



Center for Infectious
Disease Research & Policy

UNIVERSITY OF MINNESOTA

MCEIRS PANDEMIC H1N1 2009 INFLUENZA TRAINING

Individual Study Guide

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PANDEMIC H1N1 2009 Influenza Virus Among Humans: Epidemiology

**Minnesota Center of Excellence for Influenza
Research and Surveillance**

Epidemiology of the pH1N1 2009 Virus

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INTRODUCTION

pH1N1 2009 Influenza Virus Among Humans: Epidemiology

This module will familiarize you with the epidemiology and clinical presentation of pH1N1 2009 influenza among humans. Key milestones in the pH1N1 2009 influenza pandemic, disease patterns, and groups at high risk for influenza complications are topics that will be covered.

LESSON 1: pH1N1 2009 INFLUENZA PANDEMIC TIMELINE

In this lesson, we will cover:

- Timeline of Key Events
- Key Challenges

TIMELINE OF KEY EVENTS

MAR 17 - First case of pH1N1 2009 influenza, Mexico.

MAR 28 - First US case of pH1N1 2009 influenza, in California.

APR 12 - First death associated with pH1N1 2009 influenza, Mexico.

APR 25 - Community outbreaks of pH1N1 2009 influenza confirmed in the US and Mexico

APR 27 - First cases confirmed in Canada, Spain, and the United Kingdom. WHO raises influenza pandemic phase from 3 to 4. (Phase 4: An animal or human-animal reassortant virus is causing or has caused sustained community outbreaks in a single country.)

APR 28 - First cases confirmed in Israel and New Zealand. Worldwide 105 laboratory-confirmed cases reported in 7 countries on 3 continents.

APR 29 - First pH1N1 2009 influenza death in the US. WHO raises influenza pandemic phase from 4 to 5. (Phase 5: An animal or human-animal reassortant virus is causing sustained community outbreaks in two or more countries in one WHO region.)

MAY 2 - First cases of pH1N1 2009 influenza in swine detected in a commercial swine herd in Alberta, Canada. Investigation suggests that pigs acquired influenza from infected humans.

MAY 31 - Community outbreaks confirmed in 10 countries on 5 continents.

JUN 1 - Worldwide 17,410 cumulative cases reported in 62 countries, including 115 deaths.

JUN 11 - WHO declares influenza pandemic phase 6. (Phase 6: The reassortant virus is causing sustained community level outbreaks in two or more countries in one WHO region AND at least one other country in another WHO region.)

JUN 29 - First case of oseltamivir resistance reported, Denmark.

JUL 16 - WHO stops counting individual influenza cases citing questionable usefulness of reporting individual case counts and the burden it puts on countries experiencing widespread transmission; case reporting is focused on hospitalizations and deaths due to influenza.

JUL 24 - The US Centers for Disease Control and Prevention (CDC) stops counting individual influenza cases; case reporting is focused on hospitalizations and deaths due to influenza.

AUG 6 - First cases of oseltamivir resistance detected in the US among 2 unrelated severely immunocompromised hospital patients in Washington State.

AUG 20 - First cases of pH1N1 2009 influenza among poultry reported on two turkey farms near Valparaiso, Chile. Infected humans reported to be the source of viral exposure.

SEP 11 - First cases reported of oseltamivir resistance among epidemiologically-linked patients receiving chemoprophylaxis, North Carolina.

SEP 21 - First lots of pH1N1 2009 vaccine for public use become available, China.

SEP 23 - WHO recommends the pH1N1 2009 strain for inclusion in seasonal influenza vaccines for use in the Southern Hemisphere.

OCT 5 - Clinically ill pet ferret in Oregon tests positive for pH1N1 2009 following exposure to a human with influenza.

OCT 12 - First lots of pH1N1 2009 vaccine for public use in the US become available - vaccine is recommended for persons at highest risk of infection and/or complications.

OCT 30 - Clinically ill pet cat in Iowa tests positive for pH1N1 2009 following exposure to humans with influenza.

NOV 20 - Clusters of oseltamivir-resistant pH1N1 2009 cases are reported among immunocompromised patients in hospital settings in North Carolina (US) and Wales.

JAN - pH1N1 2009 vaccine availability in the US expands beyond those at higher risk of infection and/or complications to include the general population.

FEB 18 - WHO recommends the pH1N1 2009 strain for inclusion in seasonal influenza vaccines for use in the Northern Hemisphere.

KEY CHALLENGES

- Will the pH1N1 2009 influenza virus evolve in humans over time to become more virulent?
- Will antiviral drug resistance among pH1N1 2009 viruses increase over time?
- Will the pH1N1 2009 virus reassort with another influenza virus, such as highly pathogenic H5N1 avian influenza virus?

LESSON 2: EPIDEMIOLOGY

In this lesson, we will cover:

- Routes of Transmission
- Incubation Period
- Infectious Period

ROUTES OF TRANSMISSION

pH1N1 2009 influenza appears to be transmitted from person to person through close contact in ways similar to other influenza viruses.

However, the proportion of cases due to each route of transmission may differ between seasonal and pH1N1 2009 influenza. Research on the specific routes of transmission for influenza A viruses, particularly the pH1N1 2009 strain, is ongoing.

Routes of transmission include:

Droplet exposure of mucosal surfaces (e.g., nose, mouth, and eyes) by respiratory secretions from coughing or sneezing.

Contact, usually of hands, with an infectious patient or fomite (a surface or item that is contaminated with secretions) followed by self-inoculation of virus onto mucosal surfaces such as those of the nose, mouth, and eyes.

Airborne transmission through small particle aerosols in the general vicinity of the infectious individual.

Transmission of influenza through the air over longer distances, such as from one patient room to another, is not well understood, but is not thought to be a significant route of transmission.

Contact with respiratory secretions and bodily fluids. (All respiratory secretions and bodily fluids, including diarrheal stools, of patients with pH1N1 2009 influenza are considered to be potentially infectious.)

INCUBATION PERIOD

In general, the estimated incubation period (time from exposure to onset of symptoms) for pH1N1 2009 influenza is from 1 to 4 days, with an average of 2 days.

INFECTIOUS PERIOD

The duration of time that a person is capable of transmitting the virus to others is considered the infectious period.

Viral Shedding

Influenza virus shedding (the time during which a person might be infectious to another person) begins the day before illness onset and can persist for 5-7 days, although some persons may shed virus for longer periods, particularly young children and severely immunocompromised persons.

The amount of virus shed is greatest in the first 2-3 days of illness and appears to correlate with fever, with higher amounts of virus shed when temperatures are highest.

Practical Application

In community settings, persons with novel H1N1 infection should be considered potentially infectious until they are fever-free without the use of medication for at least 24 hours.

In healthcare settings, ill employees should not return to work until 7 days after symptom onset or until the resolution of symptoms, whichever is longer.

LESSON 3: CLINICAL FEATURES

In this lesson, we will cover:

- Overview of Viral Pathogenesis and Immune Response
- General Signs, Symptoms, and Spectrum of Disease

Viral Pathogenesis

Like other viruses, pH1N1 2009 influenza viruses are obligate intracellular parasites (i.e., the virus requires suitable host cells to survive).

In humans, influenza viruses preferentially infect cells of the respiratory tract. The viral hemagglutinin and neuraminidase glycoproteins interact with sialic-acid containing glycoprotein or glycolipid receptor binding sites on human respiratory cells.

Entry of influenza viruses into the respiratory tract causes cell damage, especially in the respiratory epithelium, which elicits an acute inflammatory response and impairs mechanical and cellular functions of the host.

Overview of Immune Response

The main immune responses that counteract an initial influenza A infection in an immunocompetent host are, in order of occurrence:

1) Innate (nonspecific) Immune Response

Interferon (an antiviral produced by some cells) and natural killer cell (inflammatory response) production. See example of natural killer cell activity in Figure 1.



Figure 1: Natural Killer Cell Interacting with Uninfected Body Cell

Natural Killer (NK) cell moves through body interacting with body cells as shown in Figure 2.



Figure 2: Natural Killer Cell Interacting with Virus-Infected Body Cell

Figure 3 shows virus-infected cell does not interact with NK cell as a normal cell would.

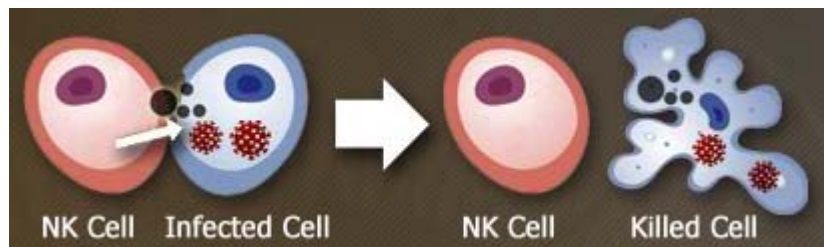


Figure 3: Natural Killer Cell Kills Virus-Infected Cell

This atypical interaction causes the NK cell to release substances that puncture and kill the infected cell.

2) Adaptive (specific) Immune Response (See Figure 4 below)

Production of antigen-specific antibodies (humoral immunity).

Proliferation of antigen-specific cytotoxic T cells (cell-mediated immunity).

3) Recovery

Virus-infected host cells and free floating viruses are cleared from the respiratory tract allowing tissue repair in the host to begin. See Figure 4.

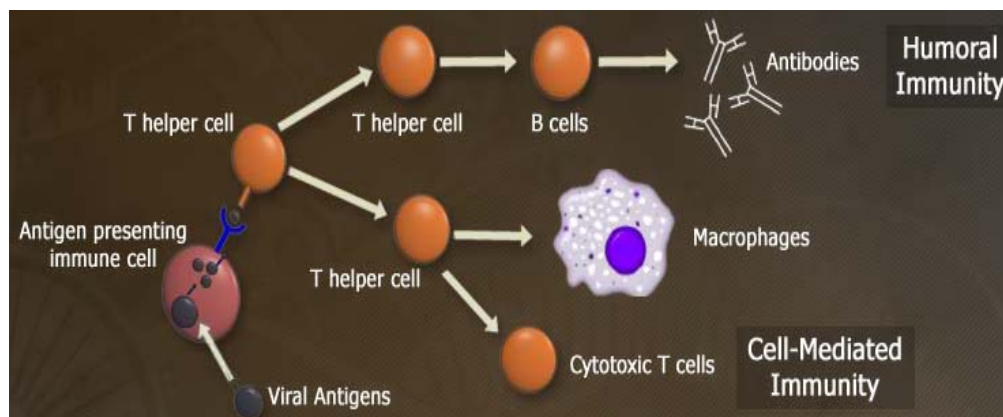


Figure 4: Tissue Repair in Host

General Signs, Symptoms, and Spectrum of Disease

Typical Presentation

Most patients have uncomplicated, typical influenza-like illness and recover spontaneously.

Like seasonal influenza, the most commonly reported symptoms for pH1N1 2009 influenza include fever, cough, sore throat, runny or stuffy nose, body aches, headache, chills, fatigue, nausea, diarrhea, and vomiting.

Of note, depending on the study, 10% to 50% of persons with laboratory-confirmed pH1N1 2009 infection do not have a fever.

Severe Presentation

Some patients experience more severe disease or death.

Typical characteristics of severe and fatal cases include:

- Patient begins to deteriorate 3-5 days after symptom onset.
- Severe viral pneumonia with multifocal infiltrates is seen on chest x-ray; bacterial coinfection may or may not be present.
- Rapid progression to acute respiratory distress syndrome (ARDS) (i.e., within 24 hours) can occur, requiring immediate admission to an intensive care unit.
- In addition to ARDS, renal or multiorgan failure may occur.
- Mechanical ventilation often is needed. Some patients do not respond well to conventional ventilatory support, further complicating treatment.

Most cases of severe or fatal disease occur in persons with underlying medical conditions, but severe disease can occur in previously healthy individuals.

In a CDC study of patients hospitalized with pH1N1 2009 influenza in the United States, 73% had at least one underlying medical condition such as asthma; diabetes; heart, lung, or neurologic diseases; or pregnancy.

Impact of Early Treatment

Early treatment with antiviral drugs (oseltamivir or zanamivir) may reduce the severity of illness and improve the chances of survival.

The pH1N1 2009 influenza strain is naturally resistant to the antiviral drug class of adamantanes (amantadine and rimantadine), but as of early 2010 it is generally susceptible to neuraminidase inhibitors (oseltamivir and zanamivir).

A limited number of oseltamivir-resistant cases of pH1N1 2009 influenza were reported through 2009. Most cases have occurred among immunocompromised patients and those receiving subtherapeutic levels of oseltamivir for prophylaxis.

No or only very limited person-to-person transmission of oseltamivir-resistant pH1N1 2009 virus was reported through 2009.

No zanamivir resistance was reported through 2009.

LESSON 4: GROUPS AT HIGH RISK FOR COMPLICATIONS

In this lesson, we will cover:

- Groups at High Risk for Complications

Seasonal Influenza

According to CDC, people at high risk for developing complications related to seasonal influenza include:

- Children less than 5 years old, but especially children younger than 2 years
- Adults 65 years of age and older
- Pregnant women
- People who have:
 - Chronic respiratory, circulatory, endocrine, neurological, blood, kidney, or liver disorders
 - Chronic metabolic disorders
 - Weakened immune system
 - People younger than 19 years of age who are receiving long-term aspirin therapy

Social factors can influence the risk for flu-related complications. Disadvantaged populations, such as minority groups and indigenous populations, are disproportionately affected by severe disease due to influenza. This may be due to the greater frequency of co-morbidities (e.g., diabetes and asthma) and lack of access to care.

pH1N1 2009 Influenza

Although pH1N1 2009 exhibits many similarities to seasonal flu, there are some differences in the pattern of severe disease.

In contrast to seasonal flu, severe and fatal cases of pH1N1 2009 influenza have occurred more often in younger rather than older age groups as Figure 5 illustrates.

Among 272 persons hospitalized with pH1N1 2009 infections in the US between April and mid-June 2009, 45% were younger than 18 years of age and 50% were 18 to 64; only 5% were 65 years of

age or older. In a typical influenza season people 65 years and older make up 60% of hospitalized influenza patients. Among 268 US patients hospitalized with pH1N1 2009 influenza, the number of deaths was highest among people 25 to 49 years of age (41%), followed by people 50 to 64 years of age (24%) and people 5 to 24 years of age (16%). This is a very different pattern from what is seen in seasonal influenza, where an estimated 90% of influenza-related deaths occur in people 65 years of age and older.

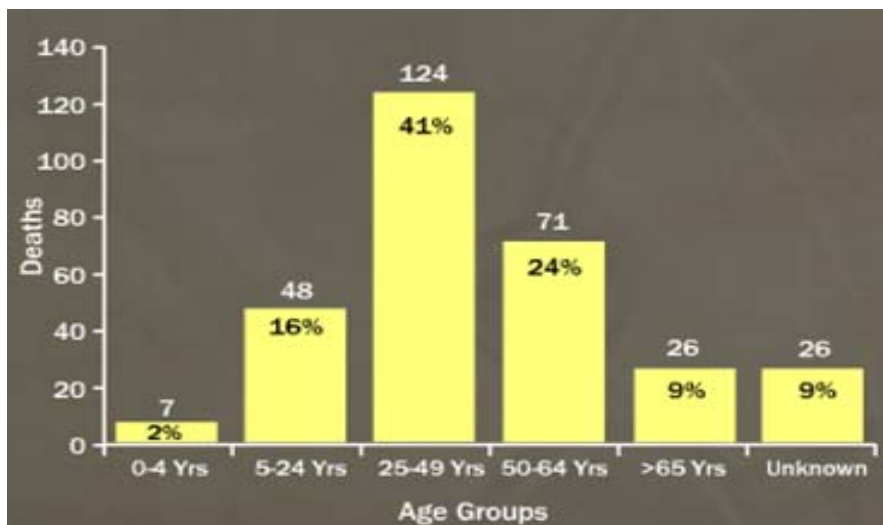


Figure 5: Deaths by Age Group among 268 pH1N1 2009 Influenza Patients in the US

Obesity is not one of the medical conditions previously recognized to place people at greater risk of serious seasonal flu-related complications; however, obesity has been noted as an underlying medical condition in some hospitalized pH1N1 2009 patients.

The percentage of obesity and morbid obesity was disproportionately high among 227 patients hospitalized with pH1N1 2009 as measured by body mass index (BMI). The role 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.

Guidance for clinical management of specific groups at high risk for pH1N1 2009 influenza complications are routinely updated and available online at the WHO and CDC Web sites.

Early treatment with antiviral drugs for groups at high risk for influenza complications may reduce the severity of illness and improve the chances of survival.

The pH1N1 2009 influenza strain is naturally resistant to the antiviral drug class of adamantanes (amantadine and rimantadine), but as of early 2010 it is generally susceptible to neuraminidase inhibitors (oseltamivir and zanamivir).

GLOSSARY

Active Surveillance - Disease surveillance approach in which routine outreach by health department staff to potential disease reporters is used to increase the completeness and/or timeliness of disease reporting.

Acute Respiratory Distress Syndrome - See ARDS.

Adamantanes - M2 inhibitors; a class of antiviral drugs used to treat influenza. This class includes amantadine and rimantadine. pH1N1 2009 influenza viruses are naturally resistant to all drugs in this class.

Adaptive Immunity - Specific immunity; The form of immunity that produces protection against infection that is highly specific and long lasting. The adaptive immune system takes time to mobilize following the first exposure to a specific antigen, but subsequent exposures produce a rapid adaptive immune response. Adaptive immunity includes humoral and cell-mediated immunity.

Amantadine - An antiviral drug used to treat influenza and belongs to the drug class called "adamantanes." pH1N1 2009 influenza viruses are naturally resistant to adamantanes.

Antibody - A type of glycoprotein molecule produced during a humoral (adaptive) immune response that binds antigens, often with a high degree of specificity and strength.

Antigen - A molecular substance foreign to the body that binds with antibodies or T-cell receptors. Antigens that produce a specific immune response can also be called "immunogens." The adaptive immune system may recognize multiple antigens in a single virus.

Antigenic Profile - The unique collection of antigens associated with a specific microorganism (e.g., a particular viral strain).

Antiviral - Drug that is used to prevent or cure a disease caused by a virus, by interfering with the ability of the virus to multiply in number or spread from cell to cell.

ARDS - Acute Respiratory Distress Syndrome; an emergency caused by failure of the lungs to work.

Cell-Mediated Immunity - A type of adaptive immune response mediated by T cells of the immune system.

Chemoprophylaxis - The use of chemicals (drugs) to prevent infection or disease.

Communicable - See Contagious.

Contagious - Communicable; A contagious or communicable disease is one that is spread from one person or animal to another by direct or indirect contact. Direct contact includes touching

any discharge from the body that contains the infectious agent. Indirect contact might include contact through something else, such as toys or eating utensils.

Cytotoxic (Killer) T Cell - A major effector cell in a cell-mediated (adaptive) immune response.

Epidemic - The occurrence in humans of an illness or health-related event in a community, region, or country in numbers clearly in excess of normal expectancy.

Epithelium - The outer covering of the organs of the body.

Fomite - Any inanimate object or substance capable of carrying infectious organisms (such as bacteria or viruses) and hence transferring them from one individual to another.

Hemagglutinin (HA) - An important surface structure protein of the influenza virus that is an essential gene for the spread of the virus throughout the respiratory tract. This protein enables the virus to attach itself to a cell in the respiratory system and penetrate it. It is used to name influenza A subtypes and is referred to as the "H" in the influenza virus subtype (e.g., H5N1). To date, 16 different influenza A hemagglutinin antigens have been identified.

Host - An organism on or in which a parasitic organism (e.g., virus, bacteria) lives.

Humoral Immunity - A type of adaptive immune response mediated by the production of antibodies.

ILI - Influenza-like illness.

Immunocompetent - Refers to a state of the immune system in which normal immune responses are produced following exposure to an antigen.

Immunocompromised - Refers to an abnormal state of the immune system in which immunity is too low and resistance to infection is decreased. May be a result of a disease process (e.g., human immunodeficiency virus [HIV] infection, leukemia) or treatment (e.g., chemotherapy for cancer).

Immunosuppression - See Immunocompromised.

Incubation Period - The time between exposure to a disease-causing organism and the onset of symptoms.

Infectious - Capable of causing infection.

Infectious Period - The time during which a person or animal infected with a disease-causing agent is capable of transmitting the agent to another.

Infectivity - A pathogen's ability to spread rapidly from one person or animal to another.

Innate Immunity - Nonspecific immunity; Protection against infection that relies on cells and mechanisms that exist before infection, are capable of a rapid response to infectious agents, and react in essentially the same way to repeated infections.

Interferon - A class of cellular signaling proteins produced as part of an innate immune response. When produced by virally-infected cells they inhibit viral replication in these and adjacent cells.

M2 Inhibitors - See Adamantanes.

Morbidity - Disease; morbidity rate is the incidence or prevalence of disease in a specific population during a specified interval of time or a specific point in time.

Mortality - Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Multifocal Infiltrates - For purposes of this module, refers to multiple areas within the lung where fluid has entered.

Neuraminidase (NA) - An important surface structure protein of the influenza virus that is an essential enzyme for the spread of the virus throughout the respiratory tract. This protein enables

the virus to escape the host cell and infect new cells. It is used to name influenza A subtypes and is referred to as the "N" in the influenza virus subtype (e.g., H5N1). To date, 9 different influenza A neuraminidase antigens have been identified.

Neuraminidase Inhibitors - A class of antiviral drugs commonly used to treat or prevent influenza. This class includes oseltamivir and zanamivir.

Nonspecific Immunity - See Innate Immunity.

Oseltamivir - An antiviral drug commonly used to treat or prevent influenza and belongs to the drug class called "neuraminidase inhibitors."

Outbreak - The occurrence of a disease or health-event in a specific geographic area or population in excess of normal expectancy; cases are usually related in time and space.

Pandemic - A worldwide outbreak of a disease in humans in numbers clearly in excess of normal. A global influenza pandemic may occur if two conditions are met:

- A new subtype of influenza A virus emerges for which there is little or no immunity in the human population.
- The virus can spread easily from person to person in a sustained manner.

Passive Surveillance - Disease surveillance approach in which healthcare clinics, providers, and/or laboratories report notifiable diseases on a case-by-case basis to a health department.

Panzootic - A worldwide outbreak of a disease in animals in numbers clearly in excess of normal.

Pathogenesis - The mechanisms by which an agent causes disease.

Pathogenic - Causing disease or capable of doing so.

Reservoir - A person or animal that serves as a host to a pathogenic agent, generally without visible symptoms of the disease or injury.

Pathogen - A disease-causing agent (e.g., virus, bacteria, fungus).

Rimantadine - An antiviral drug used to treat influenza and belongs to the drug class called "adamantanes." pH1N1 2009 influenza viruses are naturally resistant to adamantanes.

Seasonal Flu ("Common Flu", "Winter Flu") - Influenza caused by one of the common influenza subtypes known to be circulating in the human population; seasonal influenza peaks in the winter months in the Northern and Southern Hemispheres and tends to be year-round in tropical regions.

Specific Immunity - See Adaptive Immunity.

Strain - Influenza virus subtypes are further characterized into strains. New strains of influenza viruses replace older strains through the process of antigenic drift (i.e., small mutations in the genetic material of the virus).

Swine Flu - A respiratory disease in pigs caused by influenza A virus. Influenza outbreaks in swine herds are common; the illness is relatively mild, and most animals recover. Domestic birds can be a source of influenza A in swine, and transmission from humans to swine and from swine to humans has occurred.

Virulence - A pathogen's ability to invade host tissues and cause severe disease.

Virulent - Highly lethal; causing severe illness or death.

Virus - Any of various simple submicroscopic parasites of plants, animals, and bacteria that often cause disease and that consist essentially of a core of RNA or DNA surrounded by a protein coat. Unable to replicate without a host cell, viruses are typically not considered living organisms.

Vital Records - Records of life events kept under governmental authority, including birth certificates, marriage licenses, and death certificates.

Zanamivir - An antiviral drug used to treat or prevent influenza and belongs to the drug class called "neuraminidase inhibitors."

Zoonoses - Diseases that transfer from animals to humans.

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