TECHNOLOGY *OVERVIEW*

An Assessment of Oseltamivir for the Treatment of Suspected Influenza

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An Assessment of Oseltamivir for the Treatment of Suspected Influenza

March 2002

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Husereau DR, Brady B, McGeer A. **Oseltamivir for the treatment of suspected influenza: a clinical and economic assessment**. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2001. Technology report no 21.

Highlights

What is already known about this topic?

- About influenza:
  - Influenza is a viral infection that can significantly burden the health care system, particularly during times of seasonal epidemics.
  - True influenza is difficult to diagnose without laboratory tests, since the symptoms are similar to those of other viral and bacterial illnesses.
  - Significant complications can occur, particularly in the elderly and those with chronic underlying conditions.

- About antivirals for influenza:
  - Three antiviral medications are available in Canada for the treatment of influenza
  - Amantadine (about $1/day or less) has been available for many years. It is ineffective against influenza B viruses. Amantadine-resistant influenza A viruses that remain pathogenic during epidemics have been documented. Amantadine is less tolerated in the elderly.
  - Zanamivir (oral inhalation, $7/day) and oseltamivir ($8.40/day) are newer treatments called neuraminidase inhibitors. They are effective against influenza A and B, but to be effective they must be used within 2 days of the onset of symptoms.

Assessment Objectives

1. To assess and quantify the efficacy and effectiveness of oseltamivir in individuals suspected of having influenza.
2. To assess the cost-effectiveness of treating patients with suspected influenza in a primary care setting, where the standard treatment is no active medical intervention.

What new information does this assessment provide?

- There is insufficient evidence to show that oseltamivir reduces complications, hospitalizations or death when used to treat:
  - normally healthy people suspected of having influenza, or;
  - those who are at risk for developing complications. In fact, there is insufficient evidence of any benefit (including recovery time) in this latter population, in which influenza is associated with higher morbidity.
- From a government payer perspective, oseltamivir is:
  - unlikely to be cost-effective for treating suspected influenza in otherwise healthy adults, based on reasonable assumptions about diagnostic accuracy in a primary care setting;
  - unlikely to be cost-effective for the treatment of adults at risk of developing influenza-related complications, but the clinical evidence for this is inconclusive at this time.

Executive Summary

The Issue

Annually, influenza causes significant morbidity and mortality. It is difficult to diagnose true influenza without a laboratory test. Mortality occurs primarily in the elderly and individuals in all age groups with chronic underlying disease represent the majority of hospitalizations. Oseltamivir has been approved for the treatment of uncomplicated, acute illness due to influenza in adults who have been symptomatic for no more than two days. However, the clinical and economic impact of oseltamivir for the treatment of influenza is not known.

Objectives

The objectives of this assessment are (1) to assess and quantify the efficacy and effectiveness[a] of oseltamivir in individuals who are suspected of having influenza; and (2) to assess the cost-effectiveness of treating suspected influenza with oseltamivir in a primary care setting where standard treatment is no active medical intervention.

Clinical Effectiveness Review

Methods: A systematic review methodology was used to search for, select and assess the quality of published and unpublished randomized controlled trials. The studies were evaluated and data from the studies were independently extracted and combined, if appropriate, by meta-analysis.

Results: Of 117 references identified, six trials with 1735 participants met the inclusion criteria of which 469 individuals were individuals at risk for developing complications. All six trials were sponsored by industry and were of moderate to high quality. Oseltamivir treatment resulted in an absolute reduction of 1% (95% CI [- 2%] to 3%) and 2% (95% CI [- 5%] to 8%) for a combined outcome of death, hospitalization, and complications of illness in otherwise-healthy and at-risk individuals suspected of having influenza, respectively. The results for these three outcomes separately were similarly small and statistically insignificant. In one trial involving 419 participants, oseltamivir reduced the median time to return to normal activity by 57 hrs (95% CI: 2.4 hrs to 111.6 hrs) when compared with placebo.

Economic Review and Analysis

Methods: To assess the cost-effectiveness of treatment, a decision analytic model was used to compare the health outcomes, resource use, and costs associated with treating suspected influenza with oseltamivir to symptomatic relief medication only. The study perspective was that of a government payer in Canada, so only direct medical costs were included. Two populations were assessed separately; the otherwise healthy population of 18 to 65 year olds and those at risk of developing influenza-related complications. Base cases for the two populations used estimates

[a] Specifically, this systematic review asks if oseltamivir 75 mg taken orally once or twice daily in individuals greater than 13 years of age has a significant measured effect on the following primary outcomes: (1) number of deaths; (2) number of hospitalized patients; (3) number of complications (i.e. pneumonia, sinusitis, bronchitis, or otitis) and recurrence of illness; and (4) the time to return to normal activity.

of oseltamivir efficacy from the meta-analysis. Estimates for health state utilities were based on a small sample of healthy adults, and data for disease epidemiology and unit costs were based on estimates for Canada, where available. Both a cost-effectiveness analysis and a cost-utility analysis were performed. Uncertainty was tested through one-way and multi-way sensitivity analyses for plausible ranges of parameters values.

Results: The results for the healthy population in terms of cost per quality-adjusted life-year (QALY) showed that treatment with oseltamivir is:

- More than $100,000 using (a) a base case diagnostic accuracy of 35%, and (b) a 50% diagnostic accuracy if there are substantial numbers of late presenting patients treated inappropriately with oseltamivir;
- Less than $50,000 only under very favourable assumptions (68% diagnosis, few inappropriately-treated late presenting patients, and optimistic assumptions about the clinical effectiveness of oseltamivir).

The cost-effectiveness results for the at-risk population are similar, although the uncertainty is considerably greater due to the inconclusive clinical evidence.

Conclusions

There is insufficient evidence that oseltamivir reduces complications, hospitalizations and/or death in individuals suspected of having influenza. In addition, there is insufficient evidence of any benefit in individuals with suspected influenza who are at risk for developing complications. Evidence from one trial suggests that otherwise healthy individuals suspected of having influenza, return to normal activity faster when treated with oseltamivir than those receiving placebo. No studies are available to compare the magnitude of this benefit to amantadine, zanamivir or symptom-relieving medications.

The cost-effective treatment of suspected influenza using oseltamivir in a primary care setting depends largely on two factors: (1) the accuracy of diagnosis of influenza by the primary care practitioner; and (2) the likelihood of patients being treated within a 48 hour period from the onset of symptoms. The economic analysis suggests that, from a government payer perspective, oseltamivir is unlikely to be cost-effective for treating suspected influenza in otherwise healthy adults. This conclusion is based on reasonable assumptions about diagnostic accuracy in a primary care setting when influenza is circulating in the community. It would appear that oseltamivir is also unlikely to be a cost-effective treatment for adults at risk of developing influenza-related complications – but the clinical evidence for this is inconclusive at this time.

Another cause for concern is the likelihood of primary care consultations from patients with little risk of complications who would not otherwise seek treatment. If oseltamivir were to be reimbursed by a government payer, additional budgetary resources would have to be allocated since it is unlikely to be a cost-saving strategy.

1. Introduction

Influenza is an infectious disease caused by the influenza A or influenza B virus.[1] Infection with the influenza virus in otherwise healthy adults and adolescents can result in chills, fever, sore throat, muscle pain, weakness, headache, loss of appetite, and cough. The general terms, influenza-like illness (ILI) is used to describe patients who present with these symptoms regardless of confirmation of the presence of influenza virus by a laboratory test. In Canada, the rate of symptomatic infection can be 10% or higher, varying from season to season. However, certain vulnerable populations, including school children or nursing home residents, may experience attack rates as high as 25% to 60%.[2,3]

The acute illness is generally self-limiting and lasts three to seven days. In addition to the acute illness, infection with the influenza virus can cause a number of complications, most commonly, respiratory complications.[4] Non-respiratory complications include febrile convulsions, post-influenza encephalitis, Reye's syndrome, encephalopathy, transverse myelitis, Guillain-Barré syndrome, myositis, cardiac muscle damage, and toxic-shock syndrome.[1]

Annually, influenza causes significant morbidity and mortality.[5] Individuals in all age groups with chronic underlying conditions, such as chronic respiratory or cardiovascular disease, chronic renal failure, diabetes, immunosupression or hematological disorders, represent the majority of hospitalizations.[6] Mortality from influenza outbreaks occurs primarily in the elderly.[7] Currently, Health Canada estimates the number of deaths attributable to influenza to be from 500 to 1500 annually.[8]

The usual recommendation for people with influenza is to rest at home, drink fluids and treat symptoms with over-the-counter medications. Individuals at risk for developing complications can be treated with antiviral medications if the diagnosis is made in an appropriate time period. There are three antiviral medications currently available in Canada to treat individuals with influenza: amantadine, zanamivir, and oseltamivir (Table 1).

Table 1: Current antiviral treatment options for individuals with influenza

	Oseltamivir	Zanamivir	Amantadine
Approved for treatment	18 years & over	12 years & over	Adults & children (1 to 9 yrs)
Class / mechanism of action	Neuraminidase inhibitor	Neuraminidase inhibitor	Blocks activity of viral M2 protein
Influenza viruses inhibited	A & B	A & B	A only
Usual dosage	75 mg bid x 5 days (will vary with body mass & renal function)	10 mg bid x 5 days	100 mg bid or 10 mL bid x 5 days (will vary with body mass & renal function)
Route of administration	Oral (capsule)	Oral inhalation (inhaler device)	Oral (capsule or syrup)
Significant adverse events	GI symptoms (nausea & vomiting)	None from drug - bronchospasm in COPD from inhaled media	CNS & GI symptoms
Viral resistance	Possible	Possible	Documented rapid emergence of resistance
Average daily cost *	$8.40	$7.00	$0.08 (syrup) – $1.04 (capsule)

* Average daily cost: oseltamivir and zanamivir are based on the manufacturer's price;[9] amantadine is based on the Ontario Drug Benefit Formulary price.[10] Note that associated pharmacy mark-up and/or dispensing fees are not included.
COPD - Chronic Obstructive Pulmonary Disease; CNS - Central Nervous System; GI – Gastrointestinal

Oseltamivir was approved for use in Canada in December 1999.[11] Oseltamivir works by inhibiting the binding of neuraminidase, a glycosylated protein that facilitates replication of the virions. Oseltamivir is currently indicated for the treatment of uncomplicated acute illness due to influenza infection in adults age 18 years old and over who have been symptomatic for no more than two days.[12, 13]

2. Objectives

(1) To assess and quantify the efficacy and effectiveness of oseltamivir in individuals who are suspected of having influenza. In particular, this systematic review asks if oseltamivir has a significant measured effect on the following primary outcomes: death and hospitalization, complications, and time to return to normal activity.

(2) To assess the cost-effectiveness of treating suspected influenza with oseltamivir in a primary care setting, where standard treatment is no active medical intervention.

3. Clinical Review

Methods

The methods used to conduct this review follow guidance for conducting systematic reviews provided by the QUOROM statement.[14]

a) Literature Search

Published literature was obtained by searching a number of electronic databases (MEDLINE®, EMBASE®, HealthSTAR®, Pascal®, SciSearch® and Toxline®) using the DIALOG® system. Searches were also performed on the CD-ROM versions of The Cochrane Library and HEED (Health Economics Evaluation Database). Additional literature was obtained by hand searching conference abstracts and bibliographies of selected articles, searching Web sites of regulatory agencies, health technology assessment and near-technology assessment agencies, and contacting experts in the field and the drug manufacturer.

b) Selection Strategy

Relevant studies were independently selected by two reviewers. Studies were included if they met the criteria described in Table 2.

Table 2: Inclusion criteria

Study Design	Randomized controlled trials
Participants	Adult and adolescent patients with ILI (natural infection) were considered. Studies with children (< 12 yrs) were excluded.
Intervention	The dosage which has been reviewed and approved by the Therapeutic Products Directorate of Health Canada (i.e., the Canadian regulatory body for the approval of human medicines) for a given population or the dosage used in studies of efficacy (e.g., Phase III studies) when no dosage has been approved.
Comparator	Placebo or current therapy (e.g., amantadine, rimantadine, zanamivir, acetaminophen, etc.)
Outcomes	Number of patient deaths, serious adverse events, number of hospitalized patients, number of complications, recurrence of illness, time to return to normal activity, time to alleviation of symptoms, reduction in symptom severity, number of adverse events, types of adverse events, number of patients with laboratory-confirmed influenza, number of patients with oseltamivir-resistant influenza

c) Quality Assessment and Data Extraction

The quality of the included studies was assessed independently by two reviewers using the Jadad scale.[15] Information on allocation concealment was also scored using a 3-item system: adequate, inadequate or unclear. In addition, the two reviewers extracted all relevant data independently. Extracted data included: information on trial design, participant characteristics, therapeutic interventions and outcomes. If a homogenous set of randomized controlled trials was found, data was combined by meta-analysis.

Results

Of 117 studies identified, six met the inclusion criteria and were reviewed in this report. All six were phase III, randomized controlled trials examining the efficacy of oseltamivir in the treatment of naturally occurring influenza.[16-21] All compared the use of oseltamivir with placebo. Quality assessment scores using the Jadad scale and information on allocation concealment indicated that two studies were of high quality and four studies were of moderate quality. The number of participants in the six studies totalled 1735, of which 469 were considered at risk of developing complications. Study characteristics are summarized in Table 3.

Table 3: Characteristics of studies included in this review

Study, influenza season, ref	ITT (*n*)	Participants	Intervention	Outcomes reported*
Kashiwagi, 1998-99[16]	313	>16 yrs; small number of elderly participants	Placebo or oseltamivir 75 mg	Duration of illness in infected patients (primary), median viral titers, and reduction of symptoms in infected patients. Adverse events for all patients
Nicholson, 1997-98[17]	476	18-65 yrs; otherwise healthy. At-risk excluded	Placebo or oseltamivir 75 mg or oseltamivir 150 mg	Duration of illness in infected patients (primary), severity of illness, duration of virus shedding, viral antibody titers, time to alleviation of individual symptoms and fever, reduction in secondary illnesses, and time to return to normal activity. Adverse events (divided into first week and following two weeks) for all patients.
Treanor, 1997-98[18]	419	18-65 yrs; otherwise healthy. At-risk excluded	Placebo or oseltamivir 75 mg or oseltamivir 150 mg	Duration of illness in infected patients (primary). Severity of illness, duration of virus shedding, viral antibody titers, time to alleviation of individual symptoms and fever, reduction in secondary illnesses, and time to return to normal activity. Adverse events (divided into first week and following two weeks) for all patients. Time to return to normal activity.
WV15812, 1998-99[19]	301	>13 yrs; small number of adolescent participants; at-risk participants include subjects with chronic cardiac and respiratory diseases	Placebo or oseltamivir 75 mg	Duration of illness in infected patients (primary). Time to afebrile state, use of symptom-relieving medication, and proportion of subjects hospitalized. Adverse events (in first week and subsequent two weeks) are reported for all patients.
WV15819, 1998-99[20]	168	>65 yrs**	Placebo or oseltamivir 75 mg	Duration of illness in infected patients (primary). Time to afebrile state, time to cessation of virus shedding, use of symptom-relieving medication, incidence of secondary illness requiring antibiotics, proportion of subjects hospitalized. Adverse events (divided into first week and following two weeks).
WV15730, 1998[21]	58	18-65 yrs; otherwise healthy. At-risk excluded	Placebo or oseltamivir 75 mg	Duration of illness in infected patients (primary). Severity of illness. Adverse events (divided into first week and following two weeks) for all patients.

* No study was specifically designed to investigate reduction in the number of hospitalizations and death, however, this information would have been recorded as a serious adverse event.

** Subjects excluded if they presented with unstable or uncontrolled disease.

a) Primary Outcome Measures

Analyses were performed on an intention-to-treat (ITT) basis whenever possible.

Reduction in death and hospitalization

Information on hospitalizations and death was reported in all six trials. In trials involving healthy adults, 0.8% (5/630) of participants were reported to have died or been hospitalized in the placebo group compared with 0.5% (3/636) of participants in the treatment group. In the at-risk population, death or hospitalization was reported to be 2.5% (6/241) in the placebo group compared with 0.9% (2/228) in the treatment group. A meta-analysis resulted in an absolute risk reduction of 0.0% (95% CI 0% to 1%) for a death or hospitalization occurring in treated participants.

Complications

Complications associated with influenza were defined as otitis, sinusitis, bronchitis, or pneumonia and were reported in all trials. In otherwise healthy individuals, complications were reported in 5.4% (34/630) of placebo-treated participants, compared with 4.7% (30/636) of oseltamivir-treated participants. In trials involving patients at risk for developing complications, complications were reported in 13.3% (32/241) of placebo participants compared with 13.2% (30/228) of oseltamivir-treated participants. A meta-analysis combining results of at-risk and healthy participants resulted in an absolute risk reduction of 0% (95% CI [-1%] to 2%).

Recurrence of illness, defined by a recurrence of flu-like symptoms, was reported in only one trial.[17] Recurrence was reported in 2.6% (6/235) of placebo-treated participants, compared with 2.1% (5/241) of oseltamivir-treated participants.

Reduction in all harmful events

The number of deaths, number of hospitalizations, and the number of patients with complications from or recurrence of influenza up to 21 days after the initiation of therapy were pooled. This resulted in an absolute risk reduction from treatment of 1% (95% CI [-2%] to 3%) in healthy participants compared with 2% (95% CI [-5%] to 8%) in at-risk participants.

Time to return to normal activity

Only one trial reported the time to return to normal activity for all randomized participants.[18] Otherwise healthy, treated individuals returned to normal activity 57 hours (95% CI 2.4 hrs to 111.6 hrs) sooner than those individuals receiving placebo.

b) Other Outcomes of Interest

Data of particular interest in the economic analysis are below.

Time to resolution of symptoms

Otherwise-healthy infected participants who were treated with oseltamivir exhibited a median reduction in time to alleviation of symptoms of 30.6 hours (95% CI 17.9 hrs to 43.2 hrs) compared to those participants receiving placebo. In infected participants at risk of developing complications, a median reduction of 17.0 hours (95% CI [-42.3] to 76.3) was observed compared to those participants receiving placebo.

Hospitalization due to complications in infected participants
In infected participants at-risk of developing complications, one oseltamivir recipient and three placebo recipients were hospitalized from complications, giving a relative risk (RR) for oseltamivir of 0.73 (95% CI 0.04 to 11.81). No hospitalizations from complications of influenza were reported in the 862 otherwise-healthy, influenza-infected participants.

Patients with secondary complications requiring antibiotic prescription
In otherwise-healthy infected recipients, 3.2% of those treated with oseltamivir received an antibiotic versus 7.6% of the placebo recipients, giving a relative risk of 0.44 (95% CI 0.16 to 1.16) for oseltamivir-treated participants. In at-risk participants, 16.8% of the oseltamivir recipients and 17.3% of the placebo recipients required an antibiotic prescription for complications of influenza, giving a relative risk of 0.94% (95% CI 0.50 to 1.74) for oseltamivir-treated participants.

Patients with laboratory-confirmed influenza
Overall, 68.2% of the participants in the six trials had laboratory-confirmed influenza.

Safety
Overall, oseltamivir appears to be well tolerated with an incidence of patient withdrawals and recorded adverse events comparable to placebo. However, two side effects, nausea and vomiting, were observed more frequently in oseltamivir-treated participants.

Conclusions

- There is insufficient evidence that oseltamivir reduces complications, hospitalizations and/or death in individuals suspected of having influenza.

- There is insufficient evidence of any benefit in individuals with suspected influenza who are at risk for developing complications.

- Evidence from one trial suggests that otherwise healthy individuals suspected of having influenza, return to normal activity faster when treated with oseltamivir than those receiving placebo.

4. Economic Review

The literature search for published economic studies identified three economic studies assessing oseltamivir for the treatment of ILI: a published cost analysis study,[22] a published cost-effectiveness study,[23] and an unpublished economic evaluation.[24]

5. Primary Economic Analysis

Methods

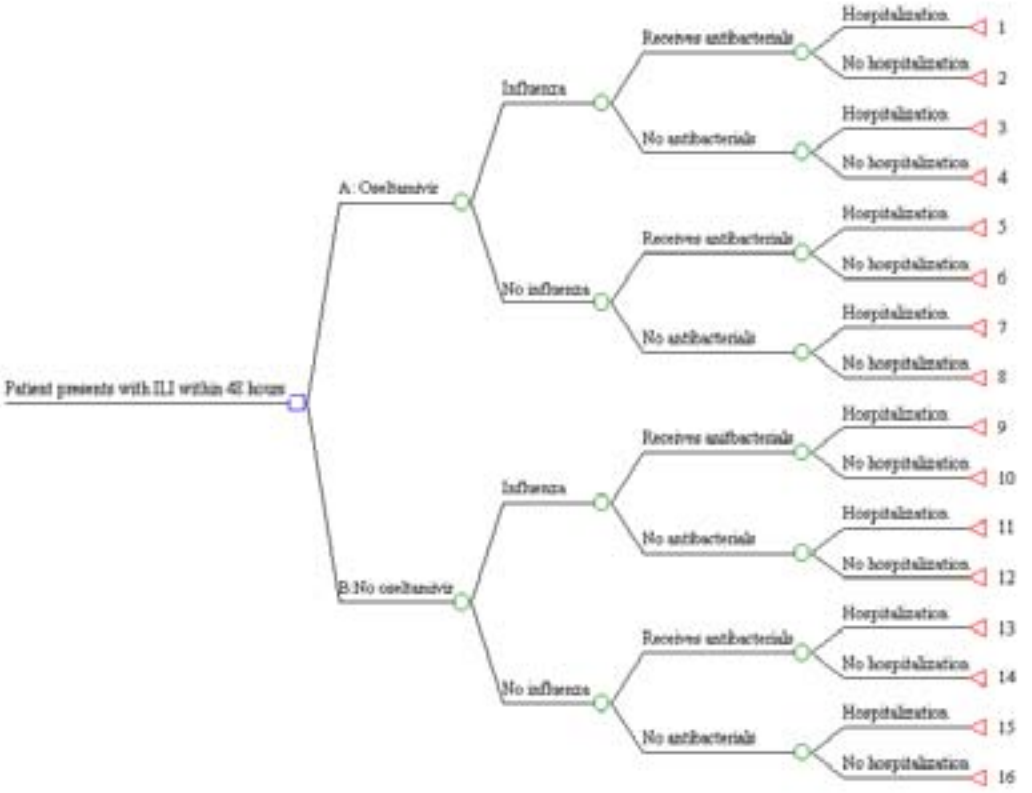
To assess the cost-effectiveness of treatment, a decision analytic model was used to compare the health outcomes, resource use, and costs associated with treating suspected influenza with oseltamivir to symptomatic relief only. Two types of economic evaluation were performed: a cost-effectiveness analysis and a cost-utility analysis. The economic results were reported in

terms of incremental cost per symptom day avoided for the cost-effectiveness analysis and incremental cost per quality-adjusted life-year (QALY) gained for the cost-utility analysis.

The study perspective was that of a government payer in Canada, so only direct medical costs were considered. Two populations were assessed separately; the otherwise healthy population 18 to 65 years old and those at-risk of developing influenza-related complications.

A pharmacoeconomic model was developed to simulate clinical management pathways for treating influenza with oseltamivir compared with standard treatment. The expected costs and outcomes of each treatment strategy were estimated by multiplying the relevant probabilities with costs and health outcomes, which were then summed to arrive at the total expected costs and health outcomes for each strategy. The incremental results are based on the difference in the expected values of the strategies. The structure of the model is based on the decision tree shown in Figure 1.

Figure 1: Treatment pathways for influenza: oseltamivir versus standard treatment



Key model parameters/inputs are:

1. Resource utilization and unit costs associated with the two treatment strategies: This includes: (a) treatment with oseltamivir ($53.20 for a five-day course of treatment, including pharmacy mark-up and a dispensing fee), (b) physician visits (including follow-up visits), (c) antibacterial use for treating influenza-related complications, and (d) hospitalization for serious influenza-related complications. Parameter estimates use data for Canada.

2. Diagnostic accuracy: This is the probability that a diagnosis of a case of influenza by a primary care physician, without the benefit of a diagnostic test, is a true positive (i.e. positive predictive value). The Base Case uses a 35% diagnostic accuracy when influenza is circulating in the community, based on information from several sources. Diagnostic accuracy in primary care practice will vary, likely substantially, and sensitivities of 14% to 68% are tested.

3. Treatment effectiveness: This is measured in terms of symptom days avoided, quality-of-life utility for influenza, and the relative risk of oseltamivir (vs standard treatment) in terms of repeat physician visits, antibacterial use and hospitalization. Evidence of the efficacy of oseltamivir is based on the meta-analysis of the trial results, and utilities are based on a small sample of healthy adults.

Parameter value uncertainty is handled through one-way and multi-way sensitivity analyses. Sensitivity analysis also considers inappropriate prescribing of oseltamivir for patients presenting with an ILI after 48 hours of symptom onset (termed "late presenters").

Results

The results of the analysis, from the government payer perspective, for both healthy and at-risk populations are summarized below. The incremental cost-effectiveness ratio (ICER) results for oseltamivir reflect the difference in expected costs and expected health outcomes of treatment with oseltamivir compared with standard treatment.

a) Healthy population

The ICER results are very sensitive to diagnostic accuracy, since oseltamivir has the potential for improving the health of only those infected with influenza.

Table 6: Healthy population — ICER results for Base Case

	Diagnostic Accuracy			
	14%	**35%**	**50%**	**68%**
Incremental cost per patient	$53.11	$52.98	$52.88	$52.76
Incremental symptom days avoided per patient	0.18	0.44	0.64	0.86
Incremental cost per day of symptoms avoided	$299	$119	$83	$61
Incremental QALYs gained per patient	0.00018	0.00044	0.00063	0.00086
Incremental cost per QALY gained	$299,500	$119,500	$83,500	$61,300

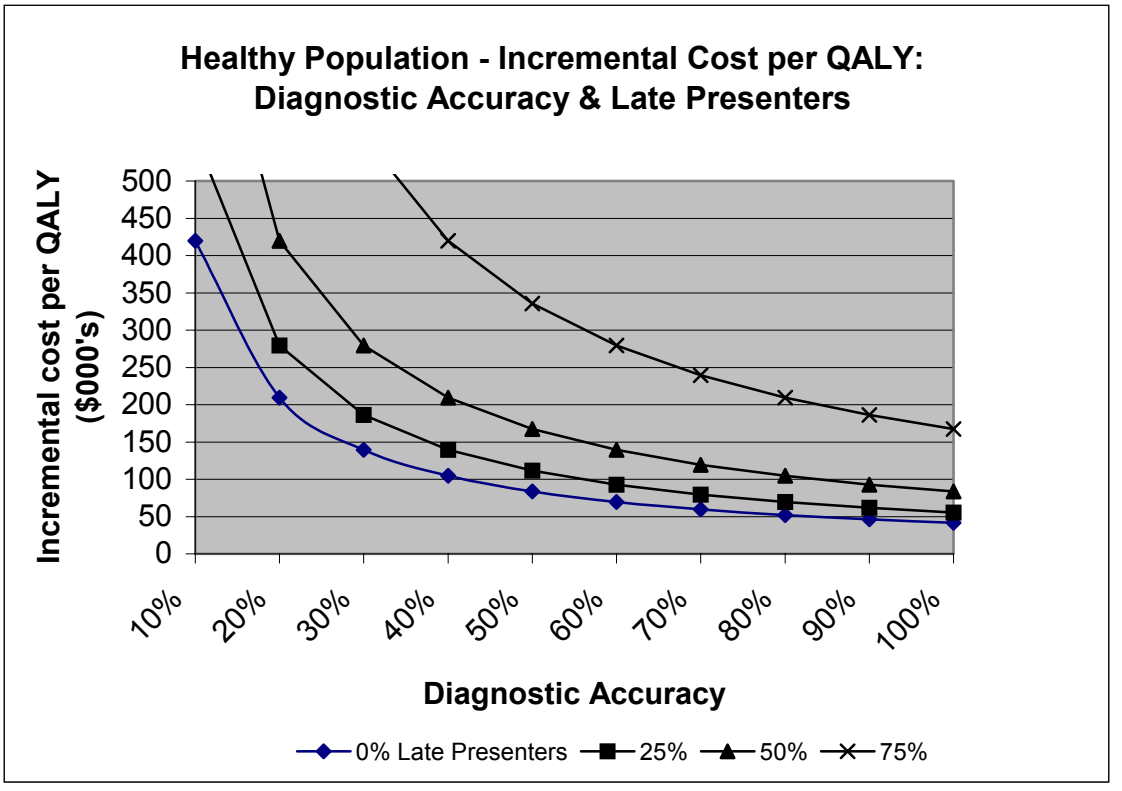
In addition to diagnostic accuracy, the proportion of late presenting patients also impacted the cost-effectiveness of oseltamivir in the healthy population. The results were relatively insensitive to changes in resource use and unit costs (Table 7).

Table 7: Healthy population - ICER results vs percentage of late presenting patients

Percentage of late presenting patients:	Diagnostic Accuracy			
	14%	35%	50%	68%
0%	$299,500	$119,500	$83,500	$61,300
6% (reduced treatment compliance)	$318,700	$127,200	$88,900	$65,200
25%	$399,500	$159,500	$111,500	$81,900
50%	$599,600	$239,500	$167,500	$123,000

The ICER results for the healthy population vs diagnostic accuracy and late presenters are shown in Figure 2.

Figure 2 Healthy population - ICER results vs diagnostic accuracy and late presenters



b) At-Risk Population

Like the healthy population, the incremental cost-effectiveness results for the at-risk population varied considerably with diagnostic accuracy and the proportion of patients treated late with oseltamivir (Table 8 and Table 9). The incremental cost-effectiveness results for the at-risk population were considerably higher than results for the healthy population under the Base Case assumptions, mainly due to lower symptoms days avoided (0.71 vs 1.27 days; see Table 7 vs Table 9). For example, at a diagnostic accuracy of 35%, the cost per QALY is about $171,000 for the at-risk population and $120,000 for the healthy population.

It should be noted that the incremental cost-effectiveness results for the at-risk population are based on estimates of parameters (symptom days avoided, relative risk of antibacterial use and relative risk of hospitalization), that are wide ranging and were not statistically significant in the meta-analysis.

Table 8: At-risk population — ICER results for Base Case

Percentage of late presenting patients	Diagnostic Accuracy			
	14%	35%	50%	68%
Incremental cost per patient	$51.11	$47.96	$45.72	$43.03
Incremental symptom days avoided per patient*	0.11	0.27	0.38	0.52
Incremental cost per day of symptoms avoided	$478	$180	$120	$83
Incremental QALYs gained per patient*	0.00011	0.00028	0.00040	0.00055
Incremental cost per QALY	$454,800	$170,700	$113,900	$78,800

* Includes hospital days avoided and associated utility

Table 9: At-risk population – ICER results for selected sensitivities

Parameter presenting patients	Variation	Diagnostic Accuracy			
		14%	35%	50%	68%
Hospitalization	1.7% vs 0.1% (lower CI of RR = 0.04)	$314,300	$95,500	$51,800	$24,700
	1.7% vs 1.7% (upper CI of RR = 1.00)	$536,500	$214,500	$150,000	$110,300
	5.0% vs 3.7% (mean RR = 0.73)	$344,300	$111,600	$65,000	$36,300
Late presenting patient as a percentage of total patients:	0%	$454,800	$170,700	$113,900	$78,800
	6% (reduced treatment compliance)	$485,000	$182,800	$122,400	$85,100
	25%	$612,600	$233,800	$158,100	$111,300
	50%	$928,200	$360,100	$246,500	$176,300
	75%	$1,875,00	$738,900	$511,600	$371,300

Note:

For the purposes of this report, the following benchmarks are used as guidelines in judging whether oseltamivir is cost-effective:

- "likely to be cost-effective" if below $50,000 per QALY gained
- "marginally cost-effective" if between $50,000 and $100,000 per QALY gained
- "unlikely to be cost-effective" if above $100,000 per QALY gained

Judging by these criteria, from a government payer perspective, oseltamivir is:

1. Unlikely to be cost-effective for the healthy populations if (a) the diagnostic accuracy is 35% when influenza is circulating in the community (reflecting diagnosis more typical for patients presenting with an ILI to primary care physicians in Canada), or (b) the diagnostic accuracy is 50% and there are substantial numbers of late presenters.
2. Marginally cost-effective for the healthy population if (a) the diagnostic accuracy is 50% and the number of late presenters is not substantial, or (b) the diagnostic accuracy is 68% (as seen in the trials).

3. Likely to be cost-effective only under very favourable assumptions (68% diagnosis, few late presenters treated inappropriately, and optimistic assumptions about the clinical effectiveness of oseltamivir).

The cost-effectiveness results for the at-risk population are similar, although the uncertainty is considerably greater due to large variability within the clinical parameters.

The cost-effectiveness of oseltamivir is sensitive to two parameters: (a) the likelihood of distinguishing influenza from other influenza-like illnesses; and (b) the likelihood that late-presenting patients (> 48 hours) will be inappropriately treated with oseltamivir. For at-risk patients, a significant reduction in hospitalization is also an important factor.

6. Conclusion

- Oseltamivir is unlikely to be cost-effective for healthy populations based on reasonable assumptions about diagnostic accuracy in primary care.
- Oseltamivir is also unlikely to be cost-effective for adults at risk of developing complications – but insufficient clinical evidence does not allow for more robust conclusions to be made at this time.
- Cost-effective prescribing of oseltamivir is complicated by several factors, including:
  - the difficulty in distinguishing influenza from other influenza-like illnesses;
  - uncertainty about how many patients will be inappropriately treated beyond 48 hours from symptom onset; and
  - the likelihood of consultations from patients with little risk of complications who would not otherwise seek treatment.
- If oseltamivir were to be reimbursed by a government payer, additional budgetary resources would have to be allocated since it is unlikely to be a cost saving strategy.

7. References

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