

# Influenza A H1N1 infection

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## Managing the ILI patient in the outpatient setting



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# Infectiousness & Incubation period

- Estimated incubation period 1-7 days, [ likely 1-4 days ].
  - **Infectious period** for a confirmed case of swine influenza A (H1N1) virus infection is defined as 1 day prior to the case's illness onset to 7 days after onset.
  - **Close contact** is defined as: within about 3 feet of an ill person who is a confirmed or suspected case of influenza A H1N1 virus infection during the case's infectious period.
  - H1N1 appears to be more contagious than seasonal influenza. The 2° attack rate of seasonal influenza ranges from 5% to 15%. **Current estimates of the 2° attack rate of H1N1 range from 22% to 33%.**
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# Clinical Features of Influenza A/H1N1

## □ Clinical Findings

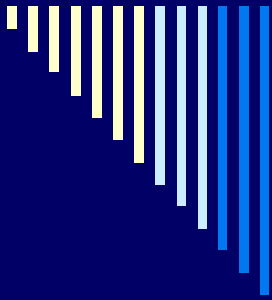
Uncomplicated disease manifest with fever, headache, upper respiratory tract symptoms (cough, sore throat, rhinorrhea), myalgia, fatigue, vomiting, or diarrhea.

## □ Complications

Insufficient information to date about clinical complications of influenza A (H1N1) virus infection. Clinical syndromes have ranged from mild respiratory illness, to lower respiratory tract illness, dehydration, or pneumonia.

Can expect complications similar to seasonal flu: exacerbation of underlying chronic medical conditions, URIs (sinusitis, otitis media, croup) LRT disease (pneumonia, bronchiolitis, status asthmaticus), cardiac (myocarditis, pericarditis), musculoskeletal (myositis, rhabdomyolysis), neurologic (acute & post-infectious encephalopathy, encephalitis, febrile seizures, status epilepticus), and 2° bacterial pneumonia.

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**Symptoms  
of 268  
hospitalized  
novel H1N1  
patients  
(US)**

Symptom	Number (%)
Fever*	249 (93%)
Cough	223 (83%)
Shortness of breath	145 (54%)
Fatigue/Weakness	108 (40%)
Chills	99 (37%)
Myalgias	96 (36%)
Rhinorrhea	96 (36%)
Sore Throat	84 (31%)
Headache	83 (31%)
Vomiting	78 (29%)
Wheezing	64 (24%)
Diarrhea	64 (24%)

*Source: CDC*



# Initial outbreak in New York schools

MMWR Weekly, May 8, 2009 / 58(17);470-472

*The most frequently reported symptoms are*

- cough (98%),
- subjective fever (96%),
- fatigue (89%),
- headache (82%),
- sore throat (82%),
- runny nose (82%),
- chills (80%),
- muscle aches (80%).
- Nausea (55%),
- stomach ache (50%),
- diarrhoea (48%),
- shortness of breath (48%)
- joint pain (46%)

*Among pts who reported a maximum temperature, the mean was 39.0 °C. In total, 95% pts reported subjective fever plus cough and/or sore throat, meeting the CDC definition for influenza-like illness (ILI).*



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## Medical care for patients with novel influenza A (H1N1) virus

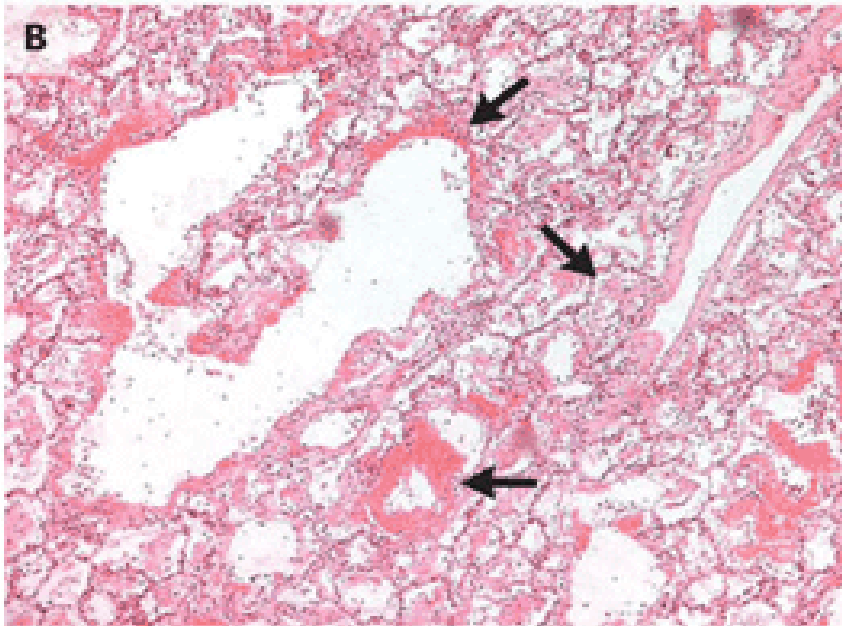
- Not all patients with suspected novel influenza (H1N1) infection need to be seen by a health care provider. For most people, the illness appears to be mild and self-limiting.
  - Minority of people with influenza A(H1N1) has had severe illness with complications. Many, but not all, have underlying risk factors (co-morbidities) that are likely to have contributed to the severity of the condition.
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# Complications of Influenza:

- Respiratory complications are the most common ones (esp secondary infections).
- At times these complications, eg. an exacerbation of COPD, may be the presenting symptom.
- Cardiac events are not uncommon.

Complications of influenza	Major clinical category
Respiratory	Pneumonia: primary viral, secondary bacterial, combined Upper respiratory: otitis media, sinusitis, conjunctivitis Acute laryngotracheo-bronchitis (croup) Bronchiolitis Complication of pre-existing disease
Cardiovascular	Myocarditis Pericarditis
Muscular	Rhabdomyositis Rhabdomyolysis with myoglobinuria and renal failure
Neurological	Encephalitis Reye's syndrome Guillain-Barré syndrome Transverse myelitis
Systemic	Toxic shock syndrome Sudden death



## Initial Radiograph of the Lung and Lung-Tissue Sample

The CXR shows bilateral alveolar opacities in the base of both lungs that progressed and became confluent. The specimen (H&E stain) shows necrosis of bronchiolar walls (top arrow), a neutrophilic infiltrate (middle arrow), and diffuse alveolar damage with prominent hyaline membranes (bottom arrow). Bacterial cultures were negative on admission, and no evidence of bacterial infection of the lungs was found. The patient ultimately died.



# Co-morbidities / Risk factors

Those considered vulnerable to severe outcomes & should be a focus of early identification, assessment and treatment, include the following:

- ❑ Chronic respiratory conditions, eg asthma, COPD, OSA
- ❑ Pregnant women, esp. in second or third trimester
- ❑ Obesity (BMI > 30) & morbid obesity (BMI > 40)
- ❑ Other predisposing conditions, such as chronic cardiac disease (not simple HPT), and chronic illnesses including diabetes mellitus, renal failure, haemoglobinopathies, immunosuppression.
- ❑ Adults  $\geq$  65 years of age esp. those with other chronic diseases
- ❑ Children under the age of 5 years, esp. those < 2 years

As more epidemiologic & clinical data become available, these risk groups might be revised.

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# Groups vulnerable to the severe outcomes

Vulnerable Group	Evidence
Chronic respiratory conditions eg asthma esp. those with moderate persistent disease, COPD, OSA	↑ hospitalisation, ICU admissions (USA, Mexico, Canada, South America, UK)
Pregnant women (esp. in 2 <sup>nd</sup> , and 3 <sup>rd</sup> . trimesters)	↑ hospitalisation, ICU admissions, spontaneous abortion, PROM, foetal and maternal death ( USA, Mexico, South America, UK)
Persons with morbid obesity	↑ hospitalisation, ICU admissions (USA, Mexico,)



# Obesity & H1N1

- Obesity (BMI  $\geq$  to 30-39.9) noted in about 15% of pts
- Morbid obesity (defined as BMI  $\geq$  40) in about 8% of pts
- Although the importance of obesity as a contributing factor to novel H1N1 complications is currently unknown, many obese persons have other known underlying diseases that put them at risk for flu complications.
- Series of 10 pts with influenza A (H1N1) virus infection and ARDS at a tertiary-care ICU in Michigan. Of the 10 pts, 9 were obese ([BMI]  $\geq$ 30), including 7 who were extremely obese (BMI  $\geq$ 40)

## Vulnerable Group

Chronic illness predisposing to severe influenza such as:

- cardiac disease (not simple HPT)
- diabetes mellitus,
- chronic renal disease (GFR <30 mL/min),
- haemoglobinopathies,
- immunosuppressed (including cancers on active therapy, HIV/AIDS, regular steroid use)
- chronic neurological conditions

## Evidence

↑ hospitalisation, ICU admissions  
(USA, Mexico, Canada, South America, UK)

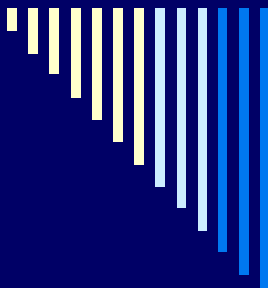


## Recognition of moderate to severe illness & deterioration

Pts with moderate / severe illness, or those who are deteriorating, whether from vulnerable grp or not, need to be provided with antiviral therapy.

Severe illness following influenza occurs in at least 3 ways:

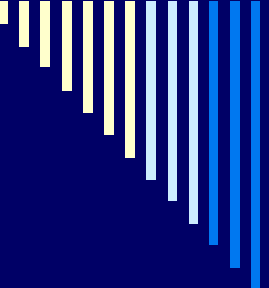
1. severe 1<sup>o</sup> viral infection with ARDS occurring relatively early in illness related to viral pneumonia (within 1<sup>st</sup> 4 days)
2. bacterial pneumonia, complicating initial bronchitis caused by influenza, or following apparent recovery from initial illness (a biphasic clinical picture can be obvious)
3. destabilisation of pre-existing chronic condition. This may present as respiratory distress related to exacerbations of COPD, asthma or CCF. Influenza can also cause acute destabilisation of diabetes, CRF, chronic liver disease etc.



# Clinical detection of severity of influenza related illness (1)

Respiratory distress –RR >20–24/min & ↑ work of breathing

- Noticeable respiratory effort, rapid breathing or noisy breathing in previously normal person at rest is abnormal. People can adopt different patterns of breathing when sick, but RR > 20 breaths/min is concerning (> 24 / min definitely abnormal)
  - People with pre-existing lung or heart conditions may already have some respiratory distress at rest. In general, this will be greatly accentuated if there are influenza complications such as exacerbations of COPD, asthma , CCF or bacterial pneumonia.
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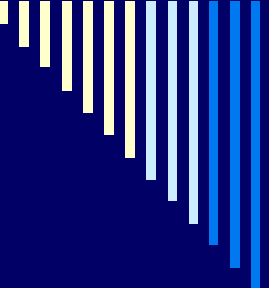
## Clinical detection of severity of influenza related illness (2)

Abnormal pulse oximetry – Significant ↓ in SpO<sub>2</sub> (<92%)

- Measurement of a low SpO<sub>2</sub> can detect severe or complicated influenza in some cases. Most useful in people with pre-existing heart / lung conditions who already have reduced SpO<sub>2</sub> (eg ≤ 92%); slight worsening of respiratory function due to influenza will cause significant fall in SpO<sub>2</sub> < 90%.
- In people with normal pre-existing respiratory and cardiac function, SpO<sub>2</sub> < mid 90's is abnormal and < low 90s is **very abnormal and indicates severe disease.**

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Due to individual patient's ability to compensate, always correlate SpO<sub>2</sub> with clinical condition of patient (esp. if SpO<sub>2</sub> is normal)



# Clinical detection of severity of influenza related illness (3)

Generalised organ dysfunction – ↓ baseline function or exercise capacity

- “Loss of function” includes confusion, incontinence & falls: common features of severe influenza and pneumonia in elderly. Hypotension, marked tachycardia & hyperthermia or hypothermia are features of significant sepsis. Diabetics with severe influenza can present with hyperglycemia .
  - “↓ effort capacity” – If significantly ↓ because of worsening breathlessness during influenza, possibility of respiratory complications should be considered.
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# RECOMMENDATION:

## Who needs medical assessment?

Patients with ILI:

- who have moderate or severe illness (based on the Home Assessment Tool) OR
  - who have significant co-morbidities and hence are at high risk for complications from influenza OR
  - who have fever ( $\geq 38^{\circ}\text{C}$ ) after 48 hrs from illness onset
- should seek EARLY professional medical assessment (preferably within first 2 days of illness) from the nearest hospital or health clinic (depending on severity of symptoms)



# Patient Home Assessment Tool

**Patients with ILI are advised to seek medical care should they develop any of the symptoms & signs listed as below :**

- 1 Respiratory Difficulties: Shortness of breath, rapid breathing or Purple or blue discoloration of lips**
- 2 Coughing out blood or blood streaked sputum
- 3 Persistent chest pains
- 4 Persistent diarrhea and / or vomiting
- 5 Fever persisting beyond 2 days or recurring after 2 days
- 6 Abnormal behavior , confusion, less responsive , convulsion
- 7 Dizziness when standing and/or reduced urine production



# RECOMMENDATION: Who needs to be Tested?

Laboratory testing (RT-PCR) for Influenza A H1N1 to assist with clinical management is indicated for those who meet the **case definition for ILI \*** and are:

- symptomatic **patients with moderate to severe disease** (see clinical assessment tool below) who will require hospitalization

\* **Influenza-like-illness (ILI)** is defined as fever (esp. temperature > 38°C) and a cough and/or a sore throat in the absence of a **KNOWN** cause other than influenza

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## Patients with and any of the following parameters should be considered for admission to the of nearest hospital

Respiratory impairment: any of the following

- Tachypnoea, respiratory rate  $> 24/\text{min}$
- Inability to complete sentence in one breath
- Use of accessory muscles of respiration, supraclavicular recession
- Oxygen saturation  $\leq 92\%$  on pulse oximetry
- Decreased effort tolerance since onset of ILI
- Respiratory exhaustion
- Chest pains

Evidence of clinical dehydration or clinical shock

- Systolic BP  $< 90\text{mmHg}$  and/or diastolic BP  $< 60\text{mmHg}$
- Capillary refill time  $> 2$  seconds, reduced skin turgor

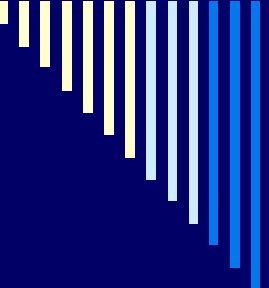
Altered Conscious level (esp. in extremes of age)

- New confusion, striking agitation or seizures

Other clinical concerns:

- Rapidly progressive (esp. high fever  $> 3$  days) or serious atypical illness
- Severe & persistent vomiting and diarrhea

**Clinical assessment tool for moderate to severe influenza**



## Patients to be hospitalized for novel influenza A / H1N1 virus

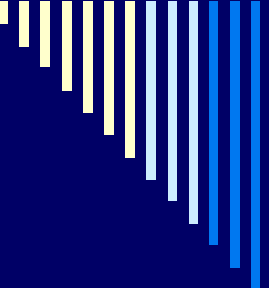
The following patients will be admitted to the flu ward / cubicle of the hospital:

- All patients fulfilling criteria of ILI with any of the parameters listed in the clinical assessment tool for moderate to severe influenza (with or without co-morbidities)

Patients with suspected influenza manifesting with mild disease will not require admission to hospital

Patients should be clinically assessed and the admission decision will be based on the severity of the illness.

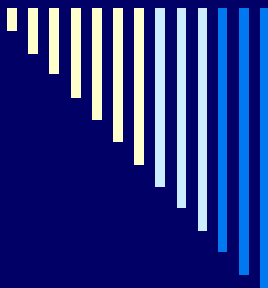
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## Defining the cause of the severe clinical illness (1)

### Severe influenza

- primary viral pneumonia or viral-induced acute lung injury usually occur within the first 4 days of the illness and are associated with respiratory distress and sometimes a dry cough, along with fever and the other symptoms of influenza like illness (ILI).
  - Bacterial pneumonia – important complication of pandemic influenza and presents as a biphasic illness with features of an ILI followed by 2<sup>nd</sup>. rise in T° or a persistent fever (>3 days from onset of ILI) with purulent sputum.
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## Defining the cause of the severe clinical illness (2)

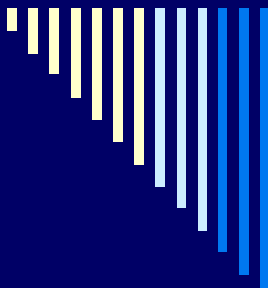
### Pneumonia

- Distinguishing between acute bacterial bronchitis and bronchopneumonia without CXR can be difficult. High persistent fever, pleuritic chest pain and respiratory distress all suggest pneumonia. In the setting of an influenza pandemic, development of purulent sputum should trigger the use of empiric antibiotics (*choice as in National Antibiotic Guidelines / standard guidelines*)
- Initial low or normal TWBC followed by neutrophilia with persistent (or recurrence) of fever may suggest a bacterial complication often a pneumonia

# Sputum production

- *Purulent sputum - in normal people, green or yellow sputum correlates reasonably well with bacterial bronchitis or pneumonia.*
- *↑ volume of sputum or deepening colour (dark yellow / green) of sputum in a COPD pt also correlates with bacterial infection.*
- *People with asthma can produce coloured sputum due to eosinophilic inflammation, but in context of an AEBA triggered by influenza, 2° bacterial infection should be considered.*





# Antiviral Treatment for Novel Influenza A / H1N1

## RECOMMENDATION:

Antiviral Treatment is recommended for:

- **All hospitalized patients (ie. those with moderate to severe disease) with confirmed or suspected novel influenza A H1N1.** Empirical therapy for suspected patients with severe disease should be considered if the turnaround time for H1N1 confirmation is prolonged. The antiviral treatment maybe stopped if the results are negative.



# Antiviral Therapy

- **Type of Antiviral:** Oseltamivir is the preferred choice; zanamivir might be used as an alternative. The quality of evidence if considered on a continuum, is lower for zanamivir compared to oseltamivir. Clinicians should not administer amantadine or rimantadine alone as a 1<sup>st</sup>. line treatment.

*Since functional groups of the 2 neuraminidase-inhibitors have differences in their binding sites, mutants resistant to 1 drug maybe susceptible to the other.*

## **Oseltamivir** dosage:

- Duration 5 days
- Adults & adolescents > 13 yrs: 75 mg bd  
(in severe cases, dosage can be doubled to 150 mg bd)
- For children (according to weight):

<15kg:	30mg bd
15-23kg:	45mg bd
23-40kg:	60mg bd
> 40kg:	75mg bd

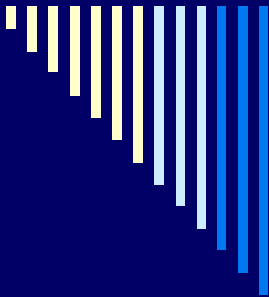
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**Renal adjustments:** patients with a serum creatinine clearance between 10 - 30 ml/min: treated with 75 mg daily for 5 days



# Antiviral Therapy

- **Zanamivir** dosage:  
10mg (2 puffs) bd for 5days (Adults & children)  
(Children < 5 yrs may have difficulty with Diskhaler™)
- **In patients with bronchospasm:** Zanamivir is not recommended for the treatment of patients with underlying airways disease (eg. asthma or COPD). Patients with pulmonary dysfunction should always have a fast-acting bronchodilator available and discontinue zanamivir if respiratory difficulty develops.
- No dosage adjustment is required in patients with renal impairment



# Managing ILI patients in the outpatient setting

Patient presenting with ILI symptoms within 2 days of onset of illness

Assessed by Primary doctor  
•Does patient have any symptoms and signs of moderate or severe illness (Clinical assessment Tool)

If NO moderate/severe illness;  
•Does patient have a co-morbidity associated with increased risk of influenza complications?

If patient HAS moderate or severe illness;  
•Admit to nearest hospital for screening and treatment

If patient has co-morbidity ;  
•Start oseltamivir / zanamivir at standard doses for 5 days & continue home care with Home assessment Tool monitoring

If patient has NO comorbidity;  
•Does patient have fever  $\geq 38^{\circ}\text{C}$  after 48hours from onset of illness ?  
•Are symptoms rapidly progressive even within first 2days?

•If patient develops moderate or severe illness with Home Assessment Tool, seek medical reassessment  
•If patient improves, complete course of antivirals

•If YES to either of the above; start oseltamivir / zanamivir at standard doses for 5 days & continue with Home Assessment Tool



# Viruses resistant to oseltamivir identified: 20<sup>th</sup>. August 2009

- ❑ WHO: notified of 12 cases of oseltamivir resistant virus.
- ❑ mutation in the neuraminidase (H275Y) that confers resistance to oseltamivir, though the viruses remain sensitive to zanamivir.
- ❑ Of these , 8 assoc. with oseltamivir post exposure prophylaxis, 1 with treatment of uncomplicated illness, and 2 from immunocompromised pts receiving oseltamivir tx.
- ❑ Japan 4, USA 2, China, Hong Kong SAR China 2, and 1 in Denmark, Canada, Singapore and China.
- ❑ There is also no evidence of onward transmission from these cases.