 34 for treatment, 398 for prophylaxis; 121 residents received late O, 22 for treatment, 99 for prophylaxis	ILI; LCI; AE	2000 to 2001, LCI, 0 influenza viruses isolated; 0% of homes documented influenza transmission; ILI activity continued in 3 homes using O for outbreak control; 2001 to 2002, ILI, 4 patients (0.8%) \geq 2 days of prophylaxis; 12 (1.8%) for those who did not receive prophylaxis; 26% of homes documented ILI outbreak	2000 to 2001, GI symptoms (nausea, vomiting, diarrhea), 26 (13%) patients receiving O; neurological reactions (tremor, spasm, fall, seizure, 5 (3%) patients receiving O; rash or skin irritation, 9 (5%) patients receiving O (1 had severe allergic reaction requiring hospitalization); discontinuation due to AE, 11 (6%) patients, mostly due to GI complaints; 2001 to 2002, GI symptoms, 9 (2%) patients receiving O; gait disturbance, 1 (<1%) patient receiving O; rash, 0 patients receiving O; discontinuation due to AE: 6 (1%) patients receiving O	virus types, 2000 to 2001, ILA+ILB; 2001 to 2002, ILA; dates and durations of outbreaks NR; 2000 to 2001, QuickVue and Flu OIA rapid antigen detection tests used; 2001 to 2002, Directigen A+B rapid diagnostic test used
Gravenstein <i>et al.</i> ¹⁴	double-blinded RCT Jadad score=3	N=482 residents; 9 nursing homes; 96% elderly or high risk; >90% vaccinated	ZAN (n=238); RIM 100 mg (n=231); PB (n=13); 14 days duration; dosage	SLCI (days 1 to 28, all randomized); complications of SLCI (days 1 to 28, all randomizations) SLCI	SLCI (days 1 to 28, all randomizations), ZAN 9 (4%); RIM 20 (9%); p=0.054; complications of SLCI (days 1 to 28, all	total AE, ZAN 137 (58%); RIM 128 (55%); drug-related AEs, ZAN 80 (34%); RIM: 74 (32%); SAE, ZAN 4	virus type ILA, data from 3 seasons 1997 to 2000; nasopharyngeal or throat swabs collected; seroconversion defined

			and frequency of ZAN NR	(days 1 to 15, all randomizations)AE; resistance	randomizations), ZAN 2 (<1%); RIM 8 (3%); p=0.109; SLCI (days 1 to 15, all randomizations) ZAN 7 (3%); RIM 18 (8%); p=0.038; SLCI (days 2 to 15, all randomizations); ZAN 5 (2%); RIM 16 (7%); p=0.024; SLCI (days 3 to 15, all randomizations); ZAN 3 (1%); RIM 13 (6%); p=0.020;	(2%) (1 fatal); RIM 3 (1%) (1 fatal); no SAE considered to be related to study drug	as ≥4-fold increase in serum antibody titers; circulating strains A/Sydney/5/97, A/Nanchang/933/95, B/Beijing/184/93; because of 3 flu seasons, 280 randomized once; 83 twice; 12 3 times; no ZAN resistance virus observed in any of 92 influenza isolates (from approximately 900 swabs); RMA resistance prevalent (38% of isolates); 6 influenza isolates from 7 symptomatic influenza subjects on ZAN prophylaxis susceptible to ZAN and RMA
Seasonal Prophylaxis							
Peters <i>et al</i> ¹⁵	double-blinded RCT Jadad score=4	N=548 frail seniors in nursing homes; mean age of 81 years, >80% vaccinated	O75 mg (n=276); PB (n=272); for 6 weeks	LCI clinical cases; flu-related complications (URI, otitis media, myocarditis); LCI	LCI clinical cases, O75 1 (0.4%); PB 12 (4.4%); p=0.002; flu-related complications, O75 1 (0.4%); PB 7 (2.6%); p=0.037; LCI, O75 15 (5.4%); PB 23 (8.5%); p=0.181; LCI among vaccinated, O75 1 of 222 (0.5%); PB 11 of 218 (5%); p=0.003	no statistical difference between groups (approximately 60% of patients reported AE); headache, O75 8.3%; PB 5.5%; withdrawal due to AE or intercurrent illness, O75 18 (6.5%) (3 due to GI events); PB 11 (4%) (3 due to GI events); deaths, O75 1; PB 1 (neither deemed treatment-related); GI complaints, O75 14.9%; PB 12.9%	1998 to 1999 flu season; ILA and ILB; 70% of patients had 100% compliance; COPD present in 80.4% of O patients and 80.1% of PB patients; 92% effectiveness in preventing clinical influenza
Prolonged prophylaxis							
no evidence							

AE=adverse event; SAE=severe adverse event; ILA=influenza A; ILB=influenza B; ILI=influenza like illness; LCI=laboratory-confirmed influenza; NR=not reported; NS=not significant; O75=oseltamivir (75 mg); O150=oseltamivir (150 mg); PB=placebo; RCT=randomized controlled trial; RI=respiratory illness; RIM=rimantadine; SLCI=symptomatic laboratory-confirmed influenza; URI=upper respiratory infection; ZAN=zanamivir.

Table 4: Health care workers with close patient contact

Study	Study Design and Quality	Participants	Intervention	Outcome Measures	Results	AEs	Comments
no evidence							

Table 5: Health care workers without close patient contact

Study, year	Study Design and Quality	Participants	Intervention	Outcome measures	Results	AEs	Comments
no evidence							

Table 6: Household contacts

Study	Study Design and Quality	Participants	Intervention	Outcome Measures	Results	AEs	Comments
Post-Exposure Prophylaxis							
Hayden <i>et al.</i> ¹⁶	double-blinded RCT Jadad score=4	N=337 families with children ≥5 years old (321 index cases and 837 contact cases)	ZAN (n=169) (10 mg inhaled, once daily); PB (n=168), for 10 days (time between exposure and intervention NR); index cases treated with inhaled ZAN (n=163) or PB (n=158) twice daily for 5 days; index cases and co-residential contacts received same intervention	families with at least symptomatic LCI; LCI development where index illness LCI; all cases (symptomatic, asymptomatic) LCI; AE; resistance	SLCI, ZAN 4%; PB 19%; p<0.001; SLCI development where index case LCI, ZAN 8%; PB 29%; p<0.001; all cases (symptomatic, asymptomatic) LCI, ZAN 22 (13%) families; PB 47 (28%) families; p=0.001; all LCI (symptomatic, asymptomatic) where index case LCI, ZAN 15 (19%); PB 33 (38%); p=0.014	drug-related AE, ZAN 30; PB 27; 11 (3%, 4 cases in ZAN group, 7 cases in PB group); patients with index illnesses, 46 (5%, 26 cases in ZAN group, 20 cases in PB group) household contacts; all AE, ZAN 219; PB 70; SAE, ZAN 1 (pneumonia); PB 0; discontinuation of drug due to AE; ZAN 2 (1 due to GI discomfort, 1 due to headache); PB 1 (due to nausea and vomiting); withdrawal due to AE, ZAN 1 (due to headache); PB 0	virus types ILA and ILB; 1998 to 1999 influenza season; family considered to be 2 to 5 members, at least 1 adult and 1 child 5 to 17 years old; viral isolates recovered from household contacts and respective family members with index infections sensitive to ZAN; no evidence of development of resistance to use of ZAN
Welliver <i>et al.</i> ¹⁸	double-blinded RCT Jadad score=3	N=374 HH with members ≥12 years old (962 contacts); 51% women, 12.5% total vaccination rate	O75 mg (n=193 HH, 493 contacts); PB (n=178 HH, 462 contacts); once daily for 7 days within 48 hours of symptom onset in index case of	LCI	SLCI among contacts of all index cases, O75 4 (0.8%) individuals in 4 (2.1%) HH; PB 34 (7.4%) individuals in 26 (14.6%) HH; p<0.001; SLCI among contacts of LCI index cases, O75 3	withdrawals due to AE, O75 5 (1%) (2 bronchitis, 1 headache, 1 vomiting, 1 dyspepsia); PB 2 (0.4%) (both due to ILI); GI tract effects, O75 46	both ILA and ILB circulating; winter 1998 to 1999; influenza infection diagnosed by isolation of virus from nose and throat swabs or

			HH; co-resident contacts received same intervention as index case in same home		(1.4%) individuals in 3 (3.6%) HH; PB 26 (13%) individuals in 18 (23%) HH; p<0.001; SLCI among contacts of non-LCI index cases, O75 1 (0.4%) individual among 1 (0.9%) HH; PB 8 (3%) individuals in 8 (8%) HH; p=0.009; LCI (asymptomatic or symptomatic) among contacts of all index cases, O75 33 (7%) individuals in 29 (15%) HH; PB 60 (13%); individuals in 45 (25%) HH; p=0.007; LCI (asymptomatic or symptomatic) among LCI index cases, O75 16 (8%) individuals in 13 (16%) HH; PB 43 (21%) individuals in 28 (35%) HH; p=0.003; LCI (asymptomatic or symptomatic) among LCI-negative index cases, O75 17 (6%) individuals in 16 (15%) HH; PB 17 (6%) individuals in 17 (17%) HH; p=0.76	(9.3%); PB 33 (7.2%); nausea, O75 27 (5.5%); PB 12 (2.6%)	detection of ≥ 4 -fold increase in influenza-specific hemagglutinin inhibition assay titer; A/Sydney/5/97 (H3N2), A/Beijing/262/95 (H1N1), B/Beijing/184/93 strains tested
Monto <i>et al.</i> ¹⁹	double-blinded RCT Jadad score=4	N=487 households with 2 to 5 people, ≥ 5 years old, with at least 1 adult	ZAN (households n=245, contacts n=661) inhaled, 10 mg; PB (households n=242, contacts n=630); once daily for 10 days; index patients not given antiviral drug; treatment of contacts began within 36 hours of index diagnosis	LCI during prophylaxis period (1 to 11 days); households with symptomatic LCI; contacts with symptomatic LCI; households with LCI; contacts with LCI; resistance	LCI, ZAN 4%; PB 19%; p<0.001; households with SLCI, ZAN 10 (4%); PB 46 (19%); p<0.001; contacts with SLCI, ZAN 12 (2%); PB 55 (9%); p<0.001; households with LCI, ZAN 35 (14%); PB 75 (31%); p<0.001; contacts with LCI, ZAN 48 (7%); PB 105 (17%); p<0.001	AE, ZAN 276 (42%); PB 325 (52%); most common AEs consistent with ILI symptoms; bronchospasm, ZAN 0; PB 2; drug-related AE, ZAN 6%; PB 7%	virus types ILA and ILB (ILA infection more common); multi-centre trial in 11 countries from June 2000 to April 2001; study began when outbreak confirmed in local community; no evidence for development of resistance in influenza clinical isolates

Outbreak Control
no evidence
Seasonal Prophylaxis
no evidence
Prolonged Prophylaxis
no evidence

AE=adverse event; SAE=severe adverse event; ILA=influenza A; ILB=influenza B; ILI=influenza like illness; LCI=laboratory-confirmed influenza; NR=not reported; NS=not significant; O75=oseltamivir (75 mg); O150=oseltamivir (150 mg); PB=placebo; RCT=randomized controlled trial; RIM=rimantadine; SLCI=symptomatic laboratory-confirmed influenza; URI=upper respiratory infection; ZAN=zanamivir; HH=household.

Table 7: Public health responders

Study	Study Design and Quality	Participants	Intervention	Outcome Measures	Results	AEs	Comments
no evidence							

Table 8: Avian influenza in healthy people

Study	Study Design and Quality	Participants	Intervention	Outcome Measures	Results	AEs	Comments
Outbreak Control							
Koopmans <i>et al.</i> ⁴	case series, quasi-experimental	453 cases (possible exposure to H7N7 and who had illness); 90 met case definition for ILI	O75 mg daily, suggested for all people handling potentially infected poultry, continued 2 days after last exposure	LCI	drug, 1 of 38 (2.4%); untreated, 5 of 52 (9.6%); p=0.38	NR	outbreak of ILA H7N7 in February 2003

ILA=influenza A; ILI=influenza like illness; LCI=laboratory-confirmed influenza; NR=not reported.