Author(s): P Whyte
Date: 2009-12-20
Question: Should oseltamivir be used for influenza?
Settings: Adults and children
Bibliography: Jefferson (2009), as well as articles by Hanshaoworakul (2009), Casscells (2009), and Piedra (2009).

Table A5.1

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oseltamivir	Control	Relative (95% CI)	Absolute		
oseltamivir 75mg - prophylaxis against influenza-like illness												
2[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	34/675 (5%)[5]	19/413 (4.6%)	RR 1.28 (0.45 to 3.66)	13 more per 1000 (from 25 fewer to 122 more)	⊕OOO VERY LOW	IMPORTANT
oseltamivir 150mg - prophylaxis for influenza-like illness												
1[6]	randomized trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[4]	6/520 (1.2%)	3/259 (1.2%)	RR 1.00 (0.25 to 3.95)	0 fewer per 1000 (from 9 fewer to 34 more)	⊕OOO VERY LOW	IMPORTANT
oseltamivir 75mg - prophylaxis against laboratory-confirmed influenza												
2[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	15/675 (2.2%)[5]	28/412 (6.8%)	RR 0.39 (0.18 to 0.85)	41 fewer per 1000 (from 10 fewer to 56 fewer)	⊕OOO VERY LOW	CRITICAL
oseltamivir 150mg - prophylaxis for laboratory-confirmed influenza												
1[6]	randomized trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[4]	7/520 (1.3%)	13/260 (5%)	RR 0.27 (0.11 to 0.67)	36 fewer per 1000 (from 16 fewer to 45 fewer)	⊕OOO VERY LOW	CRITICAL
alleviation of symptoms												
3[9]	randomized trials	no serious limitations[10]	no serious inconsistency	no serious indirectness	serious[11]	reporting bias[4]	1118	679	-	1.20 higher (1.06 to 1.35 higher)[12]	⊕⊕OO LOW	IMPORTANT
oseltamivir 75mg - nausea												
2[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	71/675 (10.5%)[5]	23/413 (5.6%)	OR 1.79 (1.1 to 2.93)	40 more per 1000 (from 5 more to 92 more)	⊕OOO VERY LOW	IMPORTANT
oseltamivir 150mg - nausea												
1[6]	randomized trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[4]	76/520 (14.6%)	18/259 (6.9%)	OR 2.29 (1.34 to 3.92)	77 more per 1000 (from 21 more to 157 more)	⊕OOO VERY LOW	IMPORTANT
complications												
3[13]	randomized trials	no serious limitations[10]	no serious inconsistency	no serious indirectness	serious[11]	none	14/402 (3.5%)	27/402 (6.7%)	RR 0.55 (0.22 to 1.35)	30 fewer per 1000 (from 52 fewer to 24 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Hayden (1999) and Kashiwagi (2000).
[2] The Jefferson (2009) review indicates that the Hayden (1999) and Kashiwagi (2000) trials would not be judged adequate by the Cochrane criteria and that the trials were at risk of bias, given poor

descriptions of methods. Although the Jefferson review does not identify which authors of the oseltamivir papers were contacted, those who were indicated that they did not have original data. Consequently, the results of these trials should be interpreted with caution.
[3] 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.
[4] Although the Jefferson (2009) review does not indicate which authors of the included-oseltamivir trials were contacted, those who were indicated that they did not have original data. Roche was not able to provide the data to the review authors in time to update the review. As such, there is the potential for reporting bias.
[5] Oral oseltamivir 75mg.
[6] Hayden 1999.
[7] The Jefferson (2009) review indicates that the Hayden (1999) trial would not be judged adequate using the Cochrane methods and is at risk of bias due to poor description of methods.
[8] The trial is 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.
[9] Li (2003), Nicholson (2000), and Treanor (2000).
[10] The Jefferson (2009) review indicates that the Nicholson (2000) and Treanor (2000) trials would be considered adequate using the Cochrane criteria, while the Li (2003) trial would not.
[11] 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.
[12] The Jefferson (2009) review states that the results from meta-analyses using hazard ratios should be interpreted with caution because of the methods used. As hazard ratios were seldom reported directly, the authors used the ratio of the observed median duration of symptoms in each group as an approximation to the hazard ratio.
[13] Nicholson (2000), Treanor (2000), and Li (2003). Complications include pneumonia, bronchitis, otitis media, and sinusitis.

Author(s): P. Whyte
Date: 2009-12-28
Question: Should oseltamivir in children be used for influenza?
Settings: children
Bibliography: Shun-Shin (2009)

Table A5.2

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oseltamivir in children	Control	Relative (95% CI)	Absolute		
vomiting												
1[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/0 (0%)[4]	0/0 (0%)	RD 0.05 (0.02 to 0.09)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	IMPORTANT

[1] Whitley (2000) (WV15758) from the Shun-Shin review (2009).
[2] Shun-Shin (2009) indicates that this trial did not report sufficient details to determine whether allocation concealment and blinding were adequate.
[3] 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.
[4] Number with event not provided in review.

Author(s): P Whyte
Date: 2009-12-20
Question: Should oseltamivir be used for influenza?
Settings: adults and children
Bibliography: Jefferson (2009), as well as articles by Hanshaoworakul (2009), Casscells (2009), and Piedra (2009).

Table A5.3

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute		
death												
1[14]	observational studies[15]	serious[16]	no serious inconsistency	no serious indirectness	serious[3]	none	5/318 (1.6%)	17/131 (13%)	OR 0.11 (0.04 to 0.3)[17]	114 fewer per 1000 (from 87 fewer to 124 fewer)		CRITICAL
recurrent cardiovascular events												
1[18]	observational studies[19]	serious[20]	no serious inconsistency	no serious indirectness	serious[21]	none	575/6771 (8.5%)	6508/30711 (21.2%)	OR 0.417 (0.349 to 0.498)[22]	111 fewer per 1000 (from 94 fewer to 126 fewer)		IMPORTANT

[3] 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.
[14] Hanshaoworakul 2009.
[15] Retrospective medical chart review
[16] This study is a retrospective review of medical charts and as such may be open to bias and does not allow for establishment of causal relationships.
[17] When cardiovascular disease and hypertension were controlled for, oseltamivir was associated with survival (OR=0.13; 95% CI: 0.04, 0.38 for cardiovascular disease and OR=0.14; 95% CI: 0.04, 0.44 for hypertension).
[18] Casscells 2009.
[19] Casscells 2009 was a retrospective review which uses a propensity-scored logistic regression model to control for demographic differences.
[20] Casscells 2009 was a retrospective review of administrative data of members of the US Department of Defense. The authors acknowledge that the study is susceptible to a number of sources of confounding, including omission of potentially important variables such as severity and prior duration of patient's symptoms, presence of specific comorbidities, prior prophylactic treatment, subject compliance with critical medications or death due to causes unrelated to influenza may have influenced attempts to balance the groups and confounded findings.
[21] Only seasonal influenza was considered and therefore the generalizability of the results to pandemic influenza is unknown. In addition, the potential for confounding due to study design (patient comorbidities, compliance with medication, previous symptoms) limit the confidence with which results can be generalized to other situations.
[22] The odds ratio was based on a propensity-scored logistic regression model which controlled for demographic differences in the population. Authors conclude the results indicate that oseltamivir provided a statistically significant protective effect against recurrent cardiovascular events in patients with a history of vascular disease.

Author(s): P Whyte
Date: 2009-12-20
Question: Should oseltamivir be used for influenza?
Settings: adults and children
Bibliography: Jefferson (2009), as well as articles by Hanshaoworakul (2009), Casscells (2009), and Piedra (2009)

Table A5.4

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute		
pneumonia in 14 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	17/1634 (1%)	71/3721 (1.9%)	HR 0.55 (0.29 to 1.03)[25]	9 fewer per 1000 (from 14 fewer to 1 more)		IMPORTANT
respiratory illnesses other than pneumonia in 14 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	324/1634 (19.8%)	885/3721 (23.8%)	HR 0.74 (0.63 to 0.87)[25]	56 fewer per 1000 (from 27 fewer to 81 fewer)		IMPORTANT
otitis media complications in 14 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	46/1634 (2.8%)	184/3721 (4.9%)	HR 0.69 (0.48 to 0.99)[25]	15 fewer per 1000 (from 0 fewer to 25 fewer)		IMPORTANT
all-cause hospitalizations in 14 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	10/1634 (0.6%)	48/3721 (1.3%)	HR 0.33 (0.13 to 0.83)[25]	9 fewer per 1000 (from 2 fewer to 11 fewer)		CRITICAL
pneumonia-related hospitalizations in 14 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	2/1634 (0.1%)	13/3721 (0.3%)	HR 0.49 (0.09 to 2.49)[25]	2 fewer per 1000 (from 3 fewer to 5 more)		CRITICAL
hospitalizations respiratory illness other than pneumonia in 14 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	1/1634 (0.1%)	9/3721 (0.2%)	HR 0.23 (0.03 to 2.09)[25]	2 fewer per 1000 (from 2 fewer to 3 more)		CRITICAL
pneumonia in 30 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	26/1634 (1.6%)	91/3721 (2.4%)	HR 0.67 (0.42 to 1.07)[25]	8 fewer per 1000 (from 14 fewer to 2 more)		IMPORTANT
respiratory illnesses other than pneumonia in 30 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	498/1634 (30.5%)	1201/3721 (32.3%)	HR 0.87 (0.77 to 0.97)[25]	35 fewer per 1000 (from 8 fewer to 64 fewer)		IMPORTANT
otitis media complications in 30 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	75/1634 (4.6%)	276/3721 (7.4%)	HR 0.70 (0.53 to 0.92)[25]	22 fewer per 1000 (from 6 fewer to 34 fewer)		IMPORTANT
all-cause hospitalizations in 30 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	15/1634 (0.9%)	61/3721 (1.6%)	HR 0.49 (0.27 to 0.89)[25]	8 fewer per 1000 (from 2 fewer to 12 fewer)		CRITICAL

pneumonia-related hospitalizations in 30 days after influenza diagnosis											
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	4/1634 (0.2%)	6/3721 (0.2%)	HR 0.56 (0.17 to 1.83)[25]	1 fewer per 1000 (from 1 fewer to 1 more)		CRITICAL
hospitalizations respiratory illness other than pneumonia in 30 days after influenza diagnosis											
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	3/1634 (0.2%)	14/3721 (0.4%)	HR 0.34 (0.09 to 1.2)[25]	2 fewer per 1000 (from 3 fewer to 1 more)		CRITICAL
adverse events infants under one year of age											
1[26]	observational studies	serious[27]	no serious inconsistency	no serious indirectness	serious[8]	none	1/47 (2.1%)	41/486 (8.4%)	RR 0 (0 to 0)[28]	84 fewer per 1000 (from 84 fewer to 84 fewer)		CRITICAL

[8] The trial is 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.
[23] Piedra 2009. This study compared children and adolescents aged 1 to 17 years who were defined as being at high risk of influenza complications (chronic medical conditions or neurologic or neuromuscular disease) who received oseltamivir or did not receive antiviral therapy.
[24] The Piedra 2009 study was a retrospective review of medical databases covering six seasons of influenza. The authors acknowledge a number of limitations, including the fact the databases are limited primarily to patients covered by employer-sponsored health insurance; the use of diagnostic coding for influenza was assigned on basis of physicians' clinical diagnoses alone; impossible to confirm if patients began antiviral treatment within recommended timeframe; patients were not assigned randomly nor matched with respect to propensity to be given oseltamivir. In regard to the last two points the authors note that there were few potentially clinically significant differences between the two patient cohorts and multivariate analyses were used to adjust for differences.
[25] Adjusted for demographic and medical history variables.
[26] Tamura 2005
[27] The Tamura (2005) study was non-randomized and little information was provided regarding the study design except to say that infants under one year of age were treated with oseltamivir and a control group of children aged 1 to 15 years was also treated with oseltamivir and a third control group of children received no treatment. The treatment groups also varied considerably in size, with n=47 for children less than one year, n=486 for children aged 1 to 15 and n=95 for the children who received no treatment.
[28] No comparative results were provided in the publication.

Author(s): P Whyte
Date: 2009-12-24
Question: Should oseltamivir vs rimantadine or amantadine be used in children <1 year old?[1]
Settings: USA
Bibliography: Kimberlin (2009)

Table A5.5

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**oseltamivir**	**rimantadine or amantadine**	**Relative (95% CI)**	**Absolute**		
neurologic abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	19/115 (16.5%)	17/65 (26.2%)	RR 0 (0 to 0)[5]	262 fewer per 1000 (from 262 fewer to 262 fewer)[5]		IMPORTANT
pulmonary abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	59/115 (51.3%)	30/65 (46.2%)	RR 0 (0 to 0)[5]	462 fewer per 1000 (from 462 fewer to 462 fewer)[5]		IMPORTANT

gastrointestinal abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	26/115 (22.6%)	14/65 (21.5%)	RR 0 (0 to 0)[5]	215 fewer per 1000 (from 215 fewer to 215 fewer)[5]		IMPORTANT
cardiovascular abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	4/115 (3.5%)	4/65 (6.2%)	RR 0 (0 to 0)[5]	62 fewer per 1000 (from 62 fewer to 62 fewer)[5]		IMPORTANT
otologic, ocular abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	2/115 (1.7%)	10/65 (15.4%)	RR 0 (0 to 0)[5,6]	154 fewer per 1000 (from 154 fewer to 154 fewer)[5]		IMPORTANT
dermatologic abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	5/115 (4.3%)	4/65 (6.2%)	RR 0 (0 to 0)[5]	62 fewer per 1000 (from 62 fewer to 62 fewer)[5]		IMPORTANT
systemic response abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	6/115 (5.2%)	4/65 (6.2%)	RR 0 (0 to 0)[5]	62 fewer per 1000 (from 62 fewer to 62 fewer)[5]		IMPORTANT
genitourinary abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	4/115 (3.5%)	2/65 (3.1%)	RR 0 (0 to 0)[5]	31 fewer per 1000 (from 31 fewer to 31 fewer)[5]		IMPORTANT
musculoskeletal abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	2/115 (1.7%)	0/65 (0%)	RR 0 (0 to 0)[5]	0 fewer per 1000 (from 0 fewer to 0 fewer)[5]		IMPORTANT
hematologic/lymphatic abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	6/115 (5.2%)	2/65 (3.1%)	RR 0 (0 to 0)[5]	31 fewer per 1000 (from 31 fewer to 31 fewer)[5]		IMPORTANT
hepatobillary/pancreatic abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	5/115 (4.3%)	0/65 (0%)	RR 0 (0 to 0)[5]	0 fewer per 1000 (from 0 fewer to 0 fewer)[5]		IMPORTANT
endocrine/metabolic abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	0/115 (0%)	1/65 (1.5%)	RR 0 (0 to 0)[5]	15 fewer per 1000 (from 15 fewer to 15 fewer)[5]		IMPORTANT

[1] Median dose of oseltamivir ranged from 2mg/kg to 2.21mg/kg and subjects were treated for a median of 5 days.
[2] Kimberlin (2009).
[3] Retrospective chart review focusing on comparative safety of oseltamivir and adamantanes in children less than a year old.
[4] This study is a retrospective chart review and as such may be open to bias due to lack of randomization, lack of blinding of outcome assessment.
[5] Only p values based on chi-square tests were provided by the paper. No statistically significant difference between the groups.
[6] Only p values based on chi-square tests were provided by the paper. There were statistically significantly more events in the rimantadine or amantadine group ($p<0.01$).

Author(s): P Whyte
Date: 2009-12-21
Question: Should zanamivir be used for influenza?
Settings: adults
Bibliography: Jefferson (2009)

Table A5.6

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute		
inhaled zanamivir 10mg - prophylaxis for influenza-like illness												
2[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	37/697 (5.3%)	21/602 (3.5%)	RR 1.51 (0.77 to 2.95)	18 more per 1000 (from 8 fewer to 68 more)	⊕⊕OO LOW	IMPORTANT
inhaled zanamivir 10mg - prophylaxis against laboratory confirmed influenza												
2[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	30/697 (4.3%)	62/602 (10.3%)	RR 0.38 (0.17 to 0.85)	64 fewer per 1000 (from 15 fewer to 85 fewer)	⊕⊕OO LOW	CRITICAL
intranasal zanamivir 6.4mg - prophylaxis for influenza-like illness												
1[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	7/141 (5%)	3/48 (6.3%)	RR 0.79 (0.21 to 2.95)	13 fewer per 1000 (from 49 fewer to 122 more)	⊕⊕OO LOW	IMPORTANT
intranasal zanamivir 6.4mg - prophylaxis against laboratory confirmed influenza												
1[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	26/141 (18.4%)	9/48 (18.8%)	RR 1.06 (0.54 to 2.08)	11 more per 1000 (from 86 fewer to 202 more)	⊕⊕OO LOW	CRITICAL
inhaled and intranasal zanamivir- prophylaxis for influenza-like illness												
1[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	3/146 (2.1%)	3/48 (6.3%)	RR 0.33 (0.07 to 1.58)	42 fewer per 1000 (from 58 fewer to 36 more)	⊕⊕OO LOW	IMPORTANT
inhaled and intranasal zanamivir- prophylaxis against laboratory confirmed influenza												
1[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	6/146 (4.1%)	9/48 (18.8%)	RR 0.22 (0.08 to 0.58)	146 fewer per 1000 (from 79 fewer to 172 fewer)	⊕⊕OO LOW	CRITICAL
alleviation of symptoms												
6[7]	randomized trials	serious[8]	no serious inconsistency	no serious indirectness	serious[3]	none	1878	1310	-	1.24 higher (1.13 to 1.36 higher)[9]	⊕⊕OO LOW	IMPORTANT

[1] Kaiser (2000) and Monto (1999).
[2] The Jefferson (2009) review indicates that the Monto (1999) trial would be judged adequate using Cochrane criteria but the Kaiser (2000) trial is not and is at risk of bias due to poor description of methods.
[3] The 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.
[4] Kaiser (2000).
[5] The Jefferson (2009) review indicates that this trial would not be judged adequate according to the Cochrane criteria and is at risk of bias due to poor reporting of methods.
[6] The trial is for seasonal influenza thus the generalizability of the results to pandemic influenza is unknown.
[7] Hayden (1997), Makela (2000), Matsumoto (1999), MIST (1998), Monto (1999), and Puhakka (2003).
[8] The Jefferson (2009) review indicates that of the 6 trials only two -- Makela (2000) and MIST (1998) -- would meet the Cochrane criteria for adequate, with the remaining trials open to bias due to poor description of methods.

[9] The Jefferson (2009) review states that the results from meta-analyses using hazard ratios should be interpreted with caution because of the methods used - as hazard ratios were seldom reported directly the authors used the ratio of the observed median duration of symptoms in each group as an approximation to the hazard ratio.

Author(s): P. Whyte
Date: 2009-06-05
Question: Should amantadine be used for influenza - adults?
Settings: adults
Bibliography: Jefferson (2006)

Table A5.7

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	control	Relative (95% CI)	Absolute	Quality	Importance
duration fever (days) (Better indicated by lower values)												
10	randomized trials	no serious limitations	no serious inconsistency	serious[1]	serious	none	250	292	-	MD 0.99 lower (1.26 to 0.71 lower)	⊕⊕OO LOW	
duration of hospitalization (Better indicated by lower values)												
1	randomized trials	no serious limitations	no serious inconsistency	serious[2]	serious[3]	none	20	16	-	MD 0.90 lower (2.2 lower to 0.4 higher)	⊕⊕OO LOW	6.5
viral nasal shedding												
3	randomized trials	no serious limitations	no serious inconsistency	serious[2]	serious[4]	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)	⊕⊕OO LOW	6

[1] All trials are were conducted in the 1960s and early 1970s; 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] Eelatively old trial (1970) with small n (36 total subjects).
[4] Two trials from the 1960s and one from the early 1980s, 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)

Table A5.8

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rimantadine	control	Relative (95% CI)	Absolute		
duration of fever (Better indicated by lower values)												
3	randomized trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	36	46	-	MD 1.24 lower (1.71 to 0.76 lower)	⊕⊕OO LOW	
viral nasal shedding												
3	randomized trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	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)	⊕⊕OO 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 1960s and one in the 1980s.

Author(s): P.Whyte
Date: 2009-12-21
Question: Should neuraminidase inhibitors - oseltamivir and zanamivir be used for influenza?
Settings: adults
Bibliography: Jefferson (2009) and Khazeni (2009).

Table A5.9

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	neuraminidase inhibitors - oseltamivir and zanamivir	control	Relative (95% CI)	Absolute		
oseltamivir only - extended prophylaxis against laboratory confirmed symptomatic influenza												
3[8]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	19/1471 (1.3%)	87/1463 (5.9%)	RR 0.236 (0.144 to 0.387)	45 fewer per 1000 (from 36 fewer to 51 fewer)	⊕⊕OO LOW	CRITICAL
zanamivir only - extended prophylaxis against laboratory confirmed symptomatic influenza												
2[9]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	18/2321 (0.8%)	66/2239 (2.9%)	RR 0.280 (0.166 to 0.474)	21 fewer per 1000 (from 16 fewer to 25 fewer)	⊕⊕OO LOW	CRITICAL

oseltamivir only - extended prophylaxis against laboratory confirmed asymptomatic influenza												
3[8]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	62/1471 (4.2%)	79/1463 (5.4%)	RR 0.781 (0.563 to 1.082)	12 fewer per 1000 (from 24 fewer to 4 more)	⊕⊕OO LOW	CRITICAL
zanamivir only - extended prophylaxis against laboratory confirmed asymptomatic influenza												
2[9]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	74/2321 (3.2%)	53/2239 (2.4%)	RR 1.402 (0.900 to 1.983)	10 more per 1000 (from 2 fewer to 23 more)	⊕⊕OO LOW	CRITICAL

[2] According to the Jefferson (2009) review, only the Monto (1999) trial is adequate according to the Cochrane criteria.
[3] 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.
[4] Hayden 1999 (both 75mg/day and 150mg/day), Kashiwagi (2000), Peters (2001), Monto (1999), and LaForce (2007). All trials had a minimum of 4 weeks prophylactic treatment.
[5] The Khazeni (2009) review indicated that recruitment methods were not specified in most studies, and this concurs with Jefferson (2009) who indicated that all trials except Monto (1999) were not adequate according to Cochrane criteria.
[6] Kashiwagi (2000), (Monto 1999), (LaForce 2007), and (Webster 1999).
[7] Results indicate no difference between neuraminidase inhibitors and placebo in the occurrence of adverse events.
[8] Hayden (1999) (both 75mg/day and 150mg/day), Kashiwagi (2000), and Peters (2001). All trials had a minimum of 4 weeks prophylactic treatment.
[9] Monto (1999) and LaForce (2007). All trials had a minimum of 4 weeks prophylactic treatment.

Author(s): P Whyte
Date: 2009-12-21
Question: Should neuraminidase inhibitors - oseltamivir and zanamivir be used for influenza?
Settings: adults
Bibliography: Jefferson (2009) and Khazeni (2009).

Table A5.10

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	neuraminidase inhibitors - oseltamivir and zanamivir	control	Relative (95% CI)	Absolute		
prophylaxis for influenza-like illness												
4[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	87/2179 (4%)	49/1370 (3.6%)	RR 1.20 (0.77 to 1.87)	7 more per 1000 (from 8 fewer to 31 more)	⊕⊕OO LOW	IMPORTANT
prophylaxis against laboratory confirmed influenza												
4[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	86/2179 (3.9%)	121/1370 (8.8%)	RR 0.41 (0.25 to 0.65)	52 fewer per 1000 (from 31 fewer to 66 fewer)	⊕⊕OO LOW	CRITICAL
extended prophylaxis against laboratory confirmed symptomatic influenza												
6[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	37/3792 (1%)	153/3702 (4.1%)	RR 0.256 (0.179 to 0.367)	31 fewer per 1000 (from 26 fewer to 34 fewer)	⊕⊕OO LOW	CRITICAL

extended prophylaxis against laboratory confirmed asymptomatic influenza												
6[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	136/3709 (3.7%)	132/3702 (3.6%)	RR 1.028 (0.81 to 1.304)	1 more per 1000 (from 7 fewer to 11 more)	⊕⊕OO LOW	CRITICAL
serious adverse events												
4[6]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	21/2456 (0.9%)	23/2460 (0.9%)	RR 0.919 (0.511 to 1.651)[7]	1 fewer per 1000 (from 5 fewer to 6 more)	⊕⊕OO LOW	CRITICAL

[1] Hayden (1999), Kashiwagi (2000), Kaiser (2000), and Monto (1999).
[2] According to the Jefferson (2009) review, only the Monto (1999) trial is adequate according to the Cochrane criteria.
[3] 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.
[4] Hayden (1999) (both 75mg/day and 150mg/day), Kashiwagi (2000), Peters (2001), Monto (1999), and LaForce (2007). All trials had a minimum of 4 weeks prophylactic treatment.
[5] The Khazeni (2009) review indicated that recruitment methods were not specified in most studies, and this concurs with Jefferson (2009) who indicated that all trials except Monto (1999) were not adequate according to Cochrane criteria.
[6] Kashiwagi (2000), Monto (1999), LaForce (2007), and Webster (1999).
[7] Results indicate no difference between neuraminidase inhibitors and placebo in the occurrence of adverse events.

Author(s): P.Whyte
Date: 2009-06-05
Question: Should oseltamivir be used for prophylaxis in adults?
Settings: adults
Bibliography: Tappenden 2009

Table A5.11

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute		
symptomatic laboratory confirmed infection												
2	randomized trials	no serious limitations	no serious inconsistency	serious[1]	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)	⊕⊕⊕O 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)

Table A5.12

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute		
symptomatic laboratory confirmed influenza												
1	randomized trials	no serious limitations	no serious inconsistency	serious[1]	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)	⊕⊕⊕O 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)

Table A5.13

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute		
symptomatic laboratory confirmed infection												
1	randomized trials	no serious limitations	no serious inconsistency	serious[1]	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)	⊕⊕⊕O 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.