



Overview information - Influenza Like Illness (ILI)

CLINICAL DEFINITION / SYMPTOMS:

- ♦ *Usually*: sudden onset of cough or fever (fever less prominent in children & elderly)
- ♦ *Common*: fatigue, aches muscle/joint, sore throat, headache, ↓appetite, runny nose; *Sometimes*: nausea, vomiting, diarrhea (GI more common in kids)

RISK FACTORS FOR COMPLICATIONS (focus on pandemic H1N1):

- ♦ Age less than 5yrs (especially less than 2yrs)
- ♦ Pregnancy (especially 2nd & 3rd trimesters; through 4 wks post-partum)
- ♦ Chronic Conditions: heart, lung, hepatic, renal, blood (esp sickle cell anemia), diabetes & metabolic, neurologic/neurodevelopmental, obesity^{severe}, immunocompromised

OTHER CONSIDERATIONS:

remote, isolated or aboriginal populations
SEVERITY INDICATORS: e.g. shortness of breath (wheezing, rapid or difficulty breathing), chest pain, other (bluish or grey skin color, bloody or coloured sputum, sudden dizziness, confusion, high fever lasting >3days, low blood pressure).
 Peds: ↓eating/drinking, ↓waking/interacting, irritability, not wanting to be held.

GENERAL:

- ♦ Wash hands! Sneeze/cough into arm! Stay home if ill. ...
- ♦ Antipyretics for symptoms (acetaminophen, ibuprofen, naproxen)
- ♦ Consider treatment for high risk; *watchful waiting* OK for others.

Expected Influenza Strains & Antiviral Sensitivities²

Influenza Strain 2009-10 (predicted)*	Oseltamivir TAMIFLU	Zanamivir RELENZA	Amantadine SYMMETREL
	Oral cap or susp powder	Inhalation	Oral cap or syrup
Seasonal Inf. A: H1N1 A/Brisbane/59/2007	Resistant	Susceptible	Susceptible mostly
Pandemic Inf. A: pH1N1 A/California/07/2009	Susceptible ²⁰ <small>Sporadic Resistance n=300</small>	Susceptible	Resistant
Seasonal Inf. A: H3N2 A/Brisbane/10/2007	Susceptible	Susceptible	Resistant
Seasonal Inf. B: B/Brisbane/60/2008	Susceptible	Susceptible	Resistant
Avian: H5N1	Susceptible	Susceptible	Variable resistant

* check current surveillance data: <http://www.phac-aspc.gc.ca/fluwatch/09-10/index-eng.php>

To treat or not to treat... (check local guidelines)

- ♦ **If ILI + no risk factors** ⇒ recuperate at home till 24hrs post-symptoms
If symptoms worsen or fails to improve within 72hrs, treat.
- ♦ **If ILI + risk factors** (or a health care worker caring for patients with risk factors) ⇒ consider antiviral medication - if within 48hr symptom onset;
Note: if severe or pregnant, may still treat even if >48hrs since onset
- ♦ **If ILI + any severity indicators** ⇒ treat, hospitalization &/or follow-up

Influenza Vaccine(s) for 2009 CANADA

pH1N1: an AS03-adjuvanted vaccine **AREPANRIX H1N1**³ used for most; a non-adjuvanted vaccine **PANVAX**, option for pregnant, esp. if <20weeks. pH1N1 vaccine given preferentially to all except elderly & LTC.^{SK}
 (⇒ Similar development process as annual influenza vaccine except adjuvanted; some concern that GBS risk unknown (in 1976 a novel swine flu vaccine had a 13 /million GBS incidence @ <4 wks as opposed to 2.6 /million).⁴
 Protection onset ~2 wks. Uncertainty if prior seasonal vaccine ↑s pH1N1 susceptibility. Cl. egg allergy, GBS hx)

SEASONAL TRIVALENT: contains 2 influenza type A, & 1 type B strain as per expected strains; priority for age ≥65 & LTC where pH1N1 less important/severe.
 {Fluvir; Influvac thimerosal free & Vaxigrip thimerosal free in single dose only; (FluMist live, attenuated, nasal, USA only)}

HIGHEST PRIORITY FOR VACCINATION pH1N1:

- ♦ those with/caring for ...
- ⇒ - Adults esp age <65 with chronic health conditions or identified as high risk
- Pregnant women (Use non-adjuvanted vaccine; adjuvanted vaccine may be OK but less data.)
- Children 6 months to <5 yrs of age (Half-dose = 0.25ml)
(Healthy Age 3-9 only single half dose; >6months-3yr or Chronic dx age 3-9: 2 half doses ≥3 weeks apart.)
- People living in remote and isolated settings or communities
- Health care workers involved in pandemic response or delivery of essential health care services
- Household contacts and care providers of persons at high risk (including infants <6mo) who cannot be immunized or may not respond to vaccines

OTHERS WHO WOULD BENEFIT FROM IMMUNIZATION pH1N1:

- ⇒ Children 5 to 18 years of age; first responders, poultry and swine workers, adults 19 to 64 years of age; adults 65 & older (in age 65+, preference for seasonal vaccine).

⁴Adjuvant is an antigen sparing component; has been used in Europe influenza vaccines but not N. America.
⁵pH1N1 adjuvanted vaccine has only 5ug thimerosal (metabolized to ethyl Hg & excreted in urine) vs 50ug in non-adjuvanted

ANTIVIRAL pH1N1 OPTIONS in Various Populations

(Note: cost totally covered in SK for pH1N1-2009 if meet criteria; otherwise usually non-formulary in SK)

Population	Treatment	Treatment Dosage	Comments	General Notes		
Pediatrics ⁵	Age < 1 {<3 months: use only if critical.}	Tamiflu x5 day (off label use)	<9mon 3mg/kg bid; ≥9-<12mon 3.5mg/kg bid; CPeds (up to 3.5mg/kg po BID NIH / FDA) ⁶ ⇒	<ul style="list-style-type: none"> ♦ limited data; info based on group's ↑mortality⁷ risk ♦ 0-1mon 2mg/kg bid; >1-3mon 2.5mg/kg bid; >3-12mon 3mg/kg bid; 19WHO ♦ Tamiflu Commercial Powder for Suspension: ⇒ 12mg/ml (tutti frutti flavour); ⇒ contains 26g sorbitol; avoid if fructose intolerant ⇒ see General Notes comment on "Dosing Errors" ♦ Compounding: Tamiflu capsules may also be used with <i>Ora-Sweet SF</i>; CPS⁹ contains directions for compounding; suspension strength differs¹⁰ or 15mg/ml; {clumping has been a problem. Alternately <i>Humco Cherry Syrup</i> USA; see instructions/info at http://www.tamiflu.com/hcp/dosing/extprep.aspx} ♦ Relenza indicated for age ≥7 yr in Canada FDA²⁵ yr. Must be able to use the diskhaler. 	<p>Antivirals for Treatment: Reserved for more complicated, moderate-severe presentations & those with risk factors such as pregnancy as may ↓ progression to severe disease / hospitalization. Ideally used within 48hr of symptom onset; used later esp. if severe disease, clinical deterioration or fever persisting. Not recommended for mild illness with no underlying risk factors as in those situations shortens course by ~ 1day & provides some symptom relief only. But if symptoms worsen or fails to improve within 72hrs, then treat.</p> <p>TAMIFLU® (Oseltamivir) Oral Capsules (30,45,75mg caps)</p> <ul style="list-style-type: none"> ♦ Duration: Treatment ⇒ po BID, usually x 5 days \$50 / 5days Prophylaxis ⇒ once daily, usually x 10+ days ♦ DI: clopidogrel may ↓ Tamiflu metabolism/effect Other: probenecid ↑ Tamiflu level, methotrexate (Clinical significance of DI's unknown!) ♦ SE: nausea +/- vomiting 10%; Rare: behaviour changes especially kids ♦ Suspension Dosing Errors: an oral dosing dispenser with 30mg, 45mg and 60mg graduations has resulted in errors if directions given in mL or teaspoons. USA⁸ Ensure units of measure in dosing instructions match those on the device given!!! Order in "mg"! ♦ Other: concerns about resistance if overused. <p>RELENZA® (Zanamivir) Inhalation - Diskhaler</p> <ul style="list-style-type: none"> ♦ Dose/Duration: Treatment ⇒ BID inhalation x 5 days \$46 / 5days {2 inhalations stat; repeat after 2 hrs then 2 inhalations q12h} Prophylaxis ⇒ once daily inhalation x 10+ days ♦ SE: nasal/throat irritation 8-19%, headache, cough; SE > with prophylaxis vs tx Very rare: behaviour changes especially in kids Other: contains lactose ♦ NOT for use in those with severe underlying airway disease asthma/CPD 	
	Age 1-6	Tamiflu x5 day	Weight			Dose (po)
			≤15kg			30mg BID
			>15-23kg			45mg BID
			>23-40kg			60mg BID
		>40kg	75mg BID			
	{adult dose at >40kg (>88lbs)}					
Other Populations	Age 7-12	Tamiflu x5 day	Weight based as above			
		Relenza x5 day	2 inhalations BID			
	Age 13-18	Tamiflu x5 day	75mg po BID			
		Relenza x5 day	2 inhalations BID			
	Healthy Adult	Tamiflu x5 day	75mg po BID			
	Relenza x5 day	2 inhalations BID				
Other Populations	Pregnancy & Lactation ¹⁰	Tamiflu x5 day	75mg po BID	<ul style="list-style-type: none"> ♦ higher risk of ILI pH1N1 complications in 3rd trimester ♦ higher risk of ILI pH1N1 through 4wks post-partum ♦ Tamiflu preferred: more data & ?fetal protection ♦ Relenza: less systemic absorption; limited data ♦ Relenza has been known to cause bronchospasm ♦ no dose adjustment required for Relenza 10-20% may be absorbed; ∴ monitor for systemic adverse effects (e.g. behavioural, suicide) ♦ Consider extending the treatment duration ICU: 10days &/or ↑ dosage to 150 mg BID (esp. if obese, >150kg) ♦ NOT for nebulizer/ventilator mechanical; not for reconstitution 	<p>RELENZA® (Zanamivir) Inhalation - Diskhaler</p> <ul style="list-style-type: none"> ♦ Dose/Duration: Treatment ⇒ BID inhalation x 5 days \$46 / 5days {2 inhalations stat; repeat after 2 hrs then 2 inhalations q12h} Prophylaxis ⇒ once daily inhalation x 10+ days ♦ SE: nasal/throat irritation 8-19%, headache, cough; SE > with prophylaxis vs tx Very rare: behaviour changes especially in kids Other: contains lactose ♦ NOT for use in those with severe underlying airway disease asthma/CPD 	
		Relenza x5 day	2 inhalations BID			
	COPD / Asthma	Tamiflu x5 day	75mg po BID			
	Renal Impairment	Tamiflu x5 day	CrCl: 10-30ml/min: 75mg OD CrCl: <10ml/min: AVOID, or 75mg q48h ¹¹			
		Relenza x5 day	2 inhalations BID			
Critically Ill / ICU - severe, progressive disease	Tamiflu x5* day	75 – 150mg po BID WHO 12, Ariano ? (depending on weight; renal fx permitting)				
	Relenza x5 day	2 inhalations BID				

CI=contraindication DI=drug interaction GBS=Guillain-Barre syndrome ILI=Influenza like illness SE=side effect; Antivirals Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-flu_drugs.pdf; CAP Pneumonia Tx Chart: <http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-CAP.pdf>; SK ILI Link: <http://www.health.gov.sk.ca/influenza-monitor>; Links: Canada <http://www.phac-aspc.gc.ca/fluwatch/>; CDC <http://www.cdc.gov/flu/about/season/index.htm>; WHO: <http://www.who.int/csr/disease/influenza/en/>; other pH1N1-Swine Flu Links at: <http://www.rxfiles.ca/rxfiles/uploads/documents/Flu-H1N1-Swine-Flu-Links.pdf>; www.fightflu.ca

Amantadine: Will it have any role? ♦ maybe if seasonal H1N1 sensitive & Tamiflu resistant strain common; ♦ option in combination with Tamiflu due to resistance ♦ Avoid in pregnancy! ♦ CNS side effects e.g. seizures; dosing adjustment required for ↓renal fx.
Prophylaxis in closed settings: Considered only if high risk of transmission or complications. Institutional exposure Tx at least 2wks & continued for 1 wk after the end of the outbreak; household post-exposure 60-90% effective Tx 10d. (More links on reference page online.)

Other: 1) **Pneumococcal vaccine**, if not previously vaccinated, for age <5 & ≥65 & others if high risk; complicating pneumonias commonly associated with *Strep. pneumoniae*. 2) Morbidity/mortality associated with 2^o bacterial (not only viral) infection e.g. pneumonia ∴ follow-up & treat (ABX, ECMO, Novalung CO₂ removal, NO steroids)^{13,14}.
 3) **Surgical masks** useful for those in proximity of ILI; **N95 respirator mask** useful for health care workers in very close contact (e.g. within 2 meters &/or swabbing/scoping) those with ILI.¹⁵

AS03-Adjuvanted H1N1 Pandemic Influenza Vaccine**AREPANRIX™ H1N1** (Link to Monograph: http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf)

- ◆ Efficacy: expected to be excellent match to the pH1N1-2009 strain with sero-conversion efficacy >95%
- ◆ Components:
 - **Antigen:** Split influenza virus, inactivated, containing antigen* equivalent to: A/California/7/2009 (H1N1)v-like strain (X-179A) 3.75µg HA** per 0.5mL dose (* isolated from virus propagated in eggs; ** HA = haemagglutinin) (egg allergy: if low risk, may administer vaccine & observe for 60mins; if high risk egg allergy, initial test dose of 10% followed by 90% after 30minutes of observation if no reaction.)
 - Preservative content is 5µg Thimerosal USP per 0.5mL dose or 2.5 micrograms organic mercury (Hg) per 0.5mL dose; metabolized to ethyl Hg & excreted in urine.
 - **Adjuvant/0.5mL dose:** DL-α-tocopherol 11.86 mg, Squalene 10.69 mg, Polysorbate 80 4.86 mg. (Adjuvants not used in previous Canadian influenza vaccines, but used in Europe & in several other Canadian vaccines.) Squalene from highly purified shark liver oil (Unknown significance with true fish allergy. May use a non-adjuvanted vaccine) (Squalene: an oil produced by plants, animals & in human skin; has been used as part of adjuvant (MF59) in vaccines for >10yrs; millions of doses have been administered & no signal of any auto-immune disease in any surveillance system. The Institute of Medicine of the U.S. National Academies of Science has issued four recent reports whose findings (1) fail to support hypotheses that vaccines are associated with multiple sclerosis, neurodevelopmental disorders (e.g., autism), or immune dysfunction; (2) provide no evidence for a temporal association of these conditions with vaccination; and (3) elucidate no biologically plausible basis for the purported relationships. Adjuvants are essential components in many routinely administered vaccines including diphtheria and tetanus toxoids, acellular pertussis vaccine, and hepatitis B vaccines.)^{16,17}
- ◆ Studies: efficacy & safety approval based on data from similar adjuvanted vaccines:
 - **Pandemrix:** an H1N1 vaccine (with 5.25 µg HA with AS03) vs non-adjuvanted data
 - Local & general side effects more common in adjuvanted group.
 - **Arepanrix™ H5N1:** an H5N1 vaccine with AS03 data (~ 3500 studied; safety summary done after ~9800)
- ◆ Adverse Effects: (**more** common) pain at injection site; muscle aches, lymphadenopathy; (see also monograph) Adverse event reporting for immunizations: <http://www.phac-aspc.gc.ca/im/aeif-form-eng.php>
A higher than expected number of reports of anaphylaxis with one lot of Arepanrix (A80CA007A) Cause is being investigated.
- ◆ Recent data suggests that acetaminophen may ↓ immune response to vaccines.¹⁸
- ◆ Available in Canada as of Oct 21, 2009.
- ◆ Note: rates of pH1N1 in Canada have risen significantly over the week preceding 24Oct09

Recent news about the pH1N1 risks & possible scenarios:

Dec 10, 2009 — H1N1 influenza **killed 10,000 Americans**, sent 213,000 to the hospital, and sickened 50 million — a sixth of the population — by mid-November, the US Centers for Disease Control and Prevention (CDC) estimates.
<http://www.reuters.com/article/marketsNews/idUSN2310824220091023> ; <http://www.digitaljournal.com/article/280948> ; <http://www.medscape.com/viewarticle/713674>

Feb/10 CDC- Estimates of 2009 H1N1 influenza cases in the U.S. from April 2009 to mid-January 2010 ranged widely, from 41 million to 84 million, according to the CDC. H1N1-related hospitalizations ranged from 183,000 to 378,000, while **deaths numbered between 8,330 and 17,160**. The majority of cases, hospitalizations, and deaths occurred among adults aged 18 to 64. http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm

Oct 24/09 Canada Public Health: The risk of experiencing severe side-effects after taking the H1N1 shot is literally one in one million, compared to the 20 to 35 per cent of the population who will get sick from this pandemic flu without protection, said Butler-Jones. **"If every single Canadian is inoculated, then 30 Canadians could have the potential for a severe side-effect, compared to 10 million people sick, 100,000 people in hospital and 10,000 people dead,"** he said.
<http://www.ctv.com/components/print.aspx?id=2142535&source=> ; <http://www.theglobeandmail.com/news/opinions/refusing-to-get-vaccinated-is-selfish/article1339120/>

Summary of **Canadian FluWatch Findings for the Week ending Nov 28, 2009**. The intensity of Pandemic (H1N1) 2009 in the population was moderately high with 804 hospitalizations, 139 ICU admissions and 56 deaths reported this week. Hospitalized cases occurred in all provinces and territories (P/T) that reported this week while the deaths were from all P/T except PE and 3 territories. From August 30 to November 28, 2009, a total of 6,314 hospitalized cases including **957 (15.2%) cases admitted to an intensive care unit (ICU)** as well as 259 deaths had been reported. The Pandemic (H1N1) 2009 strain accounted for nearly 100% of the positive influenza A subtyped specimens. <http://www.phac-aspc.gc.ca/fluwatch/index-eng.php> http://www.phac-aspc.gc.ca/fluwatch/09-10/w47_09/index-eng.php

Other

- ◆ Zanamivir IV (Special Access in Canada)
- ◆ Peramivir IV (USA Investigational in Canada): for emergency investigational use in pts not responding to po/inhaled antivirals FDA Oct09
Isolates resistant to oseltamivir may be resistant to peramivir.
Adults: 600mg IV daily x 5-10days over 30mins; Pediatric Treatment: 6-12mg/kg IV daily over 60mins. Adjust for renal function. See www.nejm.org November 2, 2009 (10.1056/NEJMp0910479): <http://content.nejm.org/cgi/content/full/NEJMp0910479?query=TOC>
- ◆ Unadjuvanted vaccine **not** recommended for everyone. For some particular groups, the unadjuvanted vaccine may not provide as strong an immune response. For this reason, it is recommended that the following groups **not** receive the unadjuvanted vaccine: People with weakened immune systems, Children between 6 months & 9 yrs, & People ≥65 yrs.

¹Public Health Agency of Canada. Portal to pH1N1 <http://www.phac-aspc.gc.ca/alert-alerthe/h1n1/index-eng.php>

²Committee on Infectious Diseases. Policy Statement--Recommendations for the Prevention and Treatment of Influenza in Children, 2009-2010. Pediatrics. 2009. Sep 7. Accessed 29Sep09 at: <http://pediatrics.aappublications.org/cgi/content/abstract/peds.2009-1806v1>

³Arepanrix – AS03 Adjuvanted H1N1 Pandemic Vaccine - Monograph http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf

⁴Marks JS, Halpin TJ. Guillain-Barré syndrome (GBS) in recipients of A/New Jersey influenza vaccine. JAMA. 1980 Jun 27;243(24):2490-4. <http://jama.ama-assn.org/cgi/content/abstract/243/24/2490?maxshow=8&HITS=10&hits=10&RESULTFORMAT=&fulltext=marks-guillain-barr%C3%A9&searchid=1&FIRSTINDEX=0&resourceype=HWCIT>

⁵<http://www.phac-aspc.gc.ca/alert-alerthe/h1n1/guidance-orientation-07-20-eng.php>

⁶FDA: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm183870.htm> ; Canadian Pediatric Society http://www.cps.ca/english/H1N1_IllnessAntiviral.htm#TABLE1

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⁷Public Health Agency of Canada. Interim Guidance for emergency use of oseltamivir (Tamiflu®) in children under one year of age in the context of 2009 (H1N1) pandemic. Accessed 29Sep09 at: <http://www.phac-aspc.gc.ca/alert-alerthe/h1n1/guidance-orientation-07-20-eng.php>

⁸Health Canada. Potential Medication Errors with Liquid Tamiflu - Information Update 2009-158; September 25, 2009. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2009/2009_158-eng.php

⁹CPHA's online *Compendium of Pharmaceuticals and Specialties* http://www.pharmacists.ca/content/products/ecps_english.cfm

¹⁰PHAC: Clinical Guidance for Pregnant and Breastfeeding Women with Influenza-Like Illness in the context of the Pandemic H1N1 2009 Virus. Accessed 30Sep09 at <http://www.phac-aspc.gc.ca/alert-alerthe/h1n1/guidance-orientation-07-09-eng.php>

¹¹Renal dosing (75mg q48hr) for CrCl <10ml/min from Saskatoon Health Region (SHR) – Pharmacy Department following personal communication with Winnipeg Regional Health Authority pharmacists (Fall 2009).

{Other from SHR Recommendations: **Peritoneal dialysis** 75 mg po now then 30mg po in 48 hours (total 2 doses).

Hemodialysis (HD) 3 or more HD sessions/week: 75 mg po after every dialysis x 3 doses; 2 HD sessions/week: 75 mg po after every dialysis x 2 doses; 1 HD session/week: 75 mg po after dialysis x 1 dose.

Continuous renal replacement therapy (CRRT): 75mg po BID.}

¹²http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html (Ariano, Robert E, Sitar, Daniel S, Zelenitsky, Sheryl A, et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. CMAJ 2010 0: cmaj.092127)

¹³The Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA. 2009 Oct 12. [Epub ahead of print]

¹⁴Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix et al; for the Canadian Critical Care Trials Group H1N1 Collaborative. Critically Ill Patients With 2009 Influenza A(H1N1) Infection. JAMA. 2009 Oct 12. [Epub ahead of print] at <http://jama.ama-assn.org/cgi/content/full/2009.1496>

¹⁵Shine, Kenneth I., Rogers, Bonnie, Goldfrank, Lewis R. Novel H1N1 Influenza and Respiratory Protection for Health Care Workers. N Engl J Med 2009 0: NEJMp0908437.

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With the official mid-range estimate for incidence of pandemic A/H1N1, the overall estimated case fatality rate was 26 (range 11-66) per 100 000.

See www.RxFiles.ca for more information about our academic detailing service and RxFiles Drug Comparison Charts book.



¹⁶ [Current Opinion in Infectious Diseases](#) Volume 20, Issue 3, June 2007, Pages 237-246

¹⁷ Harrison's Principles of Internal Medicine

¹⁸ Prymula R, Siegrist CA, Chlibek R, et al. Effect of prophylactic paracetamol/acetaminophen administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet*. 2009 Oct 17;374(9698):1339-50

¹⁹ WHO updated Nov/09 H1N1 Revised Guidance http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf

²⁰ Baz M, Abed Y, Papenburg J, Bouhy X, Hamelin ME, Boivin G. Emergence of Osetamivir-Resistant Pandemic H1N1 Virus during Prophylaxis. *N Engl J Med*. 2009 Nov 11. (see: Osetamivir resistant swine flu spreads in Welsh hospital *BMJ* Nov 28/09)

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