2009 H1N1 INFLUENZA PANDEMIC

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Outline

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Influenza is reportable for the following situations: fatal cases of lab-confirmed influenza in persons 0-64 years, outbreaks of undiagnosed influenza-like illness in residents of large group or institutional settings (e.g. long-term care, rehabilitation, or assisted living facilities, college dormitories) or one or more lab-confirmed cases of influenza in residents of large group or institutional settings. For more information visit: www.sfdph.org/cdcp

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INTRODUCTION

In April 2009 a novel H1N1 influenza A virus of swine-origin, capable of human-to-human transmission, was first isolated from two epidemiologically unlinked pediatric patients in Southern California, and soon thereafter in Texas and Mexico [1, 2]. The earliest recognized case occurred in Mexico with symptom onset on March 17, 2009 [3]. 2009 H1N1 influenza virus spread rapidly to over 74 countries by early June 2009, and on June 11, 2009 the Center for Disease Control (CDC) declared the first influenza pandemic since 1968 [4]. A worldwide pandemic influenza response prompted rapid development and mass production of 2009 H1N1 influenza vaccine, and a variety of containment strategies were implemented throughout the world, for both individuals and communities. In general, the clinical presentation of 2009 H1N1 influenza was similar to seasonal influenza. Unlike previous influenza pandemics, disease was relatively mild for most people. The pandemic showed obesity as a risk factor for severe disease, and it reinforced that people with chronic medical conditions, who were pregnant, or of certain ethnic minority groups were at increased risk for complications from influenza. In contrast to seasonal influenza, 2009 H1N1 influenza disproportionately affected the nonelderly adult population [5].

EPIDEMIOLOGY

Mechanism of Transmission to Humans:

The 2009 H1N1 influenza virus was a novel strain. It contained a combination of swine, avian, and human gene segments that previously had not been reported in swine or human influenza viruses in the United States or elsewhere [6]. Due to the lack of immunity in human populations to the novel virus, 2009 H1N1 influenza spread quickly around the world, and an influenza pandemic emerged.

The emergence of a novel influenza virus subtype that can infect the human population requires antigenic shift. This can happen when a subtype of avian or swine influenza acquires genes from human influenza viruses that enable person-to-person transmission [7, 8]. Because pigs are susceptible to infection with avian, swine, and human influenza strains, they can serve as a "mixing vessel" for the scrambling of genetic material from these strains, resulting in a novel subtype of influenza.

Influenza Surveillance:

National seasonal influenza surveillance data prior to 2009 H1N1 influenza

In the Northern hemisphere, seasonal influenza activity generally peaks in the winter from December through February [9]. CDC estimates that about 200,000 influenza-related hospitalizations occur in the United States each year. Furthermore, CDC estimates that about 23,600 people died of influenza-related causes each year, on average, during the 1990s in the United States. This includes people dying from secondary complications of the flu [10].

Laboratory-confirmed influenza-associated deaths in children (ages 0-18 years) have been a nationally notifiable condition since 2004, and deaths are reported through the CDC's *Influenza-Associated Pediatric Mortality Surveillance Program.* There were more pediatric deaths (153) in the 2003-04 influenza season compared to recent influenza seasons (134 reported deaths in 2008-09, 88 deaths in 2007-08, and 77 deaths in 2006-07) [11, 12].

National 2009 H1N1 flu surveillance data 2009-present

2009 H1N1 influenza emerged in an atypical time for influenza during the late spring of 2009. There were 2 "waves" of 2009 H1N1 swine influenza activity: The first wave peaked in June. Influenza activity then decreased, although it remained above epidemic thresholds. The second wave peaked in late October /early November 2009. Fortunately, the feared third wave never materialized in the winter 2009-2010, but a third wave could occur at any time [5]. 2009 H1N1 influenza became the predominant influenza strain in the U.S. from its emergence in April 2009 [13]. Surprisingly, hardly any seasonal influenza strains circulated in the U.S. in the winter 2009-2010 (Influenza B circulated to some degree in other countries, especially in Asia) [5]. The WHO officially declared the end of 2009 H1N1 influenza pandemic on August 10, 2010 [14].

The true impact of 2009 H1N1 influenza pandemic on the population won't be known for some time to come, as pandemic viruses often dominate flu seasons over several years and it takes 2-3 years to develop accurate flu mortality data for a given season [5]. Attempting to compare estimates of the numbers of 2009 H1N1 influenza hospitalizations and deaths to those of seasonal flu is problematic because the methods for ascertaining these estimates were different. But there is no question that the effects of 2009 H1N1 influenza were felt world-wide. As of August 1, 2010, over 214 countries and territories have laboratory-cases of 2009 H1N1 swine flu, including over 18,449 laboratory-confirmed deaths [15].

Below is a table of CDC's estimates of 2009 H1N1 influenza cases, hospitalizations, and deaths based on Emerging Infections Program (EIP) data by age group from April 2009 – April 10, 2010:

2009 H1N1	Mid-Level Range*	Estimated Range*
Cases		
0-17 years	~20 million	~14 million to ~28 million
18-64 years	~35 million	~25 million to ~52 million
65 years and older	~6 million	~4 million to ~9 million
Cases Total	~61 million	~43 million to ~89 million
Hospitalizations		
0-17 years	~87,000	~62,000 to ~128,000
18-64 years	~160,000	~114,000 to ~235,000
65 years and older	~27,000	~19,000 to ~40,000
Hospitalizations Total	~274,000	~195,000 to ~403,000
Deaths		
0-17 years	~1,280	~910 to ~1,880
18-64 years	~9,570	~6,800 to ~14,040
65 years and older	~1,620	~1,160 to ~2,380
Deaths Total	~12,470	~8,870 to ~18,300

*Deaths have been rounded to the nearest ten. Hospitalizations have been rounded to the nearest thousand and cases have been rounded to the nearest million. Exact numbers are available at: **http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm**

Of note, most of the deaths occurred in the 18-64 year old age group rather than in the elderly or pediatric age groups [10].

From August 30, 2009 – May 22, 2010, the CDC received 276 reports of influenza-associated pediatric deaths (49 deaths in children less than 2 years old, 30 deaths in children 2-4 years old, 103 deaths in children 5-11 years old, and 94 deaths in children 12-17 years old) via CDC's *Influenza-Associated Pediatric Mortality Surveillance Program*. 225 (82%) of the 276 deaths were due to 2009 H1N1 influenza infections, 50 were associated with an influenza A virus for which the subtype was undetermined, and one was associated with an influenza B virus infection [12]. The total number of pediatric lab-confirmed deaths from 2009 H1N1 influenza was higher than recent previous influenza seasons (see "Seasonal influenza surveillance data prior to 2009 H1N1 swine flu" section above).

Risk factors

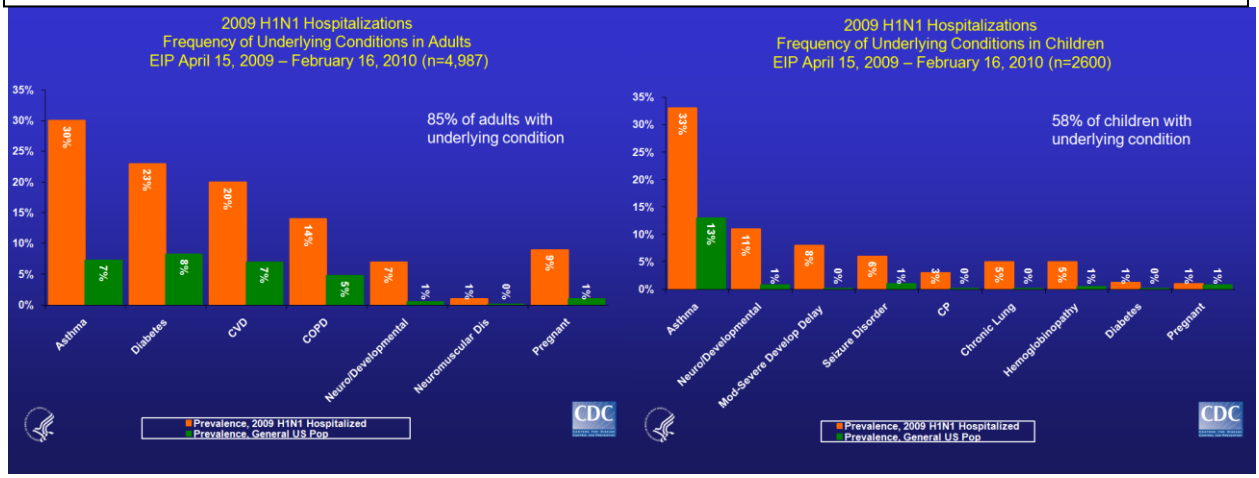
Similar to seasonal influenza, persons with chronic medical conditions, who were pregnant, or of certain ethnic minority groups were at increased risk for complications from 2009 H1N1 swine flu. In contrast to seasonal influenza, nonelderly individuals were affected more severely by 2009 H1N1 swine flu, and obesity emerged as a risk factor for severe disease from 2009 H1N1 swine flu.

Chronic Medical Conditions and 2009 H1N1

People with chronic medical conditions such as asthma, neurological and neurodevelopmental conditions, chronic lung disease, weakened immune systems due to disease or medications, and disorders of the blood, endocrine, kidney, liver, or metabolic systems, are more likely to develop complications from seasonal influenza [12]. This was also found to be true for 2009 H1N1 swine flu. The CDC reported that approximately 85% of hospitalized adults and 58% of hospitalized children in the US with 2009 H1N1 influenza infections had one or more chronic medical conditions. In adults, asthma was the most common underlying health condition reported accounting for 30% of those hospitalized. This was followed by diabetes (23%) and chronic cardiovascular disease (20%). Asthma was also the most common underlying health condition

reported among children hospitalized with 2009 H1N1 influenza (33%); however, in children, neurological/developmental disabilities were the second highest conditions reported (11%) followed by moderate to severe developmental delays (8%) [16]. Below are graphs that demonstrate the frequency of underlying medical conditions in adults and children hospitalized with 2009 H1N1 influenza compared to the prevalence of these medical conditions in the general population [17]:

2009 H1N1 Hospitalizations Frequency of Underlying Conditions in Adults and Children EIP April 15, 2009 – February 16, 2010*



*Adapted from CDC: **http://www.cdc.gov/h1n1flu/yearinreview/yir5.htm**

Similarly, chronic medical conditions were found to be a risk factor for 2009 H1N1 influenza-associated complications in California. For example, a study that examined the first 1088 hospitalized and fatal cases due to 2009 H1N1 influenza in California found that 68% (60% of all children and 72% of all adults) had risk factors previously associated with severe influenza. In hospitalized adults the most common chronic comorbid illness was chronic lung disease, followed by metabolic disease. In hospitalized children the most common chronic comorbid illness was asthma followed by immunosuppressive conditions [18].

Pregnancy and 2009 H1N1

Previous research has shown that pregnant women are at increased risk for severe disease and worse outcomes from influenza [19]. 2009 H1N1 influenza followed a similar pattern [20-22]. Pregnant women and postpartum women had higher rates of hospitalizations, ICU admissions and deaths when compared to their numbers in the general population [20]. Complications were higher in the third trimester of pregnancy. One study found that pregnant women in New York were approximately 7 times more likely to be hospitalized and 4 times more likely to be admitted to the ICU when compared to their non-pregnant peers [22]. Risk for severe disease continued into the postpartum period. Pregnant women with underlying conditions such as asthma and obesity were more likely to be hospitalized in the ICU or to die from 2009 H1N1 influenza [23]. Pregnant women are thought to be vulnerable to severe disease secondary to physiologic changes that occur during pregnancy, including cardiac, respiratory and immune system changes. A few studies showed that neonatal outcomes were also worse for pregnant women admitted to the

hospital secondary to 2009 H1N1 swine flu. Outcomes such as delivery by Cesarean-section, preterm delivery and admission into the neonatal intensive care unit occurred at high rates in pregnant women infected with 2009 H1N1 influenza [21, 24]. Preterm deliveries occurred at more than 2 times the usual rate [23]. Pregnant women who were treated early with antivirals tended to have better outcomes. Pregnant women, who make up 1% of the population, accounted for 5% of 2009 H1N1 influenza deaths.

Ethnicity/Race and 2009 H1N1

Certain minority groups were at a higher risk for adverse outcomes from 2009 H1N1 swine flu. Nationally, Alaskan Natives and American Indians had higher rates of death [25]. Death rates were 4 times greater than all other ethnic populations combined. Alaskan natives and American Indians also experienced higher rates of hospitalizations. This mimicked the global trend of indigenous populations having a higher rate of morbidity and mortality from 2009 H1N1 influenza. Poverty, poor access to health care and chronic conditions have all been proposed as causes for increased mortality [26]. Previous pandemics have similarly affected Alaskan Natives and Native Americans disproportionately.

Morbidity and mortality was also increased among Hispanics and Blacks*. Nationally, both groups had higher hospitalizations and death rates when compared to Whites* and Asian/Pacific Islanders. California data concurred with national data in that hospitalizations and mortality were higher in the Hispanic and Black populations. However Asian/Pacific Islanders had a higher rate of hospitalizations when compared to Whites but a lower death rate [27]. Interestingly CDC data showed that reported influenza-like illness (ILI) symptoms and health care seeking behavior were the same in Hispanic and Black populations as compared to Whites. Increased morbidity and mortality may have been due to socioeconomic factors as well as underlying chronic conditions. Data from previous influenza seasons has shown that Hispanics and Blacks are less likely to get vaccinated. This trend, along with the constraints of vaccine availability early on in the pandemic, may have contributed to worse outcomes in these groups.

Age Groups and 2009 H1N1

Unlike seasonal influenza but similar to previous influenza pandemics, 2009 H1N1 influenza virus affected non-elderly populations more severely. The CDC reported that approximately 90% of estimated 2009 H1N1 influenza related hospitalizations and 87% of estimated deaths from April 2009 through April 10, 2010 occurred in people younger than 65 years old. Infants less than one had the highest hospitalization rates and persons aged 50-64 years had the highest mortality rate. In contrast, about 60% of seasonal influenza related hospitalizations and 90% of deaths occur in people 65 years and older [10]. While elderly persons age 65 and older were the least likely to be infected with 2009 H1N1 influenza, those who did get sick had a high risk of developing serious complications [28].

In California as of April 3, 2010, there were 8, 917 hospitalization and/or fatalities reported to the California Department of Public Health (CDPH) [29]. Similar to national data, hospitalization rates

*For this chapter Blacks refers to Black, non-Hispanics and Whites refers to White, non-Hispanics

in California from 2009 H1N1 influenza were highest in infants under one year of age and mortality rates in California were highest among individuals aged 50-64 years [30].

Obesity and 2009 H1N1

Obesity was initially not included as a condition that placed patients in a high risk group for severe 2009 H1N1 influenza disease, nor were obese individuals a priority group for vaccination. However, evolving literature during the pandemic found that obesity was a risk factor for severe disease. An early case series of severely ill patients infected with 2009 H1N1 admitted to the ICU found a large proportion were obese or morbidly obese [25]. California and New York data also supported obesity as a risk factor for severe disease and death [18, 26]. It was unclear from these initial reports whether increased morbidity and mortality was associated with obesity or with other underlying conditions that often go along with obesity (such as diabetes and asthma) and put patients at higher risk for severe influenza illness.

CDC data released in March 2010 showed that in adults, obesity and especially morbid obesity, was in fact an independent risk factor for severe disease due to 2009 H1N1 influenza [21]. Morbidly obese patients were 5 times more likely to be hospitalized for 2009 H1N1 influenza. This was true for morbidly obese patients with and without chronic medical conditions. Fatality rates may also have been higher in obese and morbidly obese patients, although further studies are needed to quantify the risk. There has been some evidence that obesity impairs the immune system, which would make obese patients more susceptible to severe disease [31]. At this time the CDC considers obesity a risk factor for severe disease due to 2009 H1N1 influenza [32] .

CLINICAL FEATURES

The typical clinical features of 2009 H1N1 influenza were similar to that of seasonal influenza, although gastrointestinal symptoms such as nausea, vomiting, and diarrhea were more common in some studies, especially in adults.

CLINICAL FEATURES OF 2009 H1N1 INFLUENZA[33]	
Incubation Period	Usually 1.5 – 3 days, but up to 7 days in a minority of patients
Signs & Symptoms	•Majority of cases had typical influenza-like illness with fever and cough •Other symptoms such as sore throat, rhinorrhea, headaches and myalgias were common •Gastrointestinal symptoms such as nausea, vomiting, or diarrhea were common (in one study up to 40% had either vomiting or diarrhea) • Mild illness without fever has been reported in 8-32% of patients
	• Leukopenia

Laboratory Findings	• A study conducted in Singapore found that one of the distinguishing markers of H1N1 compared to seasonal flu was the absence of leukocytosis [34] • Lymphopenia • A study in Greece found 90% of patients with probable influenza had relative lymphopenia and/or monocytosis [35] • Lymphocyte count <800 was one of the factors associated with respiratory failure secondary 2009 H1N1 influenza [36] • Thrombocytopenia

LABORATORY TESTING

Most patients with clinical illness consistent with uncomplicated influenza do not require diagnostic influenza testing for clinical management.

The following table lists tests that are available for confirming influenza infection[37]:

Features of Common Influenza Tests			
Procedure	**Influenza Virus Types Detected**	**Acceptable Specimens**	**Test Time**
Viral culture	A and B	NP swab/aspirate, nasal swab/aspirate/wash, throat swab, bronchioalveolar lavage	3-10 days[a]
Immunofluorescence (direct fluorescent antibody [DFA] or indirect fluorescent antibody [IFA] staining)	A and B	NP swab/aspirate, nasal swab/aspirate/wash, throat swab,	2-4 hours
RT-PCR	A and B	NP swab/aspirate, nasal swab/aspirate/wash, throat swab, bronchioalveolar lavage, sputum	2-4 hours
Serology[b]	A and B	paired acute and convalescent serum samples	2 weeks or more
Enzyme immunoassay (EIA)	A and B	NP swab/aspirate, nasal swab/aspirate/wash, throat swab	2 hours
Rapid diagnostic tests	Dependent on the specific test used	Dependent on the specific test used	10-15 minutes

Abbreviations: NP, nasopharyngeal; RT-PCR, reverse-transcription polymerase chain reaction. [a] Shell vial culture, if available, may reduce time for results to 2 days.
[b] Serology is not recommended for routine diagnostic testing, only for research purposes or sero-epidemiologic investigations, and cannot produce timely results for clinical decision-making. A fourfold or greater rise in antibody titer from the acute-phase sample (collected within the 1st week of illness) to the convalescent-phase sample (collected 2-4 weeks after the acute sample) is indicative of recent infection.

Rapid Tests [38]

Rapid influenza antigen tests are widely available to clinicians and provide test results at the point of care. Immunofluorescence tests (e.g., DFA) are also available at many laboratories. When influenza virus is circulating in the community, a positive rapid antigen test or

immunofluorescence test for influenza is predictive of infection. However, these tests have important limitations:

1. Low sensitivity for detecting influenza (10 – 70% for 2009 H1N1 influenza and 60 – 80% for seasonal flu with rapid antigen tests; sensitivities with immunofluorescence testing is slightly higher). Therefore, a negative rapid antigen test or immunofluorescence test does not rule out infection with seasonal or 2009 H1N1 influenza. Based on the clinical presentation, confirmatory diagnostic testing and/or empiric treatment may be appropriate.
2. Some rapid antigen tests can distinguish between influenza A and B, while others cannot. Check the product information or http://www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm to determine test capabilities.
3. Currently, there is no rapid antigen test or immunofluorescence test for influenza A that can distinguish between seasonal influenza A virus and 2009 H1N1 influenza A virus.
4. If a person has recently received the live attenuated influenza vaccine (LAIV), he or she could test positive on a rapid influenza antigen test.

Confirmatory Tests [38]

Real-time PCR is the recommended test for confirmation of 2009 H1N1 influenza cases. Viral culture is also diagnostic of influenza infection, but may not yield timely results for clinical management.

TREATMENT AND PROPHYLAXIS

Vaccine (This section has been adapted from the Centers for Infectious Disease Research and Policy[39]).

On September 15, 2009, the FDA announced approval of four 2009 H1N1 influenza vaccines, and in November 2009 approved a fifth one. By October 9, 2009, all states had placed orders for the vaccine. Initially, the CDC's Advisory Committee on Immunization Practices (ACIP) recommended that vaccination efforts focus on five target groups of persons at high risk for influenza. These groups included:

- Pregnant women
- Persons who live with or provide care for infants younger than 6 months (eg, parents, siblings, and day-care providers)
- Healthcare and emergency medical services personnel
- Persons aged 6 months to 24 years
- Persons aged 25 to 64 who have medical conditions that put them at higher risk for influenza-related complications

As vaccine supply increased, restrictions to target groups were eased, and by late December 2009, vaccination became available to the general public. By the end of 2009, approximately 61 million persons had been vaccinated in the United States, and by January 29, 2010, 124 million doses had been distributed.

The CDC currently recommends annual seasonal influenza vaccination for all persons age 6 months and older. When vaccine supply is limited, the CDC recommends that vaccination efforts

should focus on delivering vaccination to:

- Children aged 6 months to 4 years (59 months)
- Adults aged ≥50 years
- Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
- Immunosuppressed persons (including immunosuppression caused by medications or by human immunodeficiency virus [HIV])
- Pregnant women
- Persons aged 6 months to 18 years and receiving long-term aspirin therapy and who therefore might be at risk for experiencing Reye's syndrome after influenza virus infection
- Residents of nursing homes and other chronic-care facilities
- American Indians/Alaska Natives
- Persons who are morbidly obese (body mass index ≥40)
- Healthcare personnel
- Household contacts and caregivers of children aged <5 years and adults aged ≥50 years, with particular emphasis on vaccinating contacts of children aged <6 months
- Household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza

Treatment and Chemoprophylaxis

Treatment and chemoprophylaxis recommendations for influenza are based on an understanding of the circulating strains and the susceptibility patterns of those circulating strains. During the 2009 H1N1 influenza pandemic the 2009 H1N1 influenza strain was dominant and few other strains circulated. The 2009 H1N1 swine flu strain was sensitive to the neuraminidase inhibitors and resistant to the adamantanes.

Dosing recommendations are outlined in the table below[40]:

Agent	Treatment Dose X 5 days	Prophylaxis Dose X 10 days after last known exposure[2]
Zanamivir (Adults; Children age ≥ 5 years[3])	10 mg (two 5mg inhalations) BID	10 mg (two 5mg inhalations) QD
Oseltamivir (Adults; Children > 40 kg)	75 mg BID[4]	75 mg QD
Oseltamivir (Children age ≥12 months) ≤ 15 kg	30 mg BID	30 mg QD
16-23 kg	45 mg BID	45 mg QD
24-40 kg	60 mg BID	60 mg QD
Oseltamivir (Children <12 months) Age 6-11 months	25 mg BID	25 mg QD
Age 3-5 months	20 mg BID	20 mg QD
Age <3 months	12 mg BID	Not recommended[5]

[1] Modified from Table in CDC Interim Guidance on Antiviral Recommendations for Patients with Novel Influenza A (H1N1) Virus Infection and their Close Contacts (www.cdc.gov/h1n1flu/recommendations.htm).

[2] Duration of antiviral chemoprophylaxis for outbreaks is for a minimum of two weeks. If new cases continue to appear, duration may be extended.

[3] Zanamivir is approved for treatment in children ≥7 years old and for chemoprophylaxis in children ≥5 years old

[4] For severely or critically ill individuals, and hospitalized obese patients, clinicians should **consider** giving oseltamivir 150 mg BID for 8 – 10 days (see www.ama-assn.org/ama/pub/physician-resources/medical-science/infectious-diseases/topics-interest/swine-flu/swine-flu-treatment.shtml).

[5] Due to limited data in this age group, Oseltamivir is not recommended for prophylaxis for children <3 months old unless the situation is judged critical. If deemed critical, the recommended dosage is 12 mg QD x 10 days after last exposure.

An increased dose of the drug (150 mg twice daily in adults) and an increased duration of therapy (a total of 10 days) with no treatment interruptions has been used in patients with pneumonia or evidence of clinical progression.

COMPLICATIONS AND ADMISSION CRITERIA

Complications include the following (this section has been adapted from the Centers for Infectious Disease Research and Policy [41]):

- Diffuse viral pneumonitis (can be associated with severe hypoxia and acute respiratory distress syndrome [ARDS])
- Shock and renal failure among some patients with ARDS
- Prolonged exacerbation of chronic obstructive pulmonary disease (COPD)
- Secondary bacterial pneumonia
- Neurologic manifestations (eg, altered mental status, seizures, encephalopathy, encephalitis)
- Myocarditis
- Dehydration
- Death

INFECTION CONTROL[42]

All healthcare facilities should adopt standard and droplet precautions when caring for patients with Influenza-like illness (ILI*), or suspected or confirmed influenza infection. Specifically:

- Request that all persons with fever and cough wear a face mask;
- Isolate unmasked patients with ILI as soon as possible, ideally in a private exam room or at a distance of at least 3 feet from others;
- Staff entering the exam room of any patient with ILI should either ensure the patient is masked, or wear either a face mask or N-95 respirator pending diagnosis.

*ILI is defined as fever and either cough or sore throat

PEARLS AND PITFALLS[42]

- **Encourage** and **facilitate** influenza vaccination for all persons 6 months of age and older and pneumococcal vaccination for those at increased risk of pneumococcal disease.
- **Treat** patients with suspected or confirmed influenza who are hospitalized for severe illness or who are at higher risk for influenza-related complications with oseltamivir or zanamivir. Treat early and empirically, without relying on lab test results.
- **Implement** infection control precautions as described below.
  - ALL PERSONS with fever and cough should wear a face mask, if tolerated, in all health care settings.
  - ALL PERSONS with ILI should be instructed to stay at home until 24 hours after fever resolves, except patients that require medical evaluation and care.

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