INFLUENZA – Overview 2009 - With Consideration for Pandemic H1N1 (pH1N1) [1]

Prepared by Loren Regier, Brent Jensen - www.RxFiles.ca - 30/09/2010

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 Sensitivities [2]

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] Sporadic Resistance n=300	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 ASO3-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 wk as opposed to 2.6 /million).[4] Protection onset ~2 wks. Uncertainty if prior seasonal vaccine ↑'s pH1N1 susceptibility. CI: 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. {Fluviral; Influvac thimerosal free & Vaxigrip thimerosal free in single dose only; 1 (FluMist live, atenuated, 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).

*Adjuvant is an antigen sparing component; has been used in Europe influenza vaccines but not N. America.

* pH1N1 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
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] ⇨	◆limited data; info based on group's ↑mortality[7] risk ◆0-1mon 2mg/kg bid; >1-3mon 2.5mg/kg bid; >3-12mon 3mg/kg bid; 19WHO
	Age 1-6	Tamiflu x5 day {adult dose at >40kg (>88lbs)}	Weight / Dose (po): ≤15kg 30mg BID; >15-23kg 45mg BID; >23-40kg 60mg BID; >40kg 75mg BID	◆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 *Ora-Sweet SF*; CPS[9] contains directions for compounding; suspension strength differs [10] or 15mg/ml; {clumping has been a problem. Alternately Humco Cherry Syrup USA; see instructions/info at http://www.tamiflu.com/hcp/dosing/extprep.aspx } ◆Relenza indicated for age ≥7 yr in Canada FDA ≥5 yr. Must be able to use the diskhaler.
	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	
Other Populations	Healthy Adult	Tamiflu x5 day	75mg po BID	
		Relenza x5 day	2 inhalations BID	
	Pregnancy & Lactation [10]	Tamiflu x5 day	75mg po BID	◆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 x5 day	2 inhalations BID	
	COPD / Asthma	Tamiflu x5 day	75mg po BID Avoid nebs to ↓ transmission; MDIs preferred & chamber.	◆Relenza has been known to cause bronchospasm
	Renal Impairment	Tamiflu x5 day	CrCl: 10-30ml/min: 75mg OD CrCl: <10ml/min: AVOID, or 75mg q48h [11]	◆no dose adjustment required for Relenza 10-20% may be absorbed; ∴ monitor for systemic adverse effects (e.g. behavioural, suicide)
		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)	◆Consider extending the treatment duration ICU:10days &/or ↑ dosage to 150 mg BID (esp. if obese, >150kg)
		Relenza x5 day	2 inhalations BID	◆NOT for nebulizer/ventilator mechanical; not for reconstitution

General Notes

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.

TAMIFLU® (Oseltamivir) Oral Capsules (30,45,75mg caps)

C

- 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.USA [8] Ensure units of measure in dosing instructions match those on the device given!!! Order in "mg"!
- Other: concerns about resistance if overused.

RELENZA® (Zanamivir) Inhalation - Diskhaler

C

- 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 x10+ 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/COPD

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. pneumonia*. 2) Morbidity/mortality associated with **2° bacterial** (not only viral) infection e.g. pneumonia ∴follow-up & treat (ABX, ECMO, Novalung CO_2 removal, NO steroids) [13,14]. 3) **Surgical masks** useful for those in proximity of ILI; **N95 respirator mask** useful option for health care workers in very close contact (e.g. within 2 meters &/or swabbing/scoping) those with ILI.[15]

www.Healthlineonline.ca ; Provincial Health Information Line (SK): 1-877-800-0002

Extras:

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 60min;
    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 ASO3) vs non-adjuvanted data
    - Local & general side effects more common in adjuvanted group.
  - **Arepanrix™ H5N1**: an H5N1 vaccine with ASO3 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/aefi-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 scenerios:

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.chtv.com/components/print.aspx?id=2142535&sponsor= ; 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

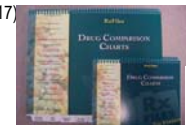
Other

- Zananamivir 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.

---

[1] Public Health Agency of Canada. Portal to pH1N1 http://www.phac-aspc.gc.ca/alert-alerte/h1n1/index-eng.php
[2] Committee 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
[3] Arepanrix – ASO3 Adjuvanted H1N1 Pandemic Vaccine - Monograph http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf
[4] Marks 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?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=marks+guillain-barre&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT
[5] http://www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance-orientation-07-20-eng.php
[6] FDA: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm183870.htm ; Canadian Pediatric Society http://www.cps.ca/english/H1N1_IllnessAntiviral.htm#TABLE1
Acosta EP, Jester P, Gal P, Wimmer J, Wade J, Whitley RJ, Kimberlin DW. Oseltamivir dosing for influenza infection in premature neonates. J Infect Dis. 2010 Aug 15;202(4):563-6.
[7] Public 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-alerte/h1n1/guidance-orientation-07-20-eng.php
[8] Health 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
[9] CPhA's online *Compendium of Pharmaceuticals and Specialties* http://www.pharmacists.ca/content/products/ecps_english.cfm
[10] PHAC: 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-alerte/h1n1/guidance-orientation-07-09-eng.php
[11] Renal 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.}
[12] http://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)
[13] The 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]
[14] Kumar 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
[15] Shine, Kenneth I., Rogers, Bonnie, Goldfrank, Lewis R. Novel H1N1 Influenza and Respiratory Protection for Health Care Workers.N Engl J Med 2009 0: NEJMp0908437.
ANZIC Influenza Investigators, Critical Care Services and 2009 H1N1 Influenza in Australia and New Zealand. N Engl J Med 2009 0: NEJMoa0908481
Birnkrant, Debra, Cox, Edward. The Emergency Use Authorization of Peramivir for Treatment of 2009 H1N1 Influenza. N Engl J Med 2009 0: NEJMp0910479.
Centers for Disease Control and Prevention (CDC). Updated interim recommendations — HIV-infected adults and adolescents: Considerations for clinicians regarding 2009 H1N1 influenza. Oct 21 , 2009. (http://www.cdc.gov/h1n1flu/guidance_HIV.htm)
Cowling BJ, Chan KH, Fang VJ, et al. Facemasks and hand hygiene to prevent influenza transmission in households: a cluster randomized trial. Ann Intern Med. 2009 Oct 6;151(7):437-46.
Garcia-Garcia L, Valdespino-Gómez JL, Lazcano-Ponce E, et al. Partial protection of seasonal trivalent inactivated vaccine against novel pandemic influenza A/H1N1 2009: case-control study in Mexico City. BMJ. 2009 Oct 6;339:b3928. doi: 10.1136/bmj.b3928.
Hessen, Margaret Trexler. In the Clinic: Influenza. Ann Intern Med November 3, 2009 151:ITC5-1; doi:10.1059/0003-4819-151-9-200911030-01011.
Jain, Seema, Kamimoto, Laurie, Bramley, et al. the 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team,. Hospitalized Patients with 2009 H1N1 Influenza in the United States, April-June 2009. N Engl J Med 2009 0: NEJMoa0906695
Jefferson T, Jones M, Doshi P, Del Mar C. Possible harms of oseltamivir—a call for urgent action. Lancet. 2009 Oct 17;374(9698):1312-3.
Loeb Mark; Dafoe Nancy; Mahony James; et al. Surgical Mask vs N95 Respirator for Preventing Influenza Among Health Care Workers: A Randomized Trial. JAMA. 2009;0(2009):2009.1466.
Louie Janice K.; Acosta Meileen; Winter Kathleen; et al. for the California Pandemic (H1N1) Working Group. Factors Associated With Death or Hospitalization Due to Pandemic 2009 Influenza A(H1N1) Infection in California. JAMA. 2009;302(17)
Cohen D. Complications: tracking down the data on oseltamivir. BMJ 2009;339:b5387.
Liam J Donaldson, Paul D Rutter, Benjamin M Ellis, et al. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study.BMJ 10 Dec 2009)
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 Oseltamivir-Resistant Pandemic H1N1 Virus during Prophylaxis. N Engl J Med. 2009 Nov 11. (see: Oseltamivir resistant swine flu spreads in Welsh hospital BMJ Nov 28/09)

Additional references:

ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System. Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study. BMJ. 2010 Mar 18;340:c1279. doi: 10.1136/bmj.c1279.
Canadian Society of Allergy and Clinical Immunology ADMINISTRATION OF H1N1 AND SEASONAL INFLUENZA VACCINE TO EGG ALLERGIC INDIVIDUALS http://www.csaci.ca/include/files/CSACI_H1N1_Statement.pdf
Cauchemez, Simon, Donnelly, Christl A., Reed, Carrie, et al. Household Transmission of 2009 Pandemic Influenza A (H1N1) Virus in the United States. N Engl J Med 2009 361: 2619-2627.
CDC data strengthen the evidence that the risk for Guillain-Barré syndrome (GBS) associated with the 2009 H1N1 vaccine is similar to the risk seen with seasonal flu vaccines, according to an *MMWR* report. The CDC's analysis of data from October 2009 through March 2010 found that the incidence of GBS was 1.92 per 100,000 person-years among vaccinated individuals and 1.21 per 100,000 person-years among the unvaccinated. If final data confirm this finding, the CDC says, then this would translate to 0.8 excess GBS cases for every 1 million vaccinations — a rate comparable to that found with seasonal flu vaccination. *MMWR* article (Free) http://www.cdc.gov/mmwr/preview/mmwrhtml/mm59e0602a1.htm?s_cid=mm59e0602a1_x
Chen Mark I. C.; Lee Vernon J. M.; Lim Wei-Yen; et al. 2009 Influenza A(H1N1) Seroconversion Rates and Risk Factors Among Distinct Adult Cohorts in Singapore. JAMA. 2010;303(14):1383-1391.
Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. Int J Antimicrob Agents. 2010 Feb 26.
Gagnon R, Primeau MN, Roches AD, et al. on behalf of the PHAC-CIHR influenza Research Network (PCIRN). Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. J Allergy Clin Immunol. 2010 Jun 23.
Gaur AH, Bagga B, Barman S, Hayden R, et al. Intravenous Zanamivir for Oseltamivir-Resistant 2009 H1N1 Influenza. N Engl J Med. 2009 Dec 23. [Epub ahead of print]
Greer LG, Sheffield JS, Rogers VL, Roberts SW, McIntire DD, Wendel GD Jr. Maternal and neonatal outcomes after antepartum treatment of influenza with antiviral medications. Obstet Gynecol. 2010 Apr;115(4):711-6.
Kelso JM, Li JT, Nicklas RA, et al. Joint Task Force on Practice Parameters. Adverse reactions to vaccines. Ann Allergy Asthma Immunol. 2009 Oct;103(4 Suppl 2):S1-14.
Lee, Vernon J., Yap, Jonathan, Cook, Alex R. et al; Oseltamivir Ring Prophylaxis for Containment of 2009 H1N1 Influenza Outbreaks, N Engl J Med 2010 362: 2166-2174.
Liang X-F et al. Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: A multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2010 Jan 2; 375:56.
Libster R, Bugna J, Coviello S, et al. Pediatric Hospitalizations Associated with 2009 Pandemic Influenza A (H1N1) in Argentina. N Engl J Med. 2009 Dec 23. [Epub ahead of print]
Loeb Mark; Russell Margaret L.; Moss Lorraine; et al. Effect of Influenza Vaccination of Children on Infection Rates in Hutterite Communities: A Randomized Trial. JAMA. 2010;303(10):943-950.
Louie, Janice K., Acosta, Meileen, Jamieson, Denise J., et al., the California Pandemic (H1N1) Working Group, Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California. N Engl J Med 2010 362: 27-35.
Mai LQ, Wertheim HF, Duong TN, et al. the Vietnam H1N1 Investigation Team. A Community Cluster of Oseltamivir-Resistant Cases of 2009 H1N1 Influenza. N Engl J Med. . [Epub ahead of print]
Memoli MJ, Hrabal RJ, Hassantoufighi A, et al. Rapid selection of oseltamivir- and peramivir-resistant pandemic H1N1 virus during therapy in 2 immunocompromised hosts. Clin Infect Dis. 2010 May 1;50(9):1252-5.
Nguyen HH, Tumpey TM, Park HJ, et al. Prophylactic and therapeutic efficacy of avian antibodies against influenza virus H5N1 and H1N1 in mice. PLoS One. 2010 Apr 13;5(4):e10152.
Nolan Terry; McVernon Jodie; Skeljo Maryanne; et al. Immunogenicity of a Monovalent 2009 Influenza A(H1N1) Vaccine in Infants and Children: A Randomized Trial. JAMA. 2009;0(2009):2009.1911.
Plennevaux E et al. Immune response after a single vaccination against 2009 influenza A H1N1 in USA: A preliminary report of two randomised controlled phase 2 trials. Lancet 2010 Jan 2; 375:41.
Shen J, Ma J, Wang Q. Evolutionary trends of A(H1N1) influenza virus hemagglutinin since 1918. PLoS One. 2009 Nov 17;4(11):e7789.
Siston AM, Rasmussen SA, Honein MA, 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 Apr 21;303(15):1517-25.
Vajo Z, Tamas F, Sinka L, et al. Safety and immunogenicity of a 2009 pandemic influenza A H1N1 vaccine when administered alone or simultaneously with the seasonal influenza vaccine for the 2009-10 influenza season: a multicentre, randomised controlled trial. Lancet. 2009 Dec 15.
Van der Vries Erhardl Emergence of a Multidrug-Resistant Pandemic Influenza A (H1N1) Virus. N Engl J Med 2010; 363:1381-1382.
van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. Arthritis Rheum. 2009 Dec 28;62(1):75-81. [Epub ahead of print]
Waddington CS, Walker WT, Oeser C, et al. Safety and immunogenicity of AS03B adjuvanted split virion versus non-adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomised, parallel group, multicentre study. BMJ.
Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, Clinical Aspects of Pandemic 2009 Influenza A (H1N1) Virus Infection. N Engl J Med 2010 362: 1708-1719.
Yu Hongjie, Liao Qiaohong, Yuan Yuan, et al. Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China. BMJ 341:doi:10.1136/bmj.c4779 (28 Sept 2010).