

**EVIDENCE-BASED TABLES  
PROVIDED TO WHO GUIDELINES  
PANEL IN JUNE 2009**

## Annex 4: Evidence summaries and summaries of findings tables

Following are the GRADE evidence tables as well as tables providing a summary of results across the different populations assessed for each drug.

**Table A4.1: Summary of oseltamivir treatment results<sup>1</sup>**

Outcome/population	Oseltamivir N	Placebo N	Pooled results (WMD, hrs)
<b>Time to alleviation of symptoms for ITT population</b>			
Healthy adults	700	710	-13.59 (-25.15, -3.43)
Children (>1 year)	514	515	-21.05 (-33.81, -8.29)
Elderly	360	376	-10.00 (-45.05, 25.05)
At-risk	729	743	-17.84 (-36.20, 0.52)
Overall	2746	2290	-16.28 (-22.70, -9.86)
Conclusion	<ul style="list-style-type: none"> <li>statistically significant advantage for oseltamivir compared to placebo in healthy adults and children</li> <li>advantage in overall population of time to alleviation of symptoms of less than a day (16.28 hours).</li> </ul>		
<b>Time to alleviation of symptoms for ITT infected population</b>			
Healthy adults (WMD, hours)	579	603	-22.19 (-37.32, -7.07)
Children (>1 year) (WMD, hours)	301	330	-28.88 (-43.77, -14.0)
Elderly (median diff, hours)	223	254	-24.9 (-68.77, 18.97)
At-risk (WMD, hours)	425	482	-14.04 (-36.34, 8.26)
Overall	1221	1320	-22.75 (-33.39, -12.11)
Conclusion	<ul style="list-style-type: none"> <li>statistically significant advantage for oseltamivir compared to placebo in healthy adults and children</li> <li>advantage in overall population of time to alleviation of symptoms of less than a day (22.75 hours).</li> </ul>		
<b>Time to resume normal activity for ITT population</b>			
Healthy adults	481	480	-31.94 (-46.95, -16.93)
Children (>1 year)	331	338	-30.08 (-43.35, -16.81)
Elderly	359	375	-98.07 (-170.98, -25.16)
At-risk	558	576	-58.84 (-116.58, -1.11)
Overall	1370	1384	-34.80 (-45.73, -23.87)
Conclusion	<ul style="list-style-type: none"> <li>statistically significant advantage for oseltamivir compared to placebo in time to return to normal activity for all populations</li> <li>reduction in time to return to normal activity of greater than 1 day (34.8 hours) for oseltamivir compared to placebo for overall population.</li> </ul>		

Outcome/population	Oseltamivir N	Placebo N	Pooled results (WMD, hrs)
<b>Time to resume normal activity for ITT infected population</b>			
Healthy adults	301	309	-63.17 (-99.08, -27.27)
Children (>1 year)	293	320	-31.85 (-46.73, -16.96)
At-risk	425	482	-19.20 (-41.42, 3.01)
Overall	1637	1376	-36.31 (-48.44, -24.17)
Conclusion	<ul style="list-style-type: none"> <li>statistically significant advantage for oseltamivir compared to placebo in time to return to normal activity for healthy adults and children</li> <li>reduction in time to return to normal activity of greater than 1 day (36.3 hours) for oseltamivir compared to placebo for overall population.</li> </ul>		
<b>Occurrence of complications requiring hospitalization for ITT population</b>			
	Oseltamivir N	Placebo N	Pooled results (OR)
Healthy adults	6/1050 (0.6%)	6/1021 (0.6%)	0.97 (0.33, 2.90)
Children (>1 year)	0/344 (0%)	2/351 (0.6%)	0.20 (0.01, 4.24)
Elderly	3/223 (1.3%)	8/254 (3.1%)	0.42 (0.11, 1.6)
At-risk	0/165 (0%)	1/164 (1.6%)	0.33 (0.01, 8.84)
Conclusion	<ul style="list-style-type: none"> <li>small number of events, no advantage for oseltamivir compared to placebo.</li> </ul>		
<b>Occurrence of adverse events for ITT population</b>			
Healthy adults	35/247 (14.2%)	26/262 (9.9%)	1.45 (0.83, 2.53)
Conclusion	<ul style="list-style-type: none"> <li>no statistically significant difference between oseltamivir and placebo in occurrence of drug-related adverse events in healthy adult population; results not available for other populations.</li> </ul>		

Author(s): P Whyte

Date: 2009-06-03

Question: Should oseltamivir be used for influenza - adult population?

Settings: adult population

Bibliography: Burch 2008

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		
<b>Alleviation of symptoms (measured with: hours until alleviation of symptoms; Better indicated by lower values)</b>												
4	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	700	710	-	13.29 lower (25.15 to 3.43 lower)	+++ MODERATE	6
<b>Time to resume normal activity (measured with: hours until resumption of normal activity; Better indicated by lower values)</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	481	480	-	31.94 lower (46.95 to 16.93 lower)	+++ MODERATE	5.5
<b>Rate of overall complications</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	18/210 (8.6%)	28/209 (13.4%)	OR 0.61 (0.32 to 1.13)	48 fewer per 1000 (from 87 fewer to 15 more)	+++ MODERATE	7
<b>Complications requiring hospitalization</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	6/1050 (0.6%)	6/1021 (0.6%)	OR 0.97 (0.33 to 2.9)	0 fewer per 1000 (from 4 fewer to 11 more)	+++ MODERATE	7
<b>Drug-related adverse events</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	35/247 (14.2%)	26/262 (9.9%)	OR 1.45 (0.83 to 2.53)	39 more per 1000 (from 15 fewer to 119 more)	+++ MODERATE	6.5
<b>Serious adverse events</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	1/488 (0.2%)	3/497 (0.6%)	OR 0.32 (0.03 to 1.17)	4 fewer per 1000 (from 6 fewer to 1 more)	+++ MODERATE	8

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Author(s):** P Whyte

**Date:** 2009-06-04

**Question:** Should oseltamivir be used for influenza - at-risk population?<sup>1</sup>

**Settings:** at-risk population

**Bibliography:** Burch 2008

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		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	729	743	-	17.84 lower (36.2 lower to 0.52 higher)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
5	randomised trials	no serious limitations	no serious inconsistency	serious		none	558	576	-	58.84 lower (116.58 to 1.11 lower)		5.5
<b>Complications requiring hospitalization</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	0/165 (0%)	1/164 (0.6%)	OR 0.33 (0.01 to 8.14)	4 fewer per 1000 (from 6 fewer to 41 more)	+++ MODERATE	7
<b>Overall adverse events</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	85/228 (37.3%)	84/224 (37.5%)	OR 0.96 (0.63 to 1.46)	10 fewer per 1000 (from 101 fewer to 92 more)	+++ MODERATE	

1. 'At-risk' population defined in Burch et al.1 as patients, including adults and children with co-morbid conditions, as well as elderly patients.
2. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

Author(s): P Whyte

Date: 2009-06-04

Question: Should oseltamivir be used for influenza - children?

Settings: children

Bibliography: Burch 2008

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		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
2 <sup>1</sup>	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	514	515	-	21.05 lower (33.81 to 8.29 lower)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	331	338	-	30.08 lower (43.35 to 16.81 lower)	+++ MODERATE	5.5
<b>Complications requiring hospitalization</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	0/344 (0%)	2/351 (0.6%)	OR 0.20 (0.01 to 4.24)	5 fewer per 1000 (from 6 fewer to 18 more)	+++ MODERATE	7
<b>Overall adverse events</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	83/170 (48.8%)	84/164 (51.2%)	OR 0.91 (0.59 to 40)	24 fewer per 1000 (from 130 fewer to 465 more)	+++ MODERATE	

1. Includes one trial with 'at-risk' children (i.e. those with co-morbidities). This trial was also included in the 'at-risk' population.
2. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Author(s):** P Whyte

**Date:** 2009-06-04

**Question:** Should oseltamivir be used for influenza - elderly?

**Settings:** elderly

**Bibliography:** Burch 2008

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		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	360	376	-	10.00 lower (45.05 lower to 25.05 higher)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	359	375	-	98.07 lower (170.98 to 25.16 lower)	+++ MODERATE	5.5
<b>Complications requiring hospitalization</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	3/223 (1.3%)	8/254 (3.1%)	OR 0.42 (0.11 to 1.6)	18 fewer per 1000 (from 28 fewer to 18 more)	+++ MODERATE	7

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

Author(s): P Whyte

Date: 2009-06-04

Question: Should oseltamivir be used for influenza - all populations combined?

Settings: all populations

Bibliography: Burch 2008

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							oseltamivir	control	Relative (95% CI)	Absolute		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
9	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	2746	2290	-	16.28 lower (22.7 to 9.86 lower)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
9	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	1370	1384	-	34.80 lower (45.73 to 23.87 lower)	+++ MODERATE	5.5

- All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

Table A4.2: Summary of zanamivir treatment results<sup>1</sup>

Outcome/population	Zanamivir N	Placebo N	Pooled results (WMD, days)
<b>Time to alleviation of symptoms for ITT population</b>			
Healthy adults	1368	1333	-0.57 (-1.07, -0.08)
Children (>1 year)	400	337	-0.94 (-1.43, -0.46)
Elderly	249	226	-1.13 (-2.90, 0.63)
At-risk	622	630	-0.98 (-1.84, -0.11)
Overall	2320	2218	-0.71 (-1.04, -0.41)
Conclusion	statistically significant advantage for zanamivir compared to placebo for healthy adults, children, at-risk and overall populations with time to alleviation of symptoms less than a day (0.71 days).		
<b>Time to alleviation of symptoms for ITT infected population</b>			
Healthy adults (WMD, days)	948	878	-0.96 (-1.38, -0.54)
Children (>1 year) (median diff, days)	164	182	-1.00 (-1.60, -0.40)
Elderly (WMD, days)	165	158	-1.85 (-4.77, 1.07)
At-risk (WMD, days)	364	366	-1.83 (-2.81, -0.86)
Overall (WMD, days)	1455	1410	-1.07 (-1.39, -0.74)
Conclusion	<ul style="list-style-type: none"> <li>statistically significant advantage for zanamivir compared to placebo for healthy adults, children, at-risk and overall populations with time to alleviation of symptoms greater than a day (1.07 days).</li> </ul>		

Outcome/population	Zanamivir N	Placebo N	Pooled results (WMD, days)
<b>Time to resume normal activity for ITT population</b>			
Healthy adults	1533	1492	-0.37 (-0.84, 0.09)
Children (>1 year)	224	247	-0.50 (-1.25, 0.25)
At-risk	304	309	-0.96 (-2.32, 0.41)
Conclusion	<ul style="list-style-type: none"> <li>no statistically significant advantage for zanamivir compared to placebo for time to resume normal activity in healthy adults, children or at-risk population.</li> </ul>		
<b>Time to resume normal activity for ITT infected population</b>			
Healthy adults (WMD, days)	1044	979	-0.39 (-0.84, 0.06)
Children (>1 year) (median diff, days)	164	182	-0.50 (-1.35, 0.35)
At-risk (WMD, days)	381	383	-1.89 (-3.95, 0.17)
Conclusion	<ul style="list-style-type: none"> <li>no statistically significant advantage for zanamivir compared to placebo for time to resume normal activity in healthy adults, children or at-risk population.</li> </ul>		
<b>Occurrence of complications requiring hospitalization for ITT population</b>			
	Zanamivir N	Placebo N	Pooled results (OR)
Healthy adults	48/293 (16.4%)	37/295 (12.5%)	1.37 (0.86, 2.17)
Children (>1 year)	1/176 (0.6%)	0/90 (0%)	1.55 (0.06, 38.36)
At-risk	3/261 (1.1%)	6/263 (2.3%)	0.50 (0.12, 2.01)
Overall	52/730 (7.1%)	43/648 (6.6%)	1.24 (0.8, 1.92)
Conclusion	<ul style="list-style-type: none"> <li>all results based on single trial for each population; no advantage for zanamivir compared to placebo.</li> </ul>		
<b>Occurrence of adverse events for ITT population</b>			
Healthy adults	62/691 (9.0%)	60/715 (8.4%)	1.11 (0.76, 1.62)
Children (>1 year)	18/400 (4.5%)	10/337 (3.3%)	1.32 (0.59, 2.92)
At-risk	23/261 (8.8%)	23/263 (8.7%)	1.01 (0.55, 1.85)
Overall	149/1771 (8.4%)	152/1737 (8.8%)	0.97 (0.76, 1.24)
Conclusion	<ul style="list-style-type: none"> <li>no statistically significant difference between zanamivir and placebo in occurrence of drug-related adverse events across all populations.</li> </ul>		

Author(s): P Whyte

Date: 2009-06-04

Question: Should zanamivir be used for influenza - adult population?

Settings: adult population

Bibliography: Burch 2008

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
6	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	1368	1333	-	0.57 lower (1.07 to 0.08 lower)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
7	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	1533	1492	-	0.37 lower (0.84 lower to 0.09 higher)	+++ MODERATE	5.5
<b>Complications requiring hospitalization</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	48/293 (16.4%)	37/295 (12.5%)	OR 1.37 (0.86 to 2.17)	39 more per 1000 (from 16 fewer to 112 more)	+++ MODERATE	7
<b>Drug-related adverse events</b>												
4	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	62/691 (9%)	60/715 (8.4%)	OR 1.11 (0.76 to 1.62)	8 more per 1000 (from 19 fewer to 45 more)	+++ MODERATE	6.5
<b>Serious adverse events</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	3/559 (0.5%)	2/571 (0.4%)	OR 1.44 (0.28 to 7.35)	2 more per 1000 (from 3 fewer to 22 more)	+++ MODERATE	8

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Author(s):** P Whyte

**Date:** 2009-06-04

**Question:** Should zanamivir be used for influenza - at-risk population?<sup>1</sup>

**Settings:** at-risk population

**Bibliography:**

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
7	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	622	630	-	0.98 lower (1.84 to 0.11 lower) <sup>3</sup>	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
6	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	304	309	-	0.96 lower (2.32 lower to 0.41 higher) <sup>4</sup>	+++ MODERATE	5.5
<b>Rate of overall complications</b>												
4	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	83/290 (28.6%)	102/285 (35.8%)	OR 0.73 (0.51 to 1.04)	69 fewer per 1000 (from 137 fewer to 9 more)	+++ MODERATE	7
<b>Complications requiring hospitalization</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	3/261 (1.1%)	6/263 (2.3%)	OR 0.50 (0.12 to 2.01)	11 fewer per 1000 (from 20 fewer to 22 more)	+++ MODERATE	7
<b>Drug-related adverse events</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	23/261 (8.8%)	23/263 (8.7%)	OR 1.01 (0.55 to 1.85)	1 more per 1000 (from 37 fewer to 63 more)	+++ MODERATE	6.5
<b>Serious adverse events</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	10/675 (1.5%)	17/535 (3.2%)	OR 0.72 (0.32 to 1.62)	9 fewer per 1000 (from 21 fewer to 19 more)	+++ MODERATE	8

1. Including children and adults with co-morbidities and elderly patients.
2. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
3. When trial with children as subjects was removed, leaving only adult subjects, results were similar, with WMD= -0.95 (95% CI: -1.83, -0.07).
4. When trial with children was removed, leaving only adult subjects, results were similar and remained non-significant with WMD= -1.07 (95% CI: -2.81, 0.68).

Author(s): P Whyte

Date: 2009-06-05

Question: Should zanamivir be used for influenza - children?

Settings: children

Bibliography: Burch 2008

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	400	337	-	0.94 lower (1.43 to 0.46 lower) <sup>2</sup>	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	224	247	-	0.50 lower (1.25 lower to 0.25 higher)	+++ MODERATE	5.5
<b>Overall complications</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	96/396 (24.2%)	81/336 (24.1%)	OR 0.88 (0.62 to 1.24)	23 fewer per 1000 (from 77 fewer to 42 more)	+++ MODERATE	7
<b>Complications requiring hospitalization</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	1/176 (0.6%)	0/90 (0%)	OR 1.55 (0.06 to 38.36)	0 more per 1000 (from 0 fewer to 0 more)	+++ MODERATE	7
<b>drug-related adverse events</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	18/400 (4.5%)	10/337 (3%)	OR 1.32 (0.59 to 2.92)	9 more per 1000 (from 12 fewer to 52 more)	+++ MODERATE	6.5
<b>Serious adverse events</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	2/400 (0.5%)	0/337 (0%)	OR 2.29 (0.24 to 22.09)	0 more per 1000 (from 0 fewer to 0 more)	+++ MODERATE	8

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
2. When the population from one of the included trials was split into healthy and at-risk children, the statistically significant advantage for zanamivir remained for healthy children although there was no difference between zanamivir and placebo in at-risk children. However the at-risk population was small, including 22 patients treated with zanamivir and 14 with placebo.

**Author(s):** P Whyte

**Date:** 2009-06-05

**Question:** Should zanamivir be used for influenza - elderly?

**Settings:** elderly

**Bibliography:** Burch 2008

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
5	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	249	226	-	1.13 lower (2.9 lower to 0.63 higher)	+++ MODERATE	6
<b>Overall complications</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	57/191 (29.8%)	56/167 (33.5%)	OR 0.84 (0.54 to 1.32)	38 fewer per 1000 (from 121 fewer to 64 more)	+++ MODERATE	7

- All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

Author(s): P Whyte

Date: 2009-06-05

Question: Should zanamivir be used for influenza - all populations combined?

Settings: all populations

Bibliography:

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
11	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	2320	2218	-	0.71 lower (1.01 to 0.41 lower)	+++ MODERATE	6
<b>Overall complications</b>												
6	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	316/1400 (22.6%)	348/1278 (27.2%)	OR 0.75 (0.63 to 0.9)	53 fewer per 1000 (from 20 fewer to 82 fewer)	+++ MODERATE	7
<b>Complications requiring hospitalization</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	52/730 (7.1%)	43/648 (6.6%)	OR 1.24 (0.8 to 1.92)	15 more per 1000 (from 13 fewer to 54 more)	+++ MODERATE	7
<b>Drug-related adverse events</b>												
8	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	149/1771 (8.4%)	152/1737 (8.8%)	OR 0.97 (0.76 to 1.24)	2 fewer per 1000 (from 20 fewer to 19 more)	+++ MODERATE	6.5
<b>Serious adverse events</b>												
11	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	23/2447 (0.9%)	26/2218 (1.2%)	OR 0.78 (0.44 to 1.4)	3 fewer per 1000 (from 7 fewer to 5 more)	+++ MODERATE	8

- All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Table A4.3: Summary of results for amantadine**

Outcome/population	Amantadine N or n/N	Placebo N or n/N	Pooled results
Adults (duration fever)	250	292	MD=-0.99 (-1.26, -0.71)
Children (>1 year; cases on day 3)	4/51 (7.8%)	12/53(22.6%)	RR=0.37 (0.08, 1.75)
Conclusion	<ul style="list-style-type: none"> <li>advantage for amantadine compared to placebo in adults (one day less of fever) and children, however trials are small.</li> </ul>		

**Author(s):** P Whyte

**Date:** 2009-06-05

**Question:** Should amantadine be used for influenza - adults?

**Settings:** adults

**Bibliography:** Jefferson 2006

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							amantadine	control	Relative (95% CI)	Absolute		
<b>Duration fever (days) (Better indicated by lower values)</b>												
10	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious	none	250	292	-	MD 0.99 lower (1.26 to 0.71 lower)	++ LOW	
<b>Duration of hospitalization (Better indicated by lower values)</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	20	16	-	MD 0.90 lower (2.2 lower to 0.4 higher)	++ LOW	6.5
<b>Viral nasal shedding</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>2</sup>	serious <sup>4</sup>	none	62/75 (82.7%)	87/95 (91.6%)	RR 0.97 (0.76 to 1.24)	27 fewer per 1000 (from 220 fewer to 220 more)	++ LOW	6

1. All trials are were conducted in the 1960's and early 1970's; in addition the trials were relatively small, with N's ranging from less than 20 to 150.
2. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
3. Relatively old trial (1970) with small n (36 total subjects).
4. Two trials from the 1960's and one from the early 1980's, all with small N.

Author(s): P Whyte

Date: 2009-06-05

Question: Should rimantadine be used for influenza - adults?

Settings: adults

Bibliography: Jefferson 2006

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							rimantadine	control	Relative (95% CI)	Absolute		
<b>Duration of fever (Better indicated by lower values)</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	36	46	-	MD 1.24 lower (1.71 to 0.76 lower)	++ LOW	
<b>Viral nasal shedding</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	46/69 (66.7%)	77/83 (92.8%)	RR 0.68 (0.3 to 1.53)	297 fewer per 1000 (from 649 fewer to 492 more)	++ LOW	6

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
2. All trials had small N's, ranging from less than 15 to 50, two trials were conduct in the 1960's and one in the 1980's.

Author(s):

Date: 2009-06-05

Question: Should amantadine be used for influenza - children?

Settings: children

Bibliography: Alves Galvao 2008

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							amantadine	control	Relative (95% CI)	Absolute		
<b>Response to treatment (cases of fever on day 3)</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	4/51 (7.8%)	12/53 (22.6%)	RR 0.37 (0.08 to 1.75)	143 fewer per 1000 (from 208 fewer to 170 more)	++ LOW	

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
2. Both trials are small (n of approximately 50) and date from the 1960's.

Table A4.4: Summary of results for rimantadine

Rimantadine	Rimantadine N or n/N	Placebo N or n/N	Pooled results
Healthy adults (duration fever)	36	46	MD=-1.24 (-1.71, -0.76)
Children (> 1 year; cases on day 3)	5/37 (13.5%)	12/32(37.5%)	RR=0.36 (0.14, 0.91)
Conclusion	<ul style="list-style-type: none"> <li>• advantage for rimantadine compared to placebo in adults (&gt;one day reduction of fever) and children, however trials are small.</li> </ul>		

**Author(s):** P Whyte

**Date:** 2009-06-05

**Question:** Should rimantadine be used for influenza - children?

**Settings:** children

**Bibliography:**

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							rimantadine	control	Relative (95% CI)	Absolute		
<b>Response to treatment (cases of fever on day 3)</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	5/37 (13.5%)	12/32 (37.5%)	RR 0.36 (0.14 to 0.91)	240 fewer per 1000 (from 34 fewer to 322 fewer) <sup>2</sup>	+++ MODERATE	

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
2. No explanation was provided.

Author(s): P Whyte

Date: 2009-06-09

Question: Should oseltamivir be used for influenza - infected adults?

Settings: adults with confirmed infection

Bibliography: Burch 2008

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		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
6	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	579	603	-	22.19 lower (37.32 to 7.07 lower)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	301	309	-	63.17 lower (99.08 to 27.27 lower)	+++ MODERATE	5.5
<b>Overall complications</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	20/277 (7.2%)	27/287 (9.4%)	OR 0.75 (0.41 to 1.37)	22 fewer per 1000 (from 53 fewer to 30 more)	+++ MODERATE	7

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Author(s):** P Whyte

**Date:** 2009-06-09

**Question:** Should oseltamivir be used for influenza - infected at-risk population?

**Settings:**

**Bibliography:** Burch 2008

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		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	425	482	-	14.04 lower (36.34 lower to 8.26 higher)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
6	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	425	482	-	19.20 lower (41.42 lower to 3.01 higher)	+++ MODERATE	5.5
<b>Overall complications</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	1/43 (2.3%)	8/51 (15.7%)	OR 0.13 (0.02 to 1.07)	133 fewer per 1000 (from 153 fewer to 9 more)	++ LOW	7
<b>Complications requiring hospitalization</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	7/334 (2.1%)	14/378 (3.7%)	OR 0.54 (0.21 to 1.37)	17 fewer per 1000 (from 29 fewer to 13 more)	+++ MODERATE	7
<b>Serious adverse events</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	1/43 (2.3%)	1/51 (2%)	OR 1.19 (0.07 to 19.62)	4 more per 1000 (from 18 fewer to 262 more)	++ LOW	8

- All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
- Only one small trial (n=94 total).

Author(s): P Whyte

Date: 2009-06-09

Question: Should oseltamivir be used for influenza - infected children?

Settings: infected children

Bibliography: Burch 2008

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		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	301	330	-	28.88 lower (43.77 to 14 lower)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	293	320	-	31.85 lower (46.73 to 16.96 lower)	+++ MODERATE	5.5
<b>Complications requiring hospitalization</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	2/301 (0.7%)	3/335 (0.9%)	OR 0.79 (0.16 to 4.02)	2 fewer per 1000 (from 8 fewer to 26 more)	+++ MODERATE	7

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Author(s):** P Whyte

**Date:** 2009-06-09

**Question:** Should oseltamivir be used for influenza - infected elderly population?

**Settings:** infected elderly

**Bibliography:** Burch 2008

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		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	223	254	-	median 24.9 lower (68.77 lower to 18.97 higher)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	223	254	-	73.68 lower (151.2 lower to 3.84 higher)	+++ MODERATE	5.5
<b>Complications requiring hospitalization</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	3/223 (1.3%)	8/254 (3.1%)	OR 0.42 (0.11 to 1.6)	18 fewer per 1000 (from 28 fewer to 18 more)	+++ MODERATE	7

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

Author(s): P Whyte

Date: 2009-06-09

Question: Should oseltamivir be used for influenza - infected overall population?

Settings: infected overall population

Bibliography: Burch 2008

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		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
10	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	1221	1320	-	22.75 lower (33.39 to 12.11 lower)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
11	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	1637	1376	-	36.31 lower (48.44 to 24.17 lower)	+++ MODERATE	5.5
<b>Overall complications</b>												
4	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	33/320 (10.3%)	41/338 (12.1%)	OR 0.88 (0.28 to 2.76)	13 fewer per 1000 (from 84 fewer to 155 more)	+++ MODERATE	7
<b>Complications requiring hospitalization</b>												
4	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	9/351 (2.6%)	21/402 (5.2%)	OR 0.47 (0.2 to 1.11)	27 fewer per 1000 (from 41 fewer to 5 more)	+++ MODERATE	7

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Author(s):** P Whyte

**Date:** 2009-06-09

**Question:** Should zanamivir be used for influenza - infected adults?

**Settings:** infected adults

**Bibliography:** Burch 2008

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
6	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	948	878	-	0.96 lower (1.38 to 0.54 lower)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
7	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>		none	1044	979	-	0.39 lower (0.84 lower to 0.06 higher)		5.5
<b>Overall complications</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	115/222 (51.8%)	108/213 (50.7%)	OR 1.04 (0.72 to 1.52)	10 more per 1000 (from 82 fewer to 103 more)	++ LOW	7

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
2. Only one trial.

Author(s): P Whyte

Date: 2009-06-09

Question: Should zanamivir be used for influenza - infected at-risk population?

Settings: infected at-risk population

Bibliography: Burch 2008

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
6	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	364	366	-	1.83 lower (2.81 to 0.86 lower)	+++ MODERATE	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
7	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	381	383	-	1.89 lower (3.95 lower to 0.17 higher) <sup>2</sup>	+++ MODERATE	5.5
<b>Overall complications</b>												
4	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	107/328 (32.6%)	121/328 (36.9%)	OR 0.82 (0.59 to 1.13)	45 fewer per 1000 (from 112 fewer to 29 more)	+++ MODERATE	7
<b>Complications requiring hospitalization</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	5/120 (4.2%)	4/114 (3.5%)	OR 1.20 (0.31 to 4.57)	7 more per 1000 (from 24 fewer to 107 more)	+++ MODERATE	7

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
2. For at-risk children only, difference is statistically significantly different, with WMD=-2.50 (95% CI: -4.37, -0.63).

**Author(s):** P Whyte

**Date:** 2009-06-09

**Question:** Should zanamivir be used for influenza - infected children?

**Settings:** infected children

**Bibliography:** Burch 2008

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	164	182	-	median 1.00 lower (1.6 to 0.4 lower)	++ LOW	6
<b>Time to resume normal activity (Better indicated by lower values)</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	164	182	-	median 0.50 lower (1.36 lower to 0.35 higher)	++ LOW	5.5
<b>Overall complications</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	26/164 (15.9%)	41/182 (22.5%)	OR 0.65 (0.38 to 1.12)	66 fewer per 1000 (from 126 fewer to 20 more)	++ LOW	7

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
2. Only one trial.

Author(s): P Whyte

Date: 2009-06-09

Question: Should zanamivir be used for influenza - infected elderly population?

Settings: infected elderly population

Bibliography: Burch 2008

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
5	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	165	158	-	1.85 lower (4.77 lower to 7 higher)	+++ MODERATE	6
<b>Overall complications</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	39/120 (32.5%)	46/114 (40.4%)	OR 0.71 (0.42 to 1.21)	79 fewer per 1000 (from 182 fewer to 47 more)	++ LOW	7
<b>Complications requiring hospitalization</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	5/120 (4.2%)	4/114 (3.5%)	OR 1.20 (0.31 to 4.57)	7 more per 1000 (from 24 fewer to 107 more)	++ LOW	7

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
2. Only one trial.

**Author(s):** P Whyte

**Date:** 2009-06-09

**Question:** Should zanamivir be used for influenza - infected overall population?

**Settings:** infected overall population

**Bibliography:** Burch 2008

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Alleviation of symptoms (Better indicated by lower values)</b>												
13	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	1455	1410	-	1.07 lower (1.39 to 0.74 lower)	+++ MODERATE	6
<b>Overall complications</b>												
7	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	352/1341 (26.2%)	403/1288 (31.3%)	OR 0.77 (0.65 to 0.92)	53 fewer per 1000 (from 18 fewer to 84 fewer)	+++ MODERATE	7
<b>Complications requiring hospitalization</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	39/342 (11.4%)	24/327 (7.3%)	OR 1.64 (0.96 to 2.81)	42 more per 1000 (from 3 fewer to 109 more)	+++ MODERATE	7

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Table A4.5: Prophylaxis - occurrence of infection**

<b>Drug/population</b>			
Oseltamivir (symptomatic laboratory confirmed infection)	<b>Oseltamivir n/N</b>	<b>Placebo n/N</b>	<b>Pooled results (RR)</b>
Healthy adults	6/520 (1.2%)	25/519 (4.8%)	0.27 (0.09, 0.83)
Elderly	1/276 (0.4%)	12/272 (4.4%)	0.08 (0.01, 0.63)
Post-exposure (mixed households)			0.19 (0.08, 0.45)
Conclusion	<ul style="list-style-type: none"> <li>statistically significantly fewer cases of infection associated with oseltamivir prophylaxis in adult and elderly populations.</li> </ul>		
Zanamivir (symptomatic laboratory confirmed infection)	<b>Zanamivir n/N</b>	<b>Placebo n/N</b>	<b>Pooled results (RR)</b>
Healthy adults	11/553 (2.0%)	34/554 (6.1%)	0.32 (0.17, 0.63)
At-risk	4/1678 (0.2%)	23/1685 (1.4%)	0.17 (0.07, 0.44)
Conclusion	<ul style="list-style-type: none"> <li>statistically significantly fewer cases of infection associated with zanamivir prophylaxis in adults and at-risk populations.</li> </ul>		
Amantadine (influenza infection)	<b>Amantadine n/N</b>	<b>Placebo n/N</b>	<b>Individual trial results (RR)</b>
Healthy adults	2/159 (1.3%)	5/159 (3.1%)	0.40 (0.08, 2.03)
Children (>1 year)	4/371 (1.1%)	40/402 (10%)	0.11 (0.04, 0.30)
Conclusion	<ul style="list-style-type: none"> <li>no advantage for amantadine prophylaxis in adults, however this is based on a small number of subjects;</li> <li>statistically significant advantage in children.</li> </ul>		
Rimantadine (influenza infection)	<b>Rimantadine N or n/N</b>	<b>Placebo N or n/N</b>	<b>Pooled results (RR)</b>
Healthy adults	20/347 (5.8%)	54/341 (15.8%)	0.28 (0.08, 1.28)
Children (> 1 year)	8/84 (9.5%)	22/94 (23.4%)	0.49 (0.21, 1.15)
Conclusion	<ul style="list-style-type: none"> <li>no statistically significant advantage for rimantadine compared to placebo for prophylaxis in adults or children, however direction of results favours rimantadine.</li> </ul>		

**Author(s):** P Whyte

**Date:** 2009-06-05

**Question:** Should amantadine be used for prophylaxis in adults?

**Settings:** adults

**Bibliography:** Tappenden 2009; Jefferson 2006

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							amantadine	control	Relative (95% CI)	Absolute		
<b>Influenza infection</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	2/159 (1.3%)	5/159 (3.1%)	RR 0.40 (0.08 to 2.03)	19 fewer per 1000 (from 29 fewer to 32 more)	+++ MODERATE	8
<b>Total adverse events</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	47/159 (29.6%)	49/159 (30.8%)	RR 0 (0 to 0) <sup>2</sup>	308 fewer per 1000 (from 308 fewer to 308 fewer)	+++ MODERATE	
<b>Influenza infection Jefferson 2006</b>												
11	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	146/2396 (6.1%)	280/2249 (12.4%)	RR 0.39 (0.24 to 0.65)	76 fewer per 1000 (from 44 fewer to 95 fewer)	+++ MODERATE	8
<b>Total adverse events Jefferson 2006</b>												
6	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	386/2624 (14.7%)	172/1650 (10.4%)	RR 1.70 (0.99 to 2.93)	73 more per 1000 (from 1 fewer to 201 more)	+++ MODERATE	
<b>Viral nasal shedding</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>3</sup>	none	36/59 (61%)	18/20 (90%)	RR 0.68 (0.53 to 0.87)	288 fewer per 1000 (from 117 fewer to 423 fewer)	++ LOW	7.5

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
2. Only proportion reporting AEs was provided, no comparison was provided.
3. Small trial with 59 subjects in the amantadine arm and 20 in the control arm.

Author(s): P Whyte

Date: 2009-06-05

Question: Should oseltamivir be used for prophylaxis in adults?

Settings: adults

Bibliography: Tappenden 2009

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							oseltamivir	control	Relative (95% CI)	Absolute		
<b>Symptomatic laboratory confirmed infection</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	6/520 (1.2%)	25/519 (4.8%)	RR 0.27 (0.09 to 0.83)	35 fewer per 1000 (from 8 fewer to 44 fewer)	+++ MODERATE	8

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

Author(s): P Whyte

Date: 2009-06-05

Question: Should oseltamivir be used for prophylaxis in the elderly?

Settings: elderly

Bibliography: Tappenden 2009

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							oseltamivir	control	Relative (95% CI)	Absolute		
<b>Symptomatic laboratory confirmed infection</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	1/276 (0.4%)	12/272 (4.4%)	RR 0.08 (0.01 to 0.63)	41 fewer per 1000 (from 16 fewer to 44 fewer)	+++ MODERATE	8

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Author(s):** P Whyte

**Date:** 2009-06-05

**Question:** Should zanamivir be used for prophylaxis for adults?

**Settings:** adults

**Bibliography:** Tappenden 2009

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Symptomatic laboratory confirmed influenza</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	11/553 (2%)	34/554 (6.1%)	RR 0.32 (0.17 to 0.63)	42 fewer per 1000 (from 23 fewer to 51 fewer)	+++ MODERATE	8

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Author(s):** P Whyte

**Date:** 2009-06-05

**Question:** Should zanamivir be used for prophylaxis for at-risk adults and adolescents?

**Settings:** at-risk adults and adolescents

**Bibliography:** Tappenden 2009

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							zanamivir	control	Relative (95% CI)	Absolute		
<b>Symptomatic laboratory confirmed infection</b>												
1	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	4/1678 (0.2%)	23/1685 (1.4%)	RR 0.17 (0.07 to 0.44)	11 fewer per 1000 (from 8 fewer to 13 fewer)	+++ MODERATE	8

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Author(s):** P Whyte

**Date:** 2009-06-08

**Question:** Should amantadine be used for prophylaxis in children?

**Settings:** children

**Bibliography:** Alves Galvao 2008

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							amantadine	control	Relative (95% CI)	Absolute		
<b>Cases of infection</b>												
2	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	4/371 (1.1%)	40/402 (10%)	RR 0.11 (0.04 to 0.3)	89 fewer per 1000 (from 70 fewer to 96 fewer)	+++ MODERATE	8

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

**Author(s):** P Whyte

**Date:** 2009-06-08

**Question:** Should rimantadine be used for prophylaxis in children?

**Settings:** children

**Bibliography:** Alves Galvao 2008

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							rimantadine	control	Relative (95% CI)	Absolute		
<b>Cases of infection</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	8/84 (9.5%)	22/94 (23.4%)	RR 0.49 (0.21 to 1.15)	119 fewer per 1000 (from 185 fewer to 35 more)	++ LOW	8

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
2. Three relatively small trials, with the total numbers across all trials less than 100 in each arm.

**Author(s):** P Whyte

**Date:** 2009-06-08

**Question:** Should rimantadine be used for prophylaxis in children and elderly?

**Settings:** both children and elderly

**Bibliography:** Alves Galvao 2008

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							rimantadine	control	Relative (95% CI)	Absolute		
<b>Cases of infection</b>												
5	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	serious <sup>2</sup>	none	14/156 (9%)	27/125 (21.6%)	RR 0.49 (0.27 to 0.92)	110 fewer per 1000 (from 17 fewer to 158 fewer)	++ LOW	8

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
2. The authors caution there may be differences across the trials in addition to age that could impact results. In addition, follow-up ranged from 3 to 11 weeks across the trials and all trials had relatively small N's with most less than 50 subjects total.

**Author(s):** P Whyte

**Date:** 2009-06-08

**Question:** Should rimantadine be used for prophylaxis in adults?

**Settings:** adults

**Bibliography:** Jefferson 2006

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							rimantadine	control	Relative (95% CI)	Absolute		
<b>Influenza infection</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	20/347 (5.8%)	54/341 (15.8%)	RR 0.28 (0.08 to 1.08)	114 fewer per 1000 (from 146 fewer to 13 more)	+++ MODERATE	8
<b>Total adverse events</b>												
3	randomised trials	no serious limitations	no serious inconsistency	serious <sup>1</sup>	no serious imprecision	none	52/279 (18.6%)	30/279 (10.8%)	RR 1.96 (1.19 to 3.22)	103 more per 1000 (from 20 more to 239 more)	+++ MODERATE	

1. All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

## Annex 5: Summary of observational data

The following table includes observational studies which the Panel members used to obtain information regarding outcomes that were not included in the systematic reviews, for example complications. Observational studies assessing efficacy outcomes are not included here.

**Table A5.1: Other outcomes observational data**

Other outcomes	Design/results
<b>Complications</b>	
Bowles 2002 <sup>13</sup>	<ul style="list-style-type: none"> <li>Assessment of use of oseltamivir in nursing home residents (n=178) found that compared to residents receiving no therapy or who became ill using amantadine, the use of oseltamivir within 48 hours of symptom onset resulted in significantly less use of antibiotics, fewer hospitalizations and fewer deaths</li> </ul>
Blumentals 2007 <sup>14</sup>	<ul style="list-style-type: none"> <li>Retrospective cohort analysis of 36,751 US patients treated with oseltamivir compared to matched sample receiving no antiviral showed reduction in risk of otitis media of 23% (HR=0.77; 95% CI: 0.65, 0.93); any respiratory disease by 18% (HR=0.82; 95% CI: 0.79, 0.86); and hospitalization for any reason by 22% (HR=0.78; 95% CI: 0.67, 0.91).</li> </ul>
Cole 2002 <sup>7</sup>	<ul style="list-style-type: none"> <li>Retrospective comparison of patients treated with zanamivir (n=2341) and those untreated (n=2337) showed occurrence of complications were similar between the two groups</li> </ul>
Gums 2008 <sup>3</sup>	<ul style="list-style-type: none"> <li>Retrospective review of health care claims for 45,751 patients treated with oseltamivir and matched untreated controls found 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). Risks of pneumonia and otitis media also lower in those aged ≤17 years. Healthcare use and costs also less for those using oseltamivir compared to those untreated.</li> </ul>
Lee 2007 <sup>15</sup>	<ul style="list-style-type: none"> <li>Retrospective cohort study of patients hospitalized for influenza (n=356) found significantly shorter length of stay for those treated with oseltamivir within 2 days of illness compared to those receiving no treatment or treatment on days 3-4.</li> </ul>
Kaiser 2003 <sup>16</sup>	<ul style="list-style-type: none"> <li>Analysis of data from 10 trials of oseltamivir versus placebo in influenza, assessing occurrence of lower respiratory tract complications leading to antibiotic use and hospitalizations. Analysis found that oseltamivir reduced overall antibiotic use for any reason by 26.7% (14.0% versus 19.1% with placebo: p&lt;0.001) and reduced incidence of influenza-related lower respiratory tract infections leading to antibiotic use by 55% (4.6% compared to 10.3% with placebo: p&lt;0.001) for patients with confirmed illness. Also statistically significantly fewer oseltamivir-treated at-risk patients required antibiotic use 34.0% reduction: p=0.02).</li> </ul>

Other outcomes	Design/results
Orzeck 2007 <sup>17</sup>	<ul style="list-style-type: none"> <li>Retrospective cohort study of patients with diabetes treated with oseltamivir (n=2919) compared to those who were not prescribed treatment (n=6171) found that patients receiving oseltamivir had 17% reduction in risk of Respiratory illness (RR=0.83; 95 % CI: 0.73, 0.93); and 30% reduction in risk of hospitalization for any reason (RR=0.70; 95% CI: 0.52, 0.94). No significant differences between groups for risk of pneumonia, otitis media or hospitalizations for pneumonia.</li> </ul>
<b>Mortality</b>	
McGeer 2007 <sup>18</sup>	<ul style="list-style-type: none"> <li>Prospective cohort study of patients hospitalized for influenza found that 106 of 327 adult patients were prescribed antivirals and antiviral treatment was associated with a significant reduction in mortality (OR=0.21; 95% CI: 0.06, 0.80).</li> </ul>
<b>Neonates</b>	
Kiso 2004 <sup>19</sup>	<ul style="list-style-type: none"> <li>6 children aged less than 1 year were treated with oseltamivir, however no efficacy results provided, only assessment of development of mutations</li> </ul>
<b>Pregnant and breastfeeding women</b>	
Tanaka 2009 <sup>5</sup>	<ul style="list-style-type: none"> <li>Assessment of use of oseltamivir and zanamivir in pregnant and breastfeeding women</li> <li>Post-marketing surveillance of oseltamivir in 61 women with pregnancies found 10 abortions; another Japanese study which followed 90 pregnant women found there was 1 malformation (which paper states is within the incidence of major malformations in the general population).</li> <li>3 pregnant women were accidentally exposed to zanamivir, with 1 pregnancy spontaneously miscarried, one terminated and 1 delivered a healthy baby; Japanese Drug Information Institute in Pregnancy has info about 1 woman who took zanamivir at 4 weeks of gestation and delivered a healthy baby.</li> </ul>
Wentges-van Holthe 2007 <sup>6</sup>	<ul style="list-style-type: none"> <li>Assessment of oseltamivir concentration in breast milk of one individual showed that oseltamivir exposure via breast milk is not expected to cause clinically significant concentrations of oseltamivir in an infant.</li> </ul>
<b>Adverse events</b>	
French 2007 <sup>20</sup>	<ul style="list-style-type: none"> <li>Post-marketing surveillance study to assess concurrent diagnosis of corneal oedema or Fuchs dystrophy and new prescription for amantadine found that 0.27% of patients prescribed amantadine were diagnosed with corneal oedema (RR=1.7; 95% CI: 1.1, 2.8)</li> </ul>
Loughlin 2002 <sup>21</sup>	<ul style="list-style-type: none"> <li>Retrospective review of patients treated with zanamivir (n=5450) showed low risk of respiratory events associated with treatment</li> </ul>
Toovey 2008 <sup>22</sup>	<ul style="list-style-type: none"> <li>Risk of neuropsychiatric events with oseltamivir - two Japanese studies reported neuropsychiatric events, however a review assessing clinical trials, post-marketing data and observational data found no relationship between oseltamivir treatment and neuropsychiatric events.</li> </ul>
Blumentals 2007 <sup>2</sup>	<ul style="list-style-type: none"> <li>Retrospective review of oseltamivir use and CNS-related and neuropsychiatric events (n=40,704) found no relationship between such outcomes and use of oseltamivir.</li> </ul>
Nordstrom 2004 <sup>23</sup>	<ul style="list-style-type: none"> <li>Retrospective review of use of oseltamivir in 32,459 patients found no evidence of increased skin reactions with oseltamivir</li> </ul>
Keyser 2000 <sup>11</sup>	<ul style="list-style-type: none"> <li>Retrospective review of use of amantadine and rimantadine as prophylaxis in nursing home patients found a significantly greater occurrence of CNS adverse events with amantadine compared to rimantadine.</li> </ul>

**Author(s):** Holger J Schunemann

**Date:** 2009-06-24

**Question:** Oseltamivir for new influenza

**Settings:** Outpatient

**Bibliography:** Blumenthals and Schulman, 2007 Orzeck et al., 2007 Gums et al., 2008

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		
<b>Hospitalization (follow-up mean 14 days)</b>												
3 <sup>1</sup>	observational studies	no serious limitations <sup>2</sup>	no serious inconsistency	no serious indirectness <sup>3</sup>	no serious imprecision	none	625/69929 (0.9%)	979/73080 (1.3%)	OR 0.73 (0.63 to 0.83) <sup>4</sup>	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.



## Annex 6: Table of recommended dosages

Adapted from CDC Table: Recommended daily dosage of seasonal influenza antiviral medications for treatment and chemoprophylaxis for the 2008-09 season, United States. Available at:

<http://www.cdc.gov/flu/professionals/antivirals/dosatable.htm#table>  
(accessed June 28 2009)

Table 6.1: Dosage recommendations

Agent	Age Groups (yrs)					
	Duration	1-6	7-9	10-12	13-64	≥ 65
<b>Amantadine<sup>d</sup></b>						
Treatment	5 days	5 mg/kg/day up to 150 mg in 2 divided doses	5 mg/kg/day up to 150 mg in 2 divided doses	100 mg twice daily for	100 mg twice daily	≤ 100 mg/day
Prophylaxis	Begin as soon as exposure identified and continue for 5-7 days after last known exposure <sup>a</sup>	5 mg/kg/day up to 150 mg in two divided doses †	5 mg/kg/day up to 150 mg in two divided doses	100 mg twice daily	100 mg twice daily	≤ 100 mg/day
<b>Rimantadine<sup>b</sup></b>						
Treatment	5 days	Not licensed for use	Not licensed for use	Not licensed for use	100 mg twice daily	100 mg/day
Prophylaxis	Begin as soon as exposure identified and continue for 5-7 days after last known exposure <sup>a</sup>	5 mg/kg/day up to 150 mg in two divided doses	5 mg/kg/day up to 150 mg in two divided doses	100 mg twice daily	100 mg twice daily	100 mg/day
<b>Oseltamivir</b>						
Treatment	5 days	Weight adjusted doses <sup>c</sup> : - 30 mg twice daily for ≤ 15 kg - 45 mg twice daily for >15 to 23 kg - 60 mg twice daily for >23 to 40kg - 75 mg twice daily for >40kg			75 mg twice daily <sup>c</sup>	75 mg twice daily <sup>c</sup>
Prophylaxis	Begin as soon as exposure identified and continue for 5-7 days after last known exposure <sup>a</sup>	Weight adjusted doses <sup>c</sup> : - 30 mg/day for ≤ 15 kg - 45 mg/day for >15 to 23 kg - 60 mg/day for >23 to 40 kg - 75 mg/day for >40 kg			75 mg/day	75 mg/day
<b>Zanamivir</b>						
Treatment	5 days	Not licensed for use		10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
Prophylaxis	Begin as soon as exposure identified and continue for 5-7 days after last known exposure <sup>a</sup>	1-4 yrs: NA	5-6 yrs: 10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily

- a For control of outbreaks in long-term care facilities and hospitals, CDC recommends chemoprophylaxis for a minimum of two weeks, and up to one week after the last known case was identified.
- b Reduction in rimantadine dosage to 100 mg/day is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance <10 ml/min. Other persons with less severe hepatic or renal dysfunctions taking 100 mg/day should be observed closely and dosage should be reduced or drug discontinued if necessary.
- c Reduction in dose of oseltamivir is recommended for persons with creatinine clearance <30 ml/min.
- d Amantadine package insert should be consulted for dosage recommendations for persons with creatinine clearance ≤50 ml/min/1.73 m<sup>2</sup>.