

Table A6.1: Summary of observational studies assessing the use of antivirals

Studies	Design	N	Population characteristics	Key results
Barr 2007	Retrospective cohort study	4,447 received oseltamivir prescription 20,407 did not receive prescription	Children aged 1 to 12 with clinically diagnosed influenza	– Patients prescribed oseltamivir were less likely to develop pneumonia, 0.7% versus 1.4% (RR=0.483; 95% CI: 0.326, 0.717).
Bowles 2002	Retrospective review	178	Nursing home residents	– Use of oseltamivir within 48 hours of symptom onset resulted in significantly less antibiotic use, fewer hospitalizations and fewer deaths compared to residents receiving no therapy or using amantadine.
Blumentals 2007	Retrospective cohort analysis Propensity score matching	36,751 treated with oseltamivir Equal number of matched sample controls	Adolescents ≥13 years and adults diagnosed with seasonal influenza	– Reduction in risk of otitis media of 23% (HR=0.77; 95% CI: 0.65, 0.93). – Reduction in any respiratory disease by 18% (HR=0.82; 95% CI: 0.79, 0.86). – Reduction in hospitalization for any reason of 22% (HR=0.78; 95% CI: 0.67, 0.91).
Casscells 2009	Retrospective review	37,482	Coded history of cardiovascular disease and influenza diagnosis	– Recurrence of CV outcomes within 30 days after influenza diagnosis was significantly lower in treated group (p=0.005). – Statistically significant protective effect associated with oseltamivir treatment (OR=0.417; 95% CI: 0.349, 0.498).
Cole 2002	Retrospective review of medical /pharmacy health insurance data	2341 treated with zanamivir 2337 untreated comparator group	US patients with diagnosis of seasonal influenza	– Fewer zanamivir-treated patients were hospitalized for complications (RR=0.58; 95% CI: 0.30, 1.12). – More outpatient visits for zanamivir-treated patients (16.9% versus 14.5% for untreated patients), RR=1.16; 95% CI: 1.02, 1.33.

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Dutkowski 2009	Safety and tolerability study	391	Healthy adults 75mg, 225mg, or 450mg for 5days	– Dose-related increases in nausea, vomiting, dizziness and hot flushes, but overall high-doses were well tolerated.
French 2007	Post-marketing surveillance	13,137	Patients prescribed amantadine	– 36 (0.27%) prescribed amantadine were diagnosed with corneal oedema (RR=1.7; 95% CI: 1.1, 2.8).
Gums 2008	Retrospective review of health care claims	45,751 treated with oseltamivir and 45,751 matched untreated controls	Patients diagnosed with influenza during 5 influenza seasons in the US	– Statistically significant reductions in risk of pneumonia (OR= 0.89, 95% CI: 0.80, 1.00), otitis media (OR=0.84, 95% CI: 0.77, 0.91) and hospitalization (OR=0.71, 95% CI: 0.62, 0.83). – Risk of pneumonia and otitis media were also lower in children and adolescents (≤ 17 years) prescribed oseltamivir (OR=0.4, 95% CI: 0.60, 0.91 and OR: 0.77, 95% CI: 0.69, 0.85, respectively).
Hanshaow-orakul 2009	Retrospective medical record review	2075	Thai individuals with influenza infection	– Treatment with oseltamivir statistically associated with survival (crude OR=0.11; 95% CI: 0.04, 0.30, controlled for age OR=0.13; 95% CI: 0.04, 0.40). – 1.5% (5/318) mortality in those oseltamivir treated, in comparison to 5% (17/131) of those untreated.
Kawai 2009	Retrospective review	291	164 H1N1 patients and 59 H3N2 patients (2008-09 influenza season); 68 H1N1 patients (2007-08 season).	– Mean duration of fever after commencing oseltamivir therapy was significantly longer in H1N1 2008-09 (49.1 \pm 30.2h) than in H3N2 (33.7 \pm 20.1h, $p < 0.01$) or H1N1 2007-08 (32.0 \pm 18.9h, $p < 0.001$). – Mean duration of fever was longer for oseltamivir than zanamivir for 2008-09 H1N1 ($P < 0.001$).
Kimberlin 2009	Retrospective chart review	180	Infants treated with oseltamivir, amantadine or rimantadine	– Children less than one year of age treated with oseltamivir were significantly less likely to develop abnormalities in the head/eyes/ears/ nose/throat system, such as otitis media, compared to children treated with rimantadine or amantadine (1.7% versus 15.4%; $p < 0.01$).
Lee 2007	Retrospective cohort study	356	Patients hospitalized with laboratory confirmed seasonal influenza	– Oseltamivir initiated within 2 days of illness was associated with shorter total length of stay (Kaplan-Meier estimated median 4 versus 6 days; adjusted HR=1.54; 95% CI: 1.23, 1.92; $p < 0.0001$).

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Lee 2009	1-year prospective observational study	147	Adults hospitalized from influenza (H3N2)	<ul style="list-style-type: none"> – Antiviral treatment initiated on presentation was an independent factor affecting viral concentration. – Treatment started on symptom days 1–4 was significantly associated with shortened viral RNA detection. – Oseltamivir started on symptom day 1–2 was also significantly associated with shortened viral RNA detection, OR=0.10 (95%CI: 0.03, 0.35; $p<0.001$). – Antiviral treatment started on symptom day 1 or days 2–3 was associated with accelerated viral concentration decrease, compared with no treatment.
Liem 2009	Retrospective review	67	Laboratory confirmed cases of H5N1 in Vietnam	<ul style="list-style-type: none"> – Risk of death was higher in patients not receiving oseltamivir treatment ($p=0.048$). – Benefit of oseltamivir was observed even after controlling for age (OR=0.24; 95% CI: 0.065, 0.916) or neutropenia as a marker of severity (Mantel-Haenszel summary OR=0.15; 95% CI: 0.026-0.893; $p=0.034$).
Madjid 2009	Retrospective cohort study Propensity score adjusted	49,238 treated with oseltamivir 102,692 no antiviral treatment	Adults with clinical influenza diagnosis	<ul style="list-style-type: none"> – Treated with oseltamivir within 1 day before or 2 days after diagnosis. – HR for stroke or transient ischaemic attack at 6 months was 0.717 (95% CI: 0.624, 0.823).
McGeer 2007	Prospective cohort study	327	Adult patients hospitalized for influenza	<ul style="list-style-type: none"> – 106 of 327 (32%) prescribed antivirals. – Antiviral treatment was associated with significant reduction in mortality (OR=0.21; 95% CI: 0.06, 0.80).
Nordstrom 2004	Post-marketing safety study	32,459	Physician diagnosis of influenza and/or prescription for oseltamivir	<ul style="list-style-type: none"> – Adjusted rate ratio for skin reactions for oseltamivir users versus non-users was 1.05 (95% CI: 0.88, 1.24) for incident cases and 0.98 (95% CI: 0.77, 1.24) for patients with history of skin reactions. – Oseltamivir not associated with increased risk of skin reactions.
Nordstrom 2005	Retrospective cohort study	11,632 taking oseltamivir 60,427 not taking oseltamivir	Individuals aged >1 year prescribed oseltamivir within 1 day of influenza diagnosis	<ul style="list-style-type: none"> – Pneumonia influenza-like illness: HR=0.72 (95% CI: 0.60, 0.86). – Hospital admission with oseltamivir: HR=0.74 (95% CI: 0.61, 0.90).

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Orzeck 2007	Retrospective cohort study	2919 treated with oseltamivir 6171 not prescribed treatment	Patients with diabetes treated with oseltamivir	<ul style="list-style-type: none"> - Patients treated with oseltamivir had 17% risk reduction for respiratory illness (RR=0.83; 95% CI: 0.73, 0.93). - A 30% risk reduction for hospitalization for any cause (RR=0.70; 95% CI: 0.52, 0.94). - No significant differences between groups for risk of pneumonia, otitis media or hospitalizations for pneumonia.
Peters 2008	Case control study	31,674 taking oseltamivir 31,674 matched controls	Children and adults taking oseltamivir within 1 day of onset of influenza symptoms	<ul style="list-style-type: none"> - Oseltamivir reduced risk of pneumonia by 15% (RR=0.85; 95% CI: 0.73, 0.98). - Risk reduction 20% for other respiratory illnesses (RR=0.80; 95% CI: 0.76, 0.83). - Risk reduction 30% for otitis media and other complications (RR=0.69; 95% CI: 0.61, 0.79). - Risk reduction 38% for overall hospital admission (RR=0.62; 95% CI: 0.52, 0.74).
Piedra 2009	Retrospective review	1634 received oseltamivir 3721 received no antiviral therapy	Paediatric patients receiving oseltamivir	<ul style="list-style-type: none"> - Oseltamivir was significantly associated with a reduction in respiratory illness other than pneumonia (OR=0.74; 95%CI: 0.63, 0.87), otitis media (OR=0.69; 95%CI: 0.48, 0.99), and all-cause hospitalizations (OR=0.33; 95%CI: 0.13, 0.83) within 14 and 30 days after diagnosis.
Tanaka 2009	Literature review	90 using oseltamivir 4 using zanamivir	Pregnant women using oseltamivir or zanamivir	<ul style="list-style-type: none"> - 1 malformation in 90 pregnancies with women using oseltamivir. - For 4 women using zanamivir, one spontaneous miscarriage, one termination and 2 healthy births.

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Settings: Outpatient
Bibliography: Blumenthals and Schulman (2007), Orzeck et al. (2007), and Gums et al. (2008).

Table A6.2

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							Oseltamivir	Control	Relative (95% CI)	Absolute		
Hospitalization (follow-up mean 14 days)												
3 ¹	observational studies	no serious limitations ²	no serious inconsistency	no serious indirectness ³	no serious imprecision	none	625/69929 (0.9%)	979/73080 (1.3%)	OR 0.73 (0.63 to 0.83) ⁴	4 fewer per 1000 (from 2 fewer to 5 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
						10%		25 fewer per 1000 (from 16 fewer to 35 fewer)				
						20%		46 fewer per 1000 (from 28 fewer to 64 fewer)				

1. Although 5 observational studies were identified, only three included the outcome hospitalization.
2. All of these studies were case-control studies. Although we did not downgrade for selection bias, this always is a concern with this study design.
3. The studies were performed in patients with seasonal influenza. We did not downgrade for indirectness in relation to Influenza H1N1 infection.
4. We used the adjusted OR or RR from each study and calculated a pooled OR. The study by Gums et al. used propensity score matching and the unadjusted OR was used.