National Essential Medicine List Medication Review Process
Primary Healthcare
Component: Respiratory medicines

Medication name: Neuraminidase inhibitors (NAIs): oseltamivir (OTV); zanamivir (ZNV)

Date of review: May 2013

Indication: Treatment and prevention of influenza

Executive summary: Current guidelines recommend the use of NAIs in influenza, but they are not listed in the EML. NAIs might reduce mortality and risk of hospitalisation, especially when given early in the disease course. OTV is associated with an increased risk of gastrointestinal side effects.

Introduction and contextualisation:

Local[i] and international[ii],[iii] guidelines recommend the use of NAIs in certain clinical settings and patient groups for the prevention and treatment of influenza. NAIs are currently not listed in the Essential Medicines List (EML) although a review conducted in August 2009 by the Adult Hospital Level expert committee recommended that they should be considered for use in pandemic and seasonal influenza A H1N1 in:

- 'Severe illness.
- Moderate to severe illness in populations at high risk for developing complicated/severe disease: pregnancy, immune suppression, cardiorespiratory disease and obesity.
- Outbreaks in specific institutions/facilities.'[iv]

This updated review presents evidence published since the 2009 review in light of consideration of NAIs for inclusion in the Primary Health Care EML.

Search strategy:

Pubmed search terms:

1. Neuraminidase inhibitors in randomised controlled trials:

("neuraminidase"[MeSH Terms] OR "neuraminidase"[All Fields]) AND ("antagonists and inhibitors"[Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields]) AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomised controlled trials"[All Fields] OR "randomized controlled trials"[All Fields])

2. Neuraminidase inhibitors in systematic reviews and meta-analyses:

(("neuraminidase"[MeSH Terms] OR "neuraminidase"[All Fields]) AND ("antagonists and inhibitors"[Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields]) AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields])) AND (Meta-Analysis[ptyp] OR systematic[sb])

CONFIDENTIAL

Selection of studies:

Inclusion criteria:

Types of studies: randomised controlled trials (RCTs) and systematic reviews

Participants: Adults and children, both healthy and with co-morbidities or risk factors

Interventions: NAIs: OTV and ZNV

Control: placebo/no treatment

Outcomes: prevention of complications; prevention of influenza; symptom duration; mortality

Results:

Search 1 identified 94 articles. Seven met the inclusion criteria. No new RCTs were published since the last EML review; all seven studies were systematic reviews of RCTs.

Search 2 identified a further 55 articles. Five additional systematic reviews met the inclusion criteria.

A PHC EML expert committee member circulated an additional article (a systematic review of observational studies) for inclusion in this review.[v]

Two articles were systematic reviews of systematic reviews[vi],[vii]. No meta-analyses were performed in either one. Two articles reported the same systematic review and meta-analysis[viii],[ix]. Two articles[x],[xi] reported updates of an earlier systematic review – only the most recent was included[xii].

The results of eight systematic reviews are described below.

Evidence synthesis:

Jefferson et al updated their Cochrane review and meta-analysis of RCTs of NAIs in healthy adults and children in 2012 in light of their finding significant publication and reporting bias in RCTs of NAIs[xiii]. They included published studies, as well as study reports and information from regulatory agencies. They found that OTV reduced symptom duration by 21.3 hours (95% CI -29.6 to -13.0). They found no significant effect on hospitalisation, odds ratio (OR) 0.95 (95% CI 0.57 to 1.61). They were unable to assess the effect on complications and transmission owing to limitations in available data, but noted that the US Food and Drug Administration (FDA) have not registered OTV for post-exposure prophylaxis, and that the FDA-approved package insert states that OTV has not been shown to reduce complications such as serious bacterial infections. In terms of adverse effects, OTV was associated with an increased risk of nausea and vomiting, with ORs of 1.62 (95% CI 1.17 to 2.26) and 2.32 (95% CI 1.62 to 3.31), and a decreased risk of diarrhoea, OR 0.72 (95% CI 0.53 to 0.97). The authors postponed their ZNV analyses pending the provision of individual patient data by the manufacturer.

Wang et al conducted a Cochrane review and meta-analysis of published RCTs in children[x]. They found that OTV and ZNV significantly reduced illness duration by 36 hours and 1.3 days respectively. There were no significant effects on complications except a reduction in otitis media in children aged 1–5 years, absolute risk reduction of 14% (95% CI -24 to -4). Post exposure prophylaxis to household contacts reduced influenza transmission, with an absolute risk reduction of 8% (95% CI -12 to -5). Overall incidence of adverse events was not significantly different in NAI and placebo arms, but those who received OTV had a significantly increased risk of vomiting, risk difference 6% (95% CI 3 to 10).

CONFIDENTIAL

Burch et al conducted a systematic review and meta-analysis of RCTs to inform NICE guidelines in the UK[viii,ix]. They found that OTV reduced symptom duration by 0.55 days (95% CI -0.96 to -0.14) in healthy adults; by 0.74 days (95% CI -1.51 to 0.02) in the at-risk population (those aged >65 years or with co-morbidities); and by 21.05 hours (95% CI -33.81 to -8.29) in children. ZNV reduced symptom duration by 0.57 days (95% CI -1.07 to -0.08) in healthy adults; by 0.98 days (95% CI -1.84 to -0.11) in the at-risk population (those aged >65 years or with co-morbidities); and by 0.94 days (95% CI -1.43 to -0.46) in children. OTV reduced antibiotic use in healthy adults, OR 0.37 (95% CI 0.29 to 0.48). There were no other significant reductions in complications. There were no significant increases in adverse events relative to placebo.

Hsu et al conducted a systematic review of observational studies to inform WHO guidelines[v]. OTV (compared with no antiviral therapy) reduced mortality, OR 0.23 (95% CI 0.13 to 0.43) based on three studies that adjusted their estimate for various factors, and OR 0.51(95%CI 0.23 to 1.14) based on 9 studies with unadjusted estimates (see Table 1). They also found that OTV reduced hospitalisation, OR 0.75 (95% CI 0.66 to 0.89), based on 4 studies (see Table 2). Those effects were greater when OTV was started within 48 hours, compared to after 48 hours, OR 0.33 (95% CI 0.12 to 0.86) for mortality and 0.52 (95% CI 0.33 to 0.81) for hospitalisation. It did not significantly reduce complications except for otitis media, RR 0.75 (95% CI 0.64 to 0.87). ZNV had no significant effect on mortality, hospitalisation or complications.

Falagas et al conducted a systematic review and meta-analysis of RCTs of NAIs in reduction of influenza complications in adults and children[xiv]. They found that NAIs reduced complications overall in otherwise healthy patients (RR 0.74, 95% CI 0.58 to 0.95), and in high risk patients (RR 0.37, 95% CI 0.24 to 0.59). However there were no significant reductions in individual complications (pneumonia, bronchitis, hospitalisation and need for an antibiotic), except for otitis media, RR 0.50 (95% CI 0.30 to 0.85).

Jackson et al conducted a systematic review and meta-analysis of RCTs of NAIs in influenza prevention[xv]. They found that OTV and ZNV post-exposure prophylaxis reduced the risk of transmission to adult and child household contacts, with relative risks (RR) 0.19 (95% CI 0.08 to 0.45) and 0.21 (95% CI 0.13 to 0.33) respectively. ZNV reduced transmission in the elderly in long-term care, but this did not reach statistical significance, with RR 0.68 (95% CI 0.33 to 1.27). OTV seasonal prophylaxis reduced the risk of influenza in both healthy adults (RR 0.24, 95% CI 0.09 to 0.54) and the frail elderly (RR 0.08, 95% CI 0.01 to 0.63). ZNV seasonal prophylaxis reduced the risk of influenza in both healthy adults (RR 0.32, 95% CI 0.17 to 0.63) and at-risk populations (RR 0.17, 95% CI 0.07 to 0.44).

Khazeni et al conducted a systematic review and meta-analysis of RCTs of NAIs in extended duration (>4 weeks) prophylaxis[xvi]. Most of the included studies were conducted in healthy adults. They found that NAIs significantly reduced the risk of symptomatic influenza, RR 0.26 (95% CI 0.18 to 0.37). OTV was associated with an increased risk of nausea and vomiting, RR 1.48 (95% CI 1.86 to 2.33).

Mosby et al conducted a systemic review on influenza in pregnancy[xvii]. They found five studies that showed that NAIs administered within 48 hours of symptom onset reduced the risk of severe disease.

CONFIDENTIAL

Study	Location	Population	n	Comparison	Effect on mortality	Adjusted for
Studies with adjusted treatment effect estimates						
[xviii]	Thailand	Fatal cases & those hospitalised for ≥2 days. Mean age 22 years 57% male	445	OTV vs no OTV	OR 0.11 (95% CI 0.04 to 0.30) OR 0.13 (95% CI 0.04 to 0.40) OR 0.13 (95% CI 0.04 to 0.38) OR 0.14 (95% CI 0.04 to 0.44)	Unadjusted Age Cardiovascular disease Hypertension
[xix]	Vietnam	Hospitalised patients Median age 25 years 55% male	67	OTV vs no OTV	OR 0.24 (95% CI 0.065 to 0.916) OR 0.39 (95% CI 0.09 to 1.71)	Unadjusted Age
[xx]	Canada	ICU patients Adults (>15 years) Median age 73 50% male 92% underlying chronic condition	161	OTV vs no OTV	OR 0.27 (95% CI 0.12 to 0.64)	Not stated
Studies with unadjusted treatment effect estimates						
[xxi]	USA	Leukaemia patients Median age 53 years	33	NAI vs no NAI	0/25 in NAI group 3/8 in no NAI group	Not applicable
[xxii]	Argentina	Patients requiring mechanical ventilation 56% male 7% pregnant 64% underlying conditions	337	OTV vs no OTV	OR 0.51 (95% CI 0.08 to 2.65)*	Unadjusted
[xxiii]	Vietnam	Hospitalised adults 52% male Mean age 35.1±14.4 years No concomitant illness	29	OTV vs no OTV	OR 0.25 (95% CI 0.03 to 2.24)	Unadjusted
[xxiv+]	Taiwan	Hospitalised children (<18 years) CNS dysfunction	74	OTV vs no OTV	OR 8.0 (95% CI 0.38 to 480)*	Unadjusted
[xxv]	Hong Kong	Hospitalised patients 52.4% <18 years	145	OTV vs no OTV	No deaths	Not applicable
[xxvi+]	Canada	Hospitalised Adults: median age 77 years (range 15–99) 51% male 75% chronic underlying illness	185 children (<15 years) 327 adults	OTV vs no OTV	Children: no deaths Adults: OR 0.36 (95% CI 0.12 to 1.1) OR 0.21 (95% CI 0.06 to 0.80)	Unadjusted Age, residence in nursing home, comorbidity, time to admission, ICU admission, season, influenza subtype, vaccination, type of diagnostic test, type of hospital
[xxvii]	USA	Pregnant women Median age 25 years (range 14–43) 509 hospitalised	788	No OTV or ZNV vs OTV or ZNV given within 2 days	RR 13.8 (95% CI 1.6 to 115.7)	
[xxviii]	China	Hospitalised ≥18 years 58% male Mean age 43±18.6 years	155	OTV vs no OTV	OR 2.14 (95% CI 0.59 to 11.87)*	Unadjusted

CONFIDENTIAL

		52.3% comorbidity 12 pregnant women				

Table 1. Characteristics and results of studies included in Hsu et al's meta-analyses of effects on mortality

*OR calculated from published data, [+]Roche funded

Study	Location	Population	n	Comparison	Effect on hospitalisation	Adjusted for
[xxix+]	USA	Outpatients (insurance claims data) Mean age 32 45% male	81408	OTV vs no OTV	Hospitalisation owing to CNS or neuropsychiatric conditions: < 12 years: not stated (no significant difference) 13–17 years: OR 0.68 (95% CI 0.50 to 0.94) 18–49 years: OR 0.78 (95% CI 0.67 to 0.90)	Age, sex, region, urban status, vaccination, influenza season, cardiac and respiratory conditions
[xxx]	USA	Not described	182	OTV vs no OTV	Not stated (not significant)	Region, age
[xxxi]	USA	Not described in abstract*	Not in abstract*	OTV vs no antivirals	0.74 (95% CI 0.61 to 0.90)	Not stated in abstract*
[xxxii+]	USA	Children 1–17 years Outpatients (insurance claims data)	5355	OTV vs no antivirals	Within 14 days of diagnosis: HR 0.47 (95% CI 0.24 to 0.93) HR 0.33 (95% CI 0.13 to 0.83)	Unadjusted Age, sex, population density, region, health care expenditures, vaccination, influenza season, and comorbidities

Table 2. Characteristics and results of studies included in Hsu et al's meta-analyses of effects on hospitalisation

*Unable to obtain full-text article, [+]Roche funded

CONFIDENTIAL

Evidence quality:

Although most of the trials included in the Hsu analysis were of GRADE low or very low quality, there are a number of reasons why it might be appropriate to consider their findings in the setting of PHC management of influenza. They were the only group who were able to report on mortality, as no deaths were reported in RCTs. In most cases the RCTs are not easily generalizable to the whole population as at-risk populations were excluded from participation. In contrast, the observational studies included special populations such as children, pregnant women and immunocompromised patients. Finally, the numbers of patients included in observational studies is far greater than those in the RCTs, allowing for more precise estimates of treatment effect.

Alternative agents:

Adamantanes: current circulating influenza viruses are resistant to adamantanes, so they are not recommended for treatment.

Influenza vaccination is indicated for disease prevention.

Summary:

RCTs show that NAIs have a modest effect on symptom duration, and a significant effect on disease transmission, but little effect on preventing complications, including hospitalisation. The RCTs were not designed to provide estimates of mortality. However observational studies show that NAIs have a significant benefit in terms of reduction in mortality and hospitalisation. That effect is greatest within 48 hours, which is of particular relevance at a PHC level. OTV, but not ZNV, is associated with an increased risk of gastrointestinal side effects. We were unable to identify a population that would benefit at PHC level.

Recommendations:

NAIs not be recommended at PHC level.

NAIs be reviewed for consideration at hospital level.

CONFIDENTIAL

[i] National Institute for Communicable Diseases. Healthcare Workers' Handbook on Influenza. Updated May 2012.
[ii] World Health Organisation. WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses. Revised February 2010.
[iii] Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clnicians. Updated 22 December 2012. Available at http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed 5 May 2013.
[iv] Adult Hospital Level Essential Drug List Medicine Review: Neuraminidase inhibitors. August 2009.
[v] Hsu, J; Santesso, N; Mustafa, R; Brozek, J; Chen, YL; Hopkins, JP; Cheung, A; Hovhannisyan, G; Ivanova, L; Flottorp, SA; Sæterdal, I; Wong, AD; Tian, J; Uyeki, TM; Akl, EA; Alonso-Coello, P; Smaill, F;Schu¨ nemann, HJ. Antivirals for Treatment of Influenza, A Systematic Review and Meta-analysis of Observational Studies. *Ann Intern Med*. 2012;156:512-524.
[vi] Michiels B, Van Puyenbroeck K, Verhoeven V, Vermeire E, Coenen S. The value of neuraminidase inhibitors for the prevention and treatment of seasonal influenza: a systematic review of systematic reviews. *PLoS One*. 2013;8(4):e60348.
[vii] Beck CR, Sokal R, Arunachalam N, Puleston R, Cichowska A, Kessel A, Zambon M, Nguyen-Van-

Tam JS; UK Antiviral Effectiveness Review Group. Neuraminidase inhibitors for influenza: a review and public health perspective in the aftermath of the 2009 pandemic. *Influenza Other Respi Viruses*. 2013 Jan;7 Suppl 1:14-24.
[viii] Burch J, Paulden M, Conti S, Stock C, Corbett M, Welton NJ, Ades AE, Sutton A, Cooper N, Elliot AJ, Nicholson K, Duffy S, McKenna C, Stewart L, Westwood M, Palmer S. Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation. Health Technol Assess. 2009 Nov;13(58):1-265.
[ix] Burch J, Corbett M, Stock C, Nicholson K, Elliot AJ, Duffy S, Westwood M, Palmer S, Stewart L. Prescription of anti-influenza drugs for healthy adults: a systematic review and meta-analysis. *Lancet Infect Dis*. 2009 Sep;9 (9):537-45.
[x] Wang K, Shun-Shin M, Gill P, Perera R, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children. *Cochrane Database Syst Rev*. 2012 Jan 18;1:CD002744.
[xi] Shun-Shin M, Thompson M, Heneghan C, Perera R, Harnden A, Mant D. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2009 Aug 10;339:b3172.
[xii] Wang K, Shun-Shin M, Gill P, Perera R, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). *Cochrane Database Syst Rev*. 2012 Apr 8;4:CD002744.
[xiii] Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev*. 2012 Jan 18;1:CD008965.
[xiv] Falagas ME, Koletsi PK, Vouloumanou EK, Rafailidis PI, Kapaskelis AM, Rello J. Effectiveness and safety of neuraminidase inhibitors in reducing influenza complications: a meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2010 Jul;65(7):1330-46.
[xv] Jackson RJ, Cooper KL, Tappenden P, Rees A, Simpson EL, Read RC, Nicholson KG. Oseltamivir, zanamivir and amantadine in the prevention of influenza: a systematic review. *J Infect*. 2011 Jan;62(1):14-25.
[xvi] Khazeni N, Bravata DM, Holty JE, Uyeki TM, Stave CD, Gould MK. Systematic review: safety and efficacy of extended-duration antiviral chemoprophylaxis against pandemic and seasonal influenza. *Ann Intern Med*. 2009 Oct 6;151(7):464-73.
[xvii] Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. *Am J Obstet Gynecol*. 2011 Jul;205(1):10-8.
[xviii] Hanshaoworakul W, Simmerman JM, Narueponjirakul U, Sanasuttipun W, Shinde V, Kaewchana S, et al. Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. *PLoS One*. 2009; 4:e6051.
xix Liem NT, Tung CV, Hien ND, Hien TT, Chau NQ, Long HT, et al. Clinical features of human influenza A (H5N1) infection in Vietnam: 2004-2006. *Clin Infect Dis*. 2009;48:1639-46.
xx McGeer A, Green K, Drews S, Davis I, Downey J, Katz K, et al. Epidemiology of influenza illness requiring intensive care unit admission in Toronto, Canada. *Clin Microbiol Infect*. 2009;15:S26.
xxi Chemaly RF, Torres HA, Aguilera EA, Mattiuzzi G, Cabanillas M, Kantarjian H, et al. Neuraminidase inhibitors improve outcome of patients with leukemia and influenza: an observational study. *Clin Infect Dis*. 2007;44:964-7.
xxii Estenssoro E, Rı´os FG, Apezteguı´a C, Reina R, Neira J, Ceraso DH, et al; Registry of the Argentinian Society of Intensive Care SATI. Pandemic 2009 influenza A in Argentina: a study of 337 patients on mechanical ventilation. *Am J Respir Crit Care Med*. 2010;182:41-8.
xxiii Hien ND, Ha NH, Van NT, Ha NT, Lien TT, Thai NQ, et al. Human infection with highly pathogenic avian influenza virus (H5N1) in northern Vietnam, 2004-2005. Emerg Infect Dis. 2009;15:19-23.
xxiv Huang YC, Li WC, Tsao KC, Huang CG, Chiu CH, Lin TY. Influenza associated central nervous system dysfunction in Taiwanese children: clinical characteristics and outcomes with and without administration of oseltamivir. *Pediatr Infect Dis J*. 2009;28:647-8.
xxv Li IW, Hung IF, To KK, Chan KH, Wong SS, Chan JF, et al. The natural viral load profile of patients with pandemic 2009 influenza A(H1N1) and the effect of oseltamivir treatment. *Chest*. 2010;137:759-68.

CONFIDENTIAL

xxvi McGeer A, Green KA, Plevneshi A, Shigayeva A, Siddiqi N, Raboud J, et al; Toronto Invasive Bacterial Diseases Network. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis*. 2007;45:1568-75.
xxvii Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al; Pandemic H1N1 Influenza in Pregnancy Working Group. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA*. 2010;303:1517-25.
xxviii Xi X, Xu Y, Jiang L, Li A, Duan J, Du B; Chinese Critical Care Clinical Trial Group. Hospitalized adult patients with 2009 influenza A(H1N1) in Beijing, China: risk factors for hospital mortality. *BMC Infect Dis*. 2010;10:256.
[xxix] Blumentals WA, Song X. The safety of oseltamivir in patients with influenza: analysis of healthcare claims data from six influenza seasons. *MedGenMed*. 2007; 9:23.
xxxDharan NJ, Gubareva LV, Klimov AI, Fiore AE, Bresee JS, Fry AM. Antiviral treatment of patients with oseltamivir-resistant and oseltamivirsusceptible seasonal Influenza A (H1N1) infection during the 2007-2008 influenza season in the United States [Letter]. *Clin Infect Dis*. 2010;50:621-2.
xxxi Nordstrom BL, Sung I, Suter P, Szneke P. Risk of pneumonia and other complications of influenza-like illness in patients treated with oseltamivir. *Curr Med Res Opin*. 2005;21:761-8.
xxxii Piedra PA, Schulman KL, Blumentals WA. Effects of oseltamivir on influenza-related complications in children with chronic medical conditions. Pediatrics. 2009;124:170-8.

CONFIDENTIAL