Influenza A (H1N1)v :
Problemi di gestione clinica

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Number and percentage of confirmed cases of novel influenza A (H1N1) virus infection, by patient age group and hospitalization status --- United States and Mexico, March 1--May 5, 2009

Age (yrs)	United States			Mexico		
	Total	Hospitalized		Total	Hospitalized	
		No.	(%)		No.	(%)
<5	**51**	7	(14)	**115**	6	(5)
5--14	**204**	9	(4)	**248**	4	(2)
15--29	**250**	9	(4)	**313**	13	(4)
30--44	**68**	9	(13)	**154**	16	(10)
45--59	**36**	1	(3)	**94**	7	(7)
≥60	**10**	0	(0)	**21**	2	(10)
Not available	**23**	0	(0)	**4**	4	(100)
Total	**642**	**35**	**(5)**	**949**	**52**	**(6)**

MMWR May 8, 2009 / 58(17);453-458

Table 1. Characteristics and Symptoms of the 642 Patients with Confirmed Swine-Origin Influenza A (H1N1).

Characteristic	Value
Male sex — no./total no. (%)	302/592 (51)
Age	
Median — yr	20
Range — yr	3 mo to 81 yr
Age group — no./total no. (%)	
0–23 mo	14/532 (3)
2–4 yr	27/532 (5)
5–9 yr	65/532 (12)
10–18 yr	212/532 (40)
19–50 yr	187/532 (35)
≥51 yr	27/532 (5)
Student in school outbreak — no./total no. (%)	104/642 (16)
Recent history of travel to Mexico — no./total no. (%)*	68/381 (18)
Clinical symptoms — no./total no. (%)	
Fever	371/394 (94)
Cough	365/397 (92)
Sore throat	242/367 (66)
Diarrhea	82/323 (25)
Vomiting	74/295 (25)
Hospitalization — no./total no. (%)	
Total	36/399 (9)
Had infiltrate on chest radiograph	11/22 (50)
Admitted to intensive care unit	8/22 (36)
Had respiratory failure requiring mechanical ventilation	4/22 (18)
Treated with oseltamivir	14/19 (74)
Had full recovery	18/22 (82)
Vaccinated with influenza vaccine during 2008–2009 season	3/19 (16)
Died	2/36 (6)

* A recent history was defined as travel to Mexico no more than 7 days before the onset of illness.

Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team *N Engl J Med 2009;361*.

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TABLE 1. Case characteristics for 30 hospitalized patients with novel influenza A (H1N1) — California, April 15, 2009–May 17, 2009

Case characteristic	No.	(%)
Age group (yrs)		
<5	6	(20)
5-19	7	(23)
20-39	8	(27)
40-59	4	(13)
>60	5	(17)
Chronic comorbid illness*		
Chronic lung disease†	11	(37)
Other immunosuppression§	6	(20)
Chronic cardiac disease¶	5	(17)
Diabetes mellitus	4	(13)
Obesity	4	(13)
Seizure disorder	3	(10)
Pregnancy	5	(17)
Symptoms and signs		
Fever	29	(97)
Cough	23	(77)
Vomiting	14	(46)
Shortness of breath	13	(43)
Chills	11	(37)
Sore throat	10	(33)
Body aches	10	(33)
Rhinorrhea	9	(30)
Headache	5	(17)
Conjunctivitis	3	(10)
Diarrhea	3	(10)
Altered mental status	2	(7)
Generalized weakness	2	(7)
Clinical findings and course		
Infiltrates on chest radiograph**	15	(60)
Intensive-care unit admission	6	(20)
Mechanical ventilation	4	(13)
Antiviral treatment	15	(50)

* Conditions listed are not mutually exclusive; certain patients had multiple underlying chronic diseases.
† Includes asthma, chronic obstructive pulmonary disorder, bronchopulmonary dysplasia/respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia, Sjogren syndrome, and obstructive sleep apnea.
¶ Includes congenital heart disease, atrial fibrillation, status-post aortic valve replacement, and coronary artery disease.
§ Includes immunosuppressive drugs, cancer, and congenital immunodeficiency.
** Out of 25 cases with chest radiographs.

JAMA. 2009;302(2):137-140

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Hospitalized Pandemic H1N1 Cases, U.S. (N = 268)

- **Median time from onset to admission**
  - 3 days (range 1-14 days)
- **Median length of stay**
  - 3 days (range 1-59)
- **Median age**
  - 22 years (range 21 days-86 years)
- **128 female (48%), 140 male (52%)**

71% with underlying co-morbidities
21% admitted to ICU
13% required mechanical ventilation
17 deaths (6.3%)

www.cdc.gov/h1n1flu/surveillanceqa.htm

Underlying Conditions among 268 Hospitalized Patients With Novel Influenza A (H1N1) Reported to CDC Compared to US Prevalence

Condition	Prevalence, hospitalized H1N1 patients	Prevalence, General US Population
Asthma or COPD	32%	8% (asthma) 4% (COPD)
Diabetes	15%	6%
Immunocompromised	13%	
Chronic cardiovascular disease*	14%	7%
Current Smoker	10%	18%
Chronic Renal Disease	9%	17%
Neurocognitive disorder	7%	
Neuromuscular disorder	7%	0.03%
Pregnant	6%	1%
Seizure disorder	6%	1%
Cancer	3%	4%
Obesity	*8%*	27%

***Excludes hypertension*Excludes hypertension**

www.cdc.gov/h1n1flu/surveillanceqa.htm

Sintomi e gravità dell'influenza

- **I sintomi**: sono quelli della classica influenza
  - Febbre, Sonnolenza, Tosse, Perdita di appetito
  - Mal di gola, Raffreddore, Nausea e Vomito, (Diarrea)

- **La gravità:** si può presentare, in genere, in forma medio-lieve; **talora in forma grave**, soprattutto quando:

  - **Colpisce persone con malattie croniche o debilitanti**
  - **Si complica con la polmonite**

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Complicanze dell'influenza

- Complicanze respiratorie
  - Polmonite da virus influenzale
  - Broncopolmonite da sovrainfezione batterica
- Complicanze extra-respiratorie
  - Miocardite
  - Encefalite, neurite, radicolite
  - Sindrome di Reye
- Aggravamento delle condizioni in pazienti con pre-esistenti malattie cardiache, broncopolmonari e renali

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- E’ impossibile distinguere su base clinica I casi di influenza H1N1 da quelli dovuti alla maggior parte dei comuni virus

- 50% dei soggetti infetti sono asintomatici o presentano una sintomatologia lieve

- bambini e giovani adulti risultano più interessati

- variabilità dello spettro clinico :

  - forme non febbrili,
  - lieve/moderato interessamento della basse vie respiratorie,
  - polmonite di grado severo e/o fatale

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Table 2: Characteristics of 32 patients who had confirmed H1N1 viral primary pneumonitis

Variables	Value
Age, yr	
Mean (SD)	40 (13.9)
Median (IQR)	36 (31-52)
Male sex , n (%)	21 (73.3)
APACHE II score, mean (SD)	13.8 (6.4)
SOFA score , mean (SD)	7.1 (3.3)
Days from onset symptoms to ICU admission	
Mean (SD)	3.9 (2.2)
Median (IQR)	3 (2- 6)
Days from ICU admission to diagnosis	
Mean (SD)	3.3 (3.1)
Median (IQR)	2 (1- 6)
Days from onset symptoms to first antiviral dose	
Mean (SD)	5.7 (5.1)
Median (IQR)	4 (1 – 8)
Laboratory finding , median (IQR)	
Leukocyte count (per mm^3)	5650 (3000 -9200)
Platelets count (per mm^3)	152.000 (124.00 – 227.000)
Serum Lactate dehydrogenase (U/L)	953 (728 – 1230)
Serum Creatine Kinase (U/L)	392 (226 -3047)
Serum creatinine (mg/dL)	0.87 (0.63 – 1.22)
AST (U/L)	62 (38 – 119)
ALT (U/L)	51 (35 – 111)
Mechanical ventilation on admission, n (%)	
NO	8 (25)
Non-invasive	2 (6.2)
Invasive	22 (68.8)
Adverse event, n (%)	
Vasopressor drugs	20 (62.5)
Hemodialysis	2 (6.2)
Hemofiltration	5 (15.6)
Refractory hypoxemia requiring prone ventilation	8 (25.0)
Secondary superinfection	3 (9.3)
Opacity in initial x-ray chest, n (%)	
1/4 quadrants	5 (15.6)
2/4 quadrants	4 (12.5)
3/4 quadrants	8 (25.0)
4/4 quadrants	15 (46.9)

Rello J et al.: Critical Care 2009, ***13:R148 doi:10.1186/cc8044***

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Transmission and Pathogenesis of Swine-Origin 2009 A(H1N1) Influenza Viruses in Ferrets and Mice

•Significant but not lethal pathogenicity from the pandemic A(H1N1)v – somewhat more than for seasonal A(H1N1) but considerably less than that seen for A (H5N1) (bird flu) in ferrets.

•In contrast to the seasonal influenza A H1N1 confined to the nasal cavity the pandemic influenza A/H1N1v isolates also replicated in the trachea, bronchi and bronchioles. No ferrets died from their infection,

•Droplet respiratory expression (but not transmission) occurring with the pandemic virus was higher than with seasonal influenza though not reaching the levels when using a 1918 pandemic virus.

•Successful and efficient ferret to ferret transmission but,

•Respiratory droplet transmission was significantly reduced compared to respiratory droplet transmission of the seasonal influenza virus.

•No systemic replication of the A(H1N1)v

•Pandemic viruses being found at higher levels in the lower respiratory tract of the infected individuals,

•Pandemic viruses in the intestinal tracts of the animals, which is consistent with some report of a explains the higher frequency of gastrointestinal symptoms observed in individuals affected by the pandemic virus.

•An ability of both viruses to infect the same cells in the respiratory tract (upper and lower) so increasing the risk of reassortment when co-infection occurs in humans.

Munster VJ et al. *Science 2009* . *Published online July 2 2009*
Maines TR et al. *Science 2009.* *Published online July 2 2009*

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Possible Pathogenesis in Severe Disease

Limited human and animal model data

- **Rapid progression of pneumonia**
  - ➢ Suggests viral infection of lower respiratory tract
    - Possible high viral replication triggering cytokine dysregulation (similar to highly pathogenic avian influenza H5N1 virus infection?)
    - Acute lung injury, rapid progression to ARDS
      - ➢ Refractory ARDS observed
- **Invasive bacterial co-infection**
- **Multi-organ failure, septic shock**
- **Muscle inflammation**
- **Potential for extrapulmonary dissemination**
  - Viremia, fecal shedding, etc.

Groups at High Risk for Complications from Influenza

- Children less than 5 years old.
- Persons aged 50 years or older.
- Children and adolescents (6 months – 18 years) who are receiving long-term aspirin therapy (risk of Reye's Syndrome).
- Pregnant women.
- Adults and children who have chronic pulmonary, cardiovascular, hepatic, hematological, neurologic, neuromuscular, or metabolic disorders.
- Adults and children who have immunosuppression (including HIV).
- Residents of nursing homes and other chronic-care facilities

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Treatment for Influenza A (H1N1) Virus

- **Hospitalized patients and those at higher risk for influenza complications should be prioritized.**
- Persons who are not at higher risk for complications or do not have severe influenza requiring hospitalization generally do not require antiviral medications for treatment or prophylaxis.
- **Antiviral treatment should be initiated within 48 hours** of symptom onset, but even those treated after 48 hours may have reduced morbidity and mortality.
- **Treatment should not wait for laboratory confirmation** of influenza because laboratory testing can delay treatment and because a negative rapid test for influenza does not rule out influenza.
- Recommended duration of treatment is 5 days.

www.cdc.gov.swineflu/recommendations

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TERAPIA ANTIVIRALE

Il trattamento con antivirali è fortemente raccomandato nei **soggetti identificati come casi** di influenza A(H1N1)v, che presentino i seguenti indicatori di gravità: ipossia (anche con radiografia del torace negativa), shock ipotensivo, alterazione del sensorio.

Il trattamento con antivirali è raccomandato nei **soggetti identificati come casi** di influenza A(H1N1)v, in persone che abbiano le seguenti condizioni che possono facilitare lo sviluppo di complicanze: gravidanza, asma in trattamento, obesi con body mass index superiore a 30.

L'uso degli antivirali deve essere considerato nei **soggetti identificati come casi** di influenza A(H1N1)v, che rientrano nelle categorie a rischio per lo sviluppo di complicanze in corso di influenza stagionale:

- bambini di età inferiore a 2 anni

- persone affette da malattie croniche polmonari, cardiovascolari (esclusa l'ipertensione), renali, epatiche, ematologiche, neurologiche, neuromuscolari, diabete ed altri disordini metabolici, infezione da HIV ed immunodepressi per cause naturali o iatrogene.

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PROFILASSI CON ANTIVIRALI

Indicazioni per la profilassi

Ppossono essere utilizzati indifferentemente sia l'oseltamivir che lo zanamivir.
La durata del trattamento profilattico è di 10 giorni dall'ultima esposizione.

La profilassi è **raccomandata** per i seguenti soggetti:

- contatti stretti che rientrano nelle categorie a rischio per lo sviluppo di complicanze in corso di influenza (come riportato per le indicazioni di trattamento);

La profilassi può essere **considerata**, almeno nell'attuale fase dell'epidemia, per i seguenti soggetti:

- bambini che a giudizio del medico siano in una condizione di rischio non contemplata nelle precedenti categorie e che hanno avuto un contatto stretto (faccia-a-faccia) con **pazienti identificati come casi** .
- **Sulla base di un'appropriata valutazione del rischio,negli operatori sanitari che abbiano riportato una esposizione a materiale contenente virus A (H1N1)v potenzialmente infettante oppure una esposizione a rischio nel corso dell'assistenza a pazienti rispondenti alla definizione di caso e che non abbiano osservato le precauzioni standard e di igiene respiratoria né utilizzato in modo adeguato i dispositivi di protezione individuale.**

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Characteristics and Symptoms of the 148 non hospitalized Patient with Confirmed/Probable Swine-Origin Influenza A (H1N1).

Characteristic	Value	
	N°	%
Male sex	86	58,1
Age		
Median	19 yr	
Range	0-69 yr	
Age group		
≤5	2	1,4
10-18	68	54,7
19-50	67	45,3
≥ 51	11	8,8
Clinical symptoms		
Cough	117	79,1
Fever	95	64,2
Asthenia	83	56,1
Headache	80	54,1
Coryza	73	49,1
Sore throat	70	47,3
Diarrhea	10	6,8
Vomiting	4	2,7

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Patients admitted to INMI: discharge diagnosis (period 04/25/09 – 09/06/09)

33 A(H1N1) Confirmed Cases

- **22 Cases** : Flu with other respiratory events
- **4 Cases**: Pneumonia
- **2 Cases**: Flu with other respiratory events, Diabetes
- **1 Case**: Flu with other respiratory events, Pneumomediastinum, Subcutaneous emphysema, Allergic bronchial asthma
- **1 Case**: Flu with other respiratory events, Pneumothorax
- **1 Case**: Flu with other respiratory events, Chronic obstructive asthma with acute flare
- **1 Case**: Vascular Purpura, Peritoneal effusion, EBV Infection
- **1 Case**: Flu with other respiratory events, HIV infection

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Clinical features of 7 patients

Risk Factors	Number
Smokers	2
Cannabis use	2
Asthma	2
Close contact (influenza-like S.)	2
Cardiopaty	1

- **7 cases of S-OIV admitted. 4 male and 3 female**
- **Age, mean: 16,4 ys (range 14 to 54 ys); median: 22 ys.**
- **Country of origine, 6 Italy and 1 Australia**
- **Average of length of stay, 9 days (range 6 to 14 days)**

Clinical features

Items	Cases	Co-infections
Pneumonia	3	1(Para-influenza 3)
Pneumomediastinum	1	
Pneumothorax	1	
Hemorrhagic Purpura	1	1 (EBV?)
Intestinal bleeding	1	
Abdominal effusion	1	

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Clinical Management*

- **Early antiviral treatment with neuraminidase inhibitors**
  (Oseltamivir, Zanamivir); treatment of hospitalized and high-risk;
  - **Consider higher dosing, longer duration of treatment for severely ill**
  - **Pandemic H1N1 virus resistant to amantadine, rimantadine**
  - **Three reports of Oseltamivir-resistance in pandemic H1N1**

- **Oxygen therapy - ensure adequate oxygenation**
- **Advanced respiratory support - mechanical ventilation - follow guidelines for sepsis-associated ARDS**

- **Antibiotic treatment following evidence-based guidance for community-acquired pneumonia**
- **Corticosteroids: no routine use**
  - **Low dose for septic shock requiring vasopressors with adrenal insuff**

- **No aspirin or aspirin-containing products for <18 years**

*WHO Clinical Management Guidance May 2009

MA…

… riflessioni critiche , punti contrversi ed in ancora in valutazione…

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Effectiveness of oseltamivir in preventing influenza

Randomised controlled trials provide evidence on the safety and efficacy of neuraminidase inhibitors in the prophylaxis of seasonal flu. Two forms of prophylaxis were tested—prolonged daily dosing regardless of exposure taken throughout the risk period and prophylaxis after household contact with a known case. The reported efficacy was 74% (95% confidence interval 53% to 88%) when using oseltamivir daily as prophylaxis over a six week period and 68% (34.9% to 84.2%) and 89% (67% to 97%) in two studies when it was used as post-exposure prophylaxis for household contacts of primary cases.

Hayden FG, et al. *N Engl J Med* 1999;341:1336-43.
Welliver R, et al. *JAMA* 2001;285:748-54.
Hayden FG, et al. *J Infect Dis* 2004;189:440-9.

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Adverse Reactions and Drug Interactions associated with Oseltamivir and Zanamivir

- Nausea and vomiting are the primary side-effects of oseltamivir (can be reduced by administration with food).
- Decline in FEV1 in patients with underlying asthma who are treated with zanamivir (zanamivir is not licensed for patients with underlying asthma or cardiac disease).
- No known drug interactions with zanamivir.
- Oseltamivir and metabolite are excreted in the urine by glomerular filtration and tubular secretion therefore co-administration with other agents (e.g. probenicid) may result in increased plasma levels of oseltamivir.

www.cdc.gov/flu/professionals/antivirals/side-effects

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The Use of the neuraminidase inhibitors

We have seen patients from high risk groups who have developed swine flu despite chemoprophylaxis; in these cases we have doubled the dose on the grounds that some resistance should be presumed.

We are also starting treatment in sick patients and those from high risk groups even when they have been symptomatic for longer than 48 hours because the suggested restriction was based on experience with seasonal flu.

The neuraminidase inhibitors licensed for swine flu treatment and prophylaxis are **oral oseltamivir** and **inhaled zanamivir**. We have few data on their use in pregnancy, and zanamivir is recommended in pregnant women largely because blood concentrations are lower after inhalation than after oral administration.

Ellis C , BMJ 2009;339:b2698

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Prolonged Shedding of Multidrug-Resistant Influenza A Virus in an Immunocompromised Patient

Immunocompromised patients can persistently shed influenza, increasing the potential for resistance to antiviral drugs and for nosocomial transmission.

Weinstock,D.M. : *N Engl J Med february 27, 2003 348;9*

Prolonged excretion of amantadine-resistant influenza A virus quasi species after cessation of antiviral therapy in an immunocompromised patient.

Boivin G, Goyette N, Bernatchez H *Clin Infect Dis 2002;34:E23-E25*

Morbidity and Mortality Associated With Nosocomial Transmission of Oseltamivir- Resistant Influenza A(H1N1) Virus

Descriptive outbreak investigation of 2 hematopoietic stem cell transplant recipients and an elderly patient who developed hospital-acquired influenza A virus infection following exposure to an index patient with community-acquired H274Y-mutated influenza A(H1N1) virus infection in a medical ward at a Dutch university hospital in February 2008.

Gooskens J,et al. JAMA 2009;301(10)

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Antiviral Resistance

	Viruses tested (n)	Resistant Viruses, Number (%) Oseltamivir	Viruses tested (n)	Resistant Viruses, Number (%) Zanamivir	Viruses tested (n)	Resistant Viruses, Number (%) Adamantanes
Seasonal Influenza A (H1N1)	1,148	1,143 (99.6%)	1,148	0 (0)	1,153	6 (0.5%)
Influenza A (H3N2)	261	0 (0)	261	0 (0)	261	261 (100%)
Influenza B	654	0 (0)	654	0 (0)	N/A*	N/A*
2009 Influenza A (H1N1)	1,497	8†‡ (0.6)	670	0 (0)	526	526 (100%)

*The adamantanes (amantadine and rimantadine) are not effective against influenza B viruses.
†Two screening tools were used to determine oseltamivir resistance: sequence analysis of viral genes and a neuraminidase inhibition assay.
‡ Additional laboratories perform antiviral resistance testing and report their results to CDC. Two additional oseltamivir resistant 2009 influenza A (H1N1) viruses have been identified by these laboratories, bringing the total number to 10.

The majority of 2009 influenza A (H1N1) viruses are susceptible to the oseltamivir; however, rare sporadic cases of oseltamivir resistant 2009 influenza A (H1N1) viruses have been detected worldwide, including nine cases in the United States.

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Oseltamivir-Resistant 2009 Pandemic Influenza A (H1N1) Virus Infection in Two Summer Campers Receiving Prophylaxis --- North Carolina, 2009

Adolescent girls receiving oseltamivir chemoprophylaxis during an ILI outbreak that had begun June 18. The two girls stayed in the same cabin, and both received oseltamivir during a mass chemoprophylaxis program in which approximately 600 campers and staff members received oseltamivir or zanamivir. On July 20 and July 22, the North Carolina State Laboratory of Public Health confirmed pandemic H1N1 virus infection in respiratory specimens from both girls. On August 14 and August 19, CDC detected the H275Y mutation (N1 numbering) in neuraminidase from both specimens by pyrosequencing . The H275Y mutation is associated with resistance to oseltamivir; zanamivir susceptibility is retained.
A second mutation (I223V) in neuraminidase also was detected in both specimens.

MMWR **September 11, 2009 / 58(35);969-972**

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V I E W P O I N T S

Influenza Virus Resistance to Antiviral Agents: A Plea for Rational Use

Cochrane review of the use of influenza antiviral agents in adults concluded that only oseltamivir or zanamivir should be used and only in the case of influenza pandemics and severe epidemics

Jefferson T, et al- : Antivirals for influenza in healthy adults: systematic review. *Lancet* ***2006; 367:303–13.***

- ❑ use of monotherapy for influenza virus infection is irrational and may contribute to mutational pressure for further selection of antiviral-resistant strains.
- ❑ **combination antiviral therapy, new guidelines for indications for treatment**, point-of-care diagnostic testing, and a universal influenza vaccination recommendation are critical to protecting the population against influenza virus and to preserving the benefits of antiviral agents.

Poland GA et al. Clinical Infectious Diseases **2009; 48:1254–6**

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Global Transmission of Oseltamivir-Resistant Influenza

A Multidrug Strategy for the Future.

Over time, influenza viruses will probably develop resistance to any single antiviral agent. Treatment with several compounds that act at different stages of the viral life cycle would be more effective and make it less likely that any single mutation could confer resistance. This strategy may become feasible as new agents, such as the following, become available[1]:

Intravenous zanamivir: A therapy for patients hospitalized with severe influenza and for those in whom neither oral nor inhaled routes are an option

Peramivir: An as-yet-unlicensed neuraminidase inhibitor that is being developed in intravenous and intramuscular formulations

Long-acting inhaled neuraminidase inhibitors: A therapy based on the enhanced potency of dimeric derivatives of zanamivir that will probably be available in the next few years; administration may be possible in a single dose for treatment or once a week for prophylaxis

Fludase (DAS181): A sialidase fusion construct that cleaves the sialic acid receptors that influenza viruses use for attachment, removing influenza receptors from the airway epithelium and preventing infection of lung cells

Cyanovirin-N: A hemagglutinin inhibitor that may block viral entry

Short interfering RNAs: A therapy that may hold promise for influenza

T-705: A substituted pyrazine compound that is active against neuraminidase-inhibitor–resistant and amantadine-resistant viruses and that probably inhibits the RNA polymerase

The recent discovery of the active site of a key endonuclease activity in the PA subunit of the influenza polymerase molecule could lead to a new class of drugs targeting the essential polymerase function of "cap-snatching."[5] Other promising antiviral avenues under investigation include signal transduction inhibitors, interferon inducers, and molecules targeting the interaction between the influenza NS1A protein and the 30-kD subunit of cleavage and polyadenylation specificity factor.

Moscona A N Engl J Med 2009 ,360;10:953-56

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Case Report

H1N1 pneumonitis treated with intravenous zanamivir

22-year-old woman, neutropenic after chemotherapy for Hodgkin's disease, referred to ICU with 3 days' (d) increasing dyspnoea, bilateral chest infiltrates, and laboratory-confi rmed pandemic H1N1 2009 influenza virus infection

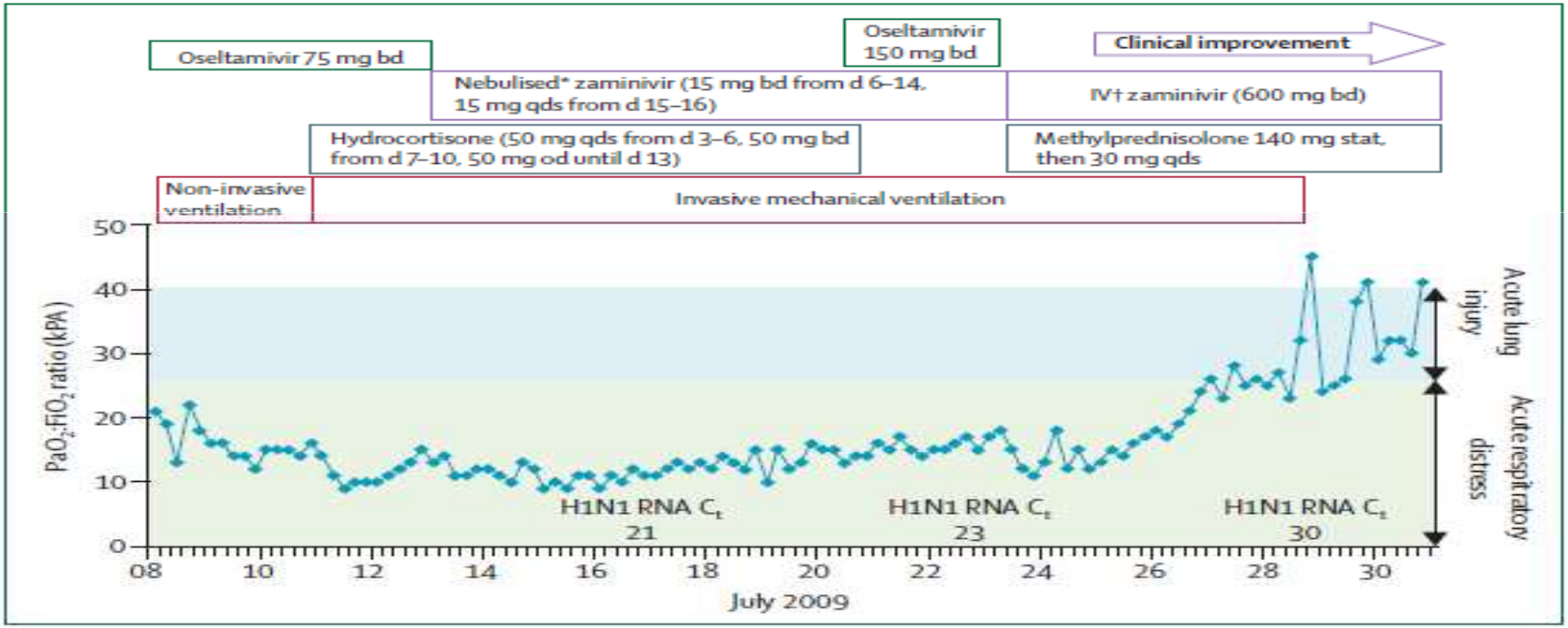
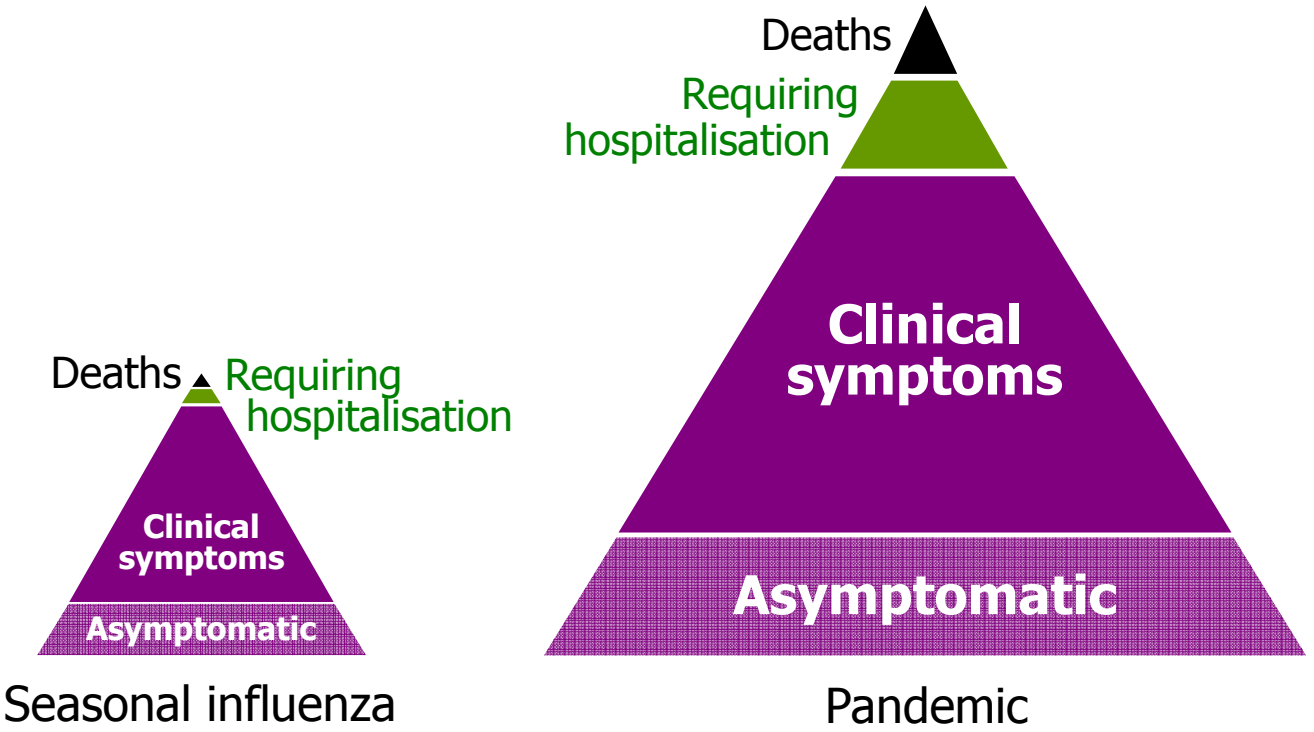


Figure: **Temporal course**
*Unlicensed route. †Unlicensed preparation.

Kidd M et al., www.thelancet.com *Published online September 4, 2009*
DOI:10.1016/S0140-6736(09)61528-2

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Seasonal influenza compared to pandemic — proportions of types of cases



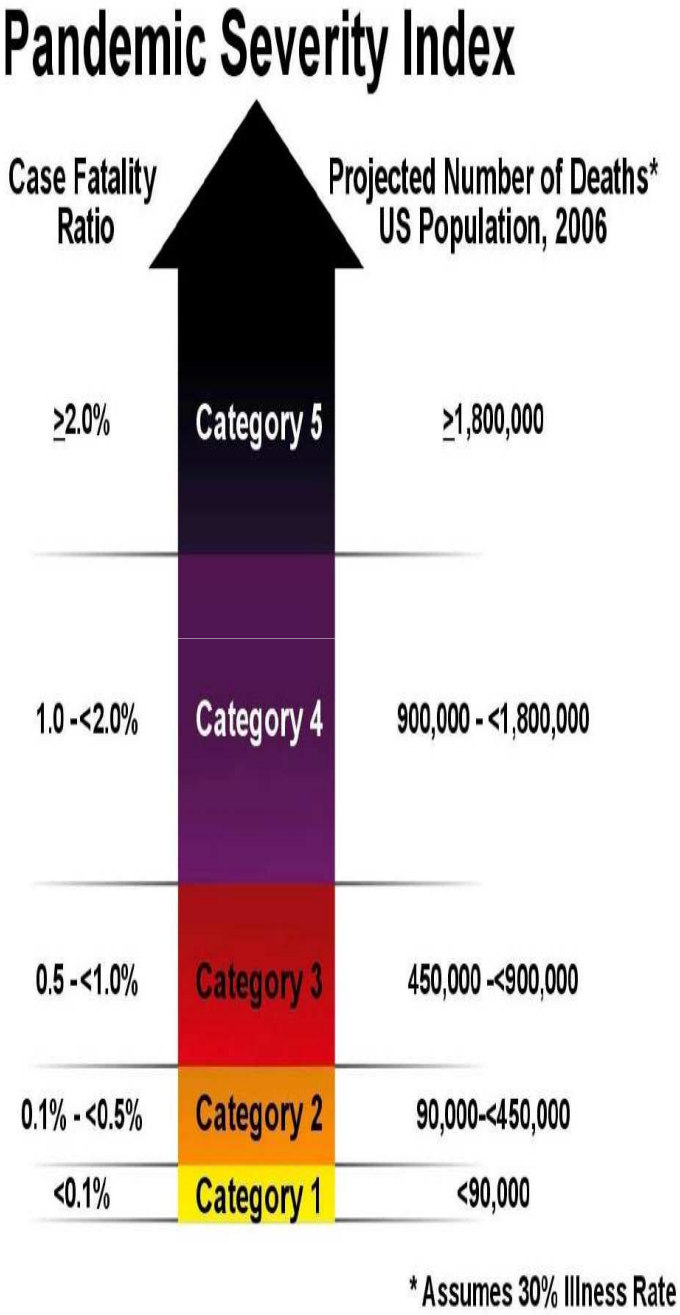
REPORT TO THE PRESIDENT ON U.S. PREPARATIONS FOR 2009-H1N1 INFLUENZA

TABLE 3-1: A POSSIBLE (NOT PREDICTIVE) SCENARIO TO HELP PLAN FOR THE FALL RESURGENCE OF 2009-H1N1 INFLUENZA IN THE UNITED STATES	
Peak incidence date (unmitigated)	October 15
Peak incidence of symptomatic disease	1–2% of U.S. population (3–6 million people) on the U.S. epidemic's single peak day
Percent of U.S. population (and approximate numbers) assuming no change in virus	
Infected (indicated by seroconversions, with or without symptoms)	30–50% (90–150 million)
Symptomatic	20–40% (60–120 million)
Needing medical attention	15–30% (45–90 million)
Needing hospital care	0.3–0.6% (0.9–1.8 million)
Needing Intensive Care Unit (ICU) facilities	0.05–0.1% (150,000–300,000)
Deaths	0.01–0.03% (30,000–90,000)
Peak occupancy of ICU beds due to 2009-H1N1	10–25 ICU beds/100,000 population[1]
Peak occupany of hospital beds due to 2009-H1N1	50–150 hospital beds/100,000 population[2]
High-risk groups for death or hospitalization	Pregnant women; children (0–4 years old); patients with neuromuscular/neurocognitive disorders, asthma, chronic obstructive pulmonary disease, cardiovascular disease, diabetes, severe obesity, or immunocompromising conditions[3]

Notes:
[1] The United States has 20 ICU beds/100,000 population. The number of ICU beds available for pediatric patients is especially limited.
[2] The United States has 211 hospital beds/100,000 population.
[3] Cetron M, 2009 Pandemic Novel Influenza A (H1N1): Community Mitigation, powerpoint presentation to PCAST H1N1 Working Group, July 16, 2009.

President's Council of Advisors on Science and Technology

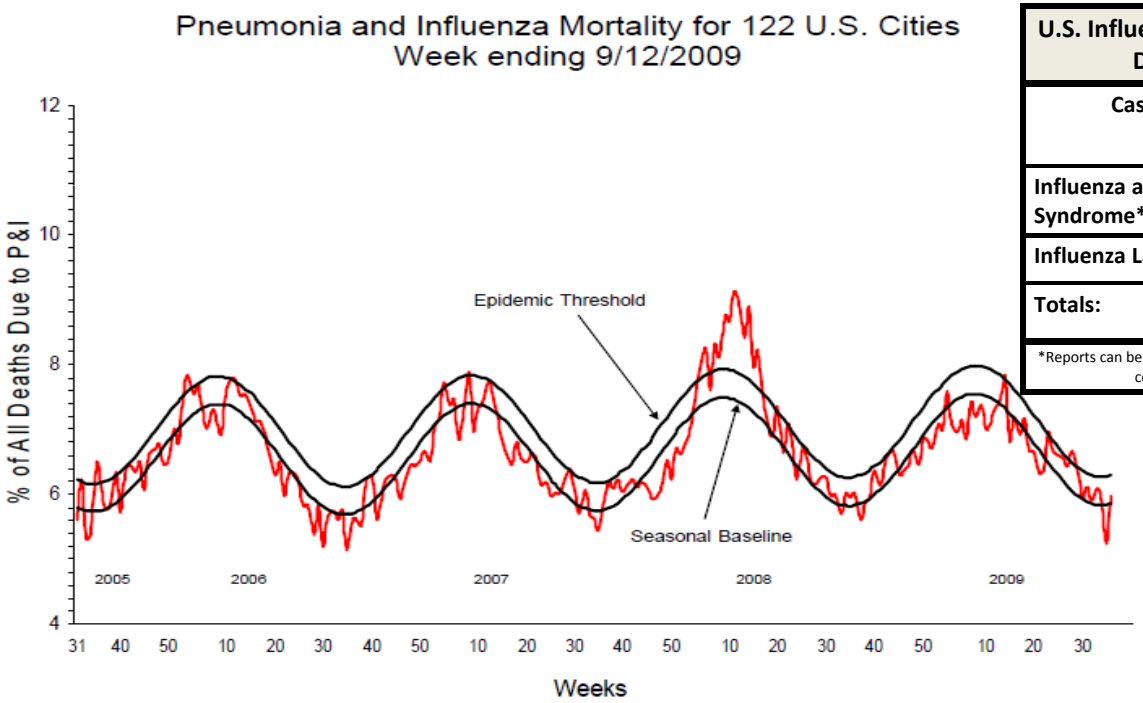
August 7, 2009



CDC reports: the proportion of deaths attributed to pneumonia and influenza (P&I) was below the epidemic threshold

From August 30-September 12, 2009 **4,569 hospitalizations** and **364 deaths** associated with influenza virus infection, or based on syndromic surveillance for influenza and pneumonia, were reported to CDC.

Pneumonia and Influenza (P&I) Mortality Surveillance:
During week 36, **6.0% of all deaths** reported through the 122-Cities Mortality Reporting System were due to P&I. This percentage was below the epidemic threshold of 6.3% for week 36.



U.S. Influenza and Pneumonia-Associated Hospitalizations and Deaths from August 30 – September 12, 2009		
Cases Defined by	**Hospitalizations**	**Deaths**
Influenza and Pneumonia Syndrome*	**3,534**	**291**
Influenza Laboratory-Tests**	**1,035**	**73**
Totals:	**4,569**	**364**

*Reports can be based on syndromic, admission or discharge data, or a combination of data elements that could include laboratory-confirmed and influenza-like illness hospitalizations

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FLUVIEW
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
2008-2009 Influenza Season
Week 36 ending September 12, 2009
CDC

Pandemic (H1N1) 2009

ECDC Update 10 September 2009

Chile (pop 16.6 million)

until **week 34: 12 190 confirmed cases** .
1 504 presented Severe Acute Respiratory Illness (SARI).
infants (69.1%), children between 1-4 years of age (15.2%).
63.8%)of the 125 laboratory-confirmed fatal cases had an underlying illness.
The majority of influenza strains identified until week 34 were A(H1N1)v .

Brazil (pop. 192 million)

until **week 34: 36 542 Severe Acute Respiratory Illness (SARI)**
of which **6 592 laboratory-confirmed as influenza A (H1N1)v : 657 (10%) died**.
reported mortality 0,34/100.000 inhabitants.
54.2% presented with at least one of risk factor

Australia (pop. 20.7 million)

35,933 confirmed cases of pandemic influenza (H1N1) v
hospitalisations associated with the pandemic influenza (H1N1)v : 4 647. **Died: 169.**
There are still 335 cases hospitalised due to (H1N1)v and 64 (19.1%) of them are in Intensive Care Units.
12%of the fatal cases and 6.6% of the hospitalised cases are indigenous Australians.

New Zealand (pop. 4.2 million)

At 6 eptember a total of **3219 confirmed cases of Pandemic Influenza (H1N1)v**,
988 cases have been hospitalised.
Pneumonia : 300 cases and ARDS 46 cases. Age standardised rate is 75.4 / 100 000 total population.
The number of **deaths from Pandemic Influenza (H1N1)v :17.**

South Africa (pop. 48.6 million)

confirmed cases of pandemic (H1N1)v :7 606,
The number of **deaths : 31**

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Pandemic (H1N1) 2009 influenza ("swine flu") in intensive care

EDITORIAL

Three predominant syndromes are associated with life-threatening infection:

- acute viral pneumonitis with bilateral pulmonary infiltrates ("flu A"-associated acute respiratory distress syndrome [FLAAARDS]);
- secondary community-acquired bacterial pneumonia;

and

- viral exacerbation of airflow limitation.

Webb S AR and Seppelt I M ,
ANZIC Influenza Investigators
Critical Care and Resuscitation • Vol 11 ,3 ,September 2009

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TRIAGE INFERMIERISTICO PER INFLUENZA A (H1N1)v

Paziente	Modalità di accesso
CASO ASINTOMATICO No sintomi	Codice 1 Verde inviare in sala attesa comune NON dedicata e consegnare allegato 5
CASO SINTOMATICO Sintomi: febbre >38°‹C e uno o più dei seguenti sintomi: Cefalea, malessere generalizzato sensazione di febbre (sudorazione, brividi)astenia ed almeno uno dei seguenti sintomi respiratori: Tosse, faringodinia, congestione nasale	**Codice 2 Giallo inviare in sala d'attesa dedicata per successiva valutazione clinica** Precauzioni standard e igiene respiratoria: -OS dovrebbe indossare DPI - far indossare una mascherina chirurgica al paziente mentre attende nella stanza
CASO SINTOMATICO CON COMPLICAZIONI ovvero dispnea grave, NON in grado di completare le frasi in un soffio, presenta variazioni dello stato mentale (disorientamento, stupore) etc	Codice 3 **Rosso** l'accesso alla sala di isolamento/visita è immediato e non vi è tempo di attesa Valutazione parametri vitali: Frequenza respiratoria >30 atti/minuto, pressione diastolica <60 mmHg o pressione sistolica < 90 mmHg, polso 125/min, TC <35 o >40 ℃, variazioni dello stato mentale (disorientamento, stupore), evidenza di siti extrapolmonari di infezione. Saturazione di O2 ≤92 % se necessario Consulenza Rianimatore, ricovero TI o stanza di isolamento



INMI

L. SPALLANZANI

Table 3. Most common risk factors for pandemic H1N1 Influenza in the ICU

Risk Factor	Cases (n=32)
Obesity	10
BMI>40	4
BMI 30-40	6
Asthma	5
COPD	4
Pregnancy	2
Heart Failure	1
Arterial Hypertension	1
Chronic Renal Failure	1
Diabetes mellitus	1
HIV	1
Neuromuscular disease	1
Hematologic disease	1
None	15

BMI= Body mass index; COPD: Chronic Obstructive Pulmonary Disease; HIV= positive human immunodeficiency virus.

Table 4: Characteristics of 32 patients according to ventilator support required

Variable	Non-Ventilated (n=8)	Non-invasive ventilation		Initially intubated n= 16
		Successful (n=2)	Failure (n=6)	
APACHE II Score Mean (SD) IQR 25-75	9.5 (4.9) 4 – 16	9.5 (0.7) 9 -10	15.3 (5.6) 10 – 24	15.2 (7.6) 8 -38
SOFA score Mean (SD) IQR 25 – 75	4.7 (1.7) 3 – 7	2.5 (0.7)* 2 – 3	8.1 (2.3)** 5 – 11	7.8 (3.5) 4 – 16
Age , yr Mean (SD) IQR 25 – 75	39.2 (14.7) 17 – 58	42.5 (13.4) 33 - 52	44.0 (15.1) 10 – 57	38.7 (14.0) 16 – 70
Opacity lung quadrants Mean (SD)	2.9 (1.2)	2.5 (2.1)	2.8 (0.9)	3.3 (1.1)
LDH , U/L Mean (SD) IQR 25 – 75	751 (361) 195 – 1166	1140 (374) 880 – 1400	918 (408) 354 – 1450	2170 (3400) 440 – 12200
CK, U/L Mean (SD) IQR 25 – 75	2480 (4500) 66 – 9300	2800 (3200) 500 – 5100	4850 (4200) 122 - 9400	2300 (3800) 207 – 10800
28-day Mortality,n(%)***	0	0	2 (33)	4 (25)

* vs. ** p=0.01

*** Two additional patients died by refractory hypoxemia after 31 and 65 days of mechanical ventilation.

APACHE II score: Acute Physiology And Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment ; IQR: Interquartil 25-75; LDH: Lactate dehidrogenase; CK: Creatine Kinasa.

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Pandemic Medical Early Warning Score: Physiological-social score (PMEWS) vs. CURB- 65

Algoritmo per l'ammissione al ricovero per sindrome influenzale

Sede .....

Data ..... Ora .....

Paziente .....

Data nascita ..... Età ..... Sesso [M] [F]

Indirizzo .....

SINTOMI DI INFLUENZA PANDEMICA (WHO)

- febbre > 38°C
- cefalea
- mal di gola
- rinorrea
- tosse
- dispnea
- mialgia
- dolori osteo-articolari

DATI DEL PAZIENTE (1 punto per ogni fattore)

- età > 65 [ ]
- isolamento sociale (vive solo, e/o senza fissa dimora: 1 punto) [ ]
- malattie croniche(polmonari, cardiache, renali, sistema immunitario, oncologiche, metaboliche: 1 punto per malattia) [ ]
- gravidanze al terzo trimestre [ ]
- performance status > 2 [ ]

PERFORMANCE STATUS

- attività normale senza restrizioni: 1 punto
- limitate le attività intense, può svolgere quelle lievi: 2 punti
- attività limitata, ma autosufficiente: 3 punti
- attività limitata, limitata autosufficienza: 4 punti
- confinato a letto/sedia, non autosufficiente: 5 punti

DATI FISIOLOGICI (indicare un solo valore per ogni fattore)

Punteggio	3	2	1	0	1	2	3
Frequenza respiratoria	≤8			9-18	19-25	26-29	≥30
Saturazione 02	<89	90-93	94-96	>96			
Frequenza cardiaca	<40	41-50		51-100	101-110	111-129	≥130
Pressione sistolica	<70	71-90	91-100	>100			
Temperatura		<35°C	35.1-36	36.1-37.9	38-38.9	>39°C	
Sintomi neurologici				Sveglio cosciente	Confuso agitato	Fortemente agitato	Elevata compromissione con disorientamento spazio-tempo-persona

PUNTEGGIO TOTALE: ..... Paziente Ricoverato [ ] Paziente Non ricoverato [ ]

Deceduto [sì] [no] Firma del Medico .....

Data eventuale decesso .....

Qualifica. .....

Figura 1. Algoritmo per l'indicazione al ricovero per sindrome influenzale

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Challen K, et al... BMC Health Services Research 2007; 7: 33

TABLE. Selected characteristics of intensive-care patients with severe novel influenza A (H1N1) virus infection — Michigan, June 2009

Patient	Age (yrs)	Sex	Underlying conditions	Initial signs or symptoms	BMI*	No. days between onset and first hospitalization	No. days between illness onset and SICU† admission	Advanced mechanical ventilation	Diagnosis		Vaso-pressors	Outcome**
									PE§	MODS¶		
1	28	M	Asthma	High fever, cough, sore throat that progressed to blood-tinged sputum, decreasing mental status	34.2	7	8	HFOV††	Yes	Yes	Yes	Death
2	21	M	None	Fever, sore throat, dry cough, sneezing; progressed to tachypnea and dyspnea	50.5	7	8	Bilevel	Yes	Yes	Yes	Improved, transferred
3	48	F	Asthma, smoker	Shortness of breath, rhinorrhea, non-productive cough	58.9	5	9	HFOV	No	Yes	Yes	Improved, transferred
4	35	M	None	Upper respiratory tract illness symptoms	51.7	6	8	HFOV	Yes	No	No	Improved, transferred
5	43	M	None	Fever, cough, malaise, chills, sweats	48.7	4	5	HFOV to ECMO§§	Yes	Yes	Yes	Death
6	52	M	None	Sinus drainage, cough with clear sputum production, decreased appetite	NA¶¶	6	13	HFOV	Yes	Yes	Yes	Improved, transferred
7	44	M	None	Fever, productive cough with black/red sputum, nausea, vomiting, diarrhea	50.2	5	7	HFOV	No	Yes	Yes	Death
8	51	M	Granulomatous chronic lung disease	Fever, worsening dyspnea, rigors, nausea, vomiting, malaise	39.7	1	9	HFOV to ECMO	No	Yes	Yes	ECMO plus ventilator
9	53	M	None	Fever, chills, cough, shortness of breath	38.5	7	16	HFOV	No	Yes	Yes	Improved, transferred
10	53	M	None	Fever, cough	47.8	6	6	HFOV	No	Yes	Yes	HFOV

* Body mass index. Based on admitting weight at University of Michigan Health System surgical intensive care unit.
† Surgical intensive care unit.
§ Pulmonary emboli.
¶ Multiorgan dysfunction syndrome.
** As of July 8, 2009.
†† High-frequency oscillatory ventilation.
§§ Extracorporeal membrane oxygenation.
¶¶ Not available. Height unknown; weight = 72 kg.

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PANDEMIC (H1N1) 2009

Life-threatening respiratory failure from H1N1 influenza 09 (human swine influenza)

Melissa A Kaufman, Graeme J Duke, Forbes McGain, Craig French, Craig Aboltins, Gary Lane and Geoff A Gutteridge

We present the first six cases of H1N1 influenza 09 (confirmed by a polymerase chain reaction test from nasopharyngeal swabs) in patients requiring admission to intensive care in Australia (in three hospitals in the north-western suburbs of Melbourne). These cases highlight the small but significant risk of life-threatening respiratory failure associated with H1N1 influenza 09 infection. **(MJA 2009; 191: 154-156)**

The four patients who were given a trial of NIV in this series all required intubation and MV.

NIV temporarily improves oxygenation and reduces the work of breathing, but does not necessarily alter the course of the disease.

The need for NIV is an indication of severe disease and the likelihood of intubation and MV.

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“influenza”

Definizione di Ippocrate 410 a.C.

Tosse secca, raucedine, stato di prostrazione in forma epidemica in coincidenza con l’equinozio d’autunno

If Florence was in the grip of an epidemic of colds, coughs and fevers, astrologers ….declared that it was caused by the *influence of an unusual* conjunction of planets. This sickeness…..came gradually to be known as “*influenza*”

Chronicles of a Florentine Family 1200-1417

“Gli astrolaghi dissero influenza delle costellazioni “

Matteo Villani 1358

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