INFLUENZA

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Introduction

- Influenza is a disease caused by influenza viruses that infect the respiratory system of many animals, birds and humans.
- Human influenza is a highly contagious disease and is usually spread by a person's cough and sneeze
- The patient is published.
- This disease is different from the common cold.
- 4 types of influenza virus have been identified so far, including: A-B-C-D

Introduction

- Type A influenza virus causes disease in humans and animals and leads to public health problems. Historical data indicate the risk of influenza transmission between animals and humans and the potential of creating a pandemic risk with this type of virus.
- Type B influenza virus circulates in human society and is the cause of seasonal epidemics (pandemics or outbreaks).
- Recent research has shown that even sea seals can be infected with this type of virus.
- Influenza type C can infect both humans and pigs, but generally causes moderate illness and is rarely reported.
- Type D influenza virus primarily infects cattle and it has not been determined that it can cause infection or disease in humans.

Introduction

- All influenza viruses are genetically unstable, and this issue raises the possibility of change and mutation changes occur over time.
- Small genetic changes in the composition of the influenza virus are called drift changes (small changes).
- On the other hand, the type A influenza virus, including the subspecies of different strains, can have genetic materials moved or rearranged and recombined during the process of rearrangement or mutation these changes are called shifts (big changes).

Introduction

- Influenza type A virus is classified into different subspecies based on different compositions of its surface proteins (hemagglutinin and neuraminidase).
- So far, 18 subspecies of hemagglutinin and 11 subspecies of neuraminidase have been identified.
- Many subspecies have been identified in birds, and subspecies H17N10 and H18N11 have been identified only in bats.
- Depending on the primary host animal, type A influenza viruses can range from avian influenza types including A(H5N1), A(H7N9), A(H9N2), swine flu is classified as A(H1N1), A(H1N2), A(H3N2), or other types of animal flu.

Introduction

- In general, influenza occurs with an estimated annual incidence of 5-10% in adults and 20-30% in children.
- The resulting illness or disease can lead to hospitalization or death, especially in high-risk groups (children, the elderly, people with chronic diseases).
- Disease epidemics can lead to absenteeism in large work groups or schools and reduced production.
- The global estimate of epidemics caused by influenza is about 3-5 million severe cases of the disease and about 250 thousand to 500 thousand deaths.
- Currently, the most effective way to prevent the disease and reduce the severity of the disease is vaccination and personal and social hygiene.

Introduction

- An influenza pandemic can occur when a new influenza virus acquires sufficient and stable human-to-human transmission ability and then spreads globally.
- So far, influenza pandemics have only been caused by new subspecies of type A virus because the human body is not immune to it and usually the resulting disease is very severe.
- Pandemic is not a one-stage event and disease stages occur in 2 or 3 time waves during 3 to 12 months of the year.
- The disease is expected to spread in all parts of the world by air travel (modern pandemic) in less than 3 months.

Introduction

- Historical data shows the occurrence of all influenza pandemics with animal origin.
- Zoonotic (animal) influenza occurs when humans are infected by influenza viruses circulating in animals.
- Human infection is primarily caused by direct contact with an infected animal or contaminated environment.

Introduction

- The care definition of severe acute respiratory infections (SARI) in 2014 was initially used by the World Health Organization for infections caused by influenza.
- This definition is accepted to identify epidemics caused by dangerous respiratory infections.
- Many infectious viral acute respiratory diseases that have the ability to progress rapidly, such as covid-19, Middle East respiratory syndrome, Ebola, Nipah, have been curbed with this definition and the resulting strategy in the origin of the outbreak.

Introduction

- On the other hand, the increase in international travel and global trade increases the need for intensified and integrated planning regarding the strengthening of diagnostic capacities and the identification and control of infectious diseases.
- Lessons learned from major health events, including outbreaks and epidemics of infectious diseases, show special attention to ONE HEALTH as a principle and HEALTH SECURITY as a basic pillar in planning.

DEFINITION

- The term *influenza* represents both a clinically defined respiratory illness accompanied by systemic symptoms of fever, malaise, and myalgia and the name of the orthomyxoviruses that cause this syndrome.
- Although this term is sometimes used more generally to denote any viral respiratory illness, many features distinguish influenza from these other illnesses, most particularly its systemic symptoms, its propensity to cause sharply peaked winter epidemics, and its capacity to spread rapidly among close contacts.
- The morbidity and mortality associated with influenza epidemics are documented closely in the United States by the Centers for Disease Control and Prevention (CDC), which records clinical cases of influenza-like illness, cases of virologically documented influenza, and excess deaths due to pneumonia and influenza combined.

ETIOLOGIC AGENTS

- Three influenza viruses occur in humans: A, B, and C.
- These viruses are irregularly circular in shape, measure 80–120 nm in diameter, and have a lipid envelope and prominent spikes that are formed by the two surface glycoproteins, hemagglutinin (H) and neuraminidase (N) **.**
- The hemagglutinin functions as the viral attachment protein, binding to sialic acid receptors on the cells that line the superficial epithelium of the respiratory tract.
- The neuraminidase cleaves the virus from the cell membrane to facilitate its release from the cell and prevents self-aggregation of viruses.

ETIOLOGIC AGENTS

- Influenza A viruses have eight single-strand negative-sense RNA segments in their genomes that encode hemagglutinin and neuraminidase as well as internal genes, including polymerase, matrix, nucleoprotein, and nonstructural genes.
- The segmented nature of the genome allows gene *reassortment*; an analogy for reassortment is the shuffling of a deck of cards.
- Reassortment takes place when a single cell is infected with two different strains.

ETIOLOGIC AGENTS

- Among the influenza viruses, the A viruses are of paramount importance for several reasons: (1) the plasticity of their genomes, which enables them to react to the prevailing immunity in the community by modifying their immunogenic epitopes, particularly on the hemagglutinin surface protein (*antigenic drift*); (2) the segmentation of their genomes, which allows genes coding both surface and internal proteins to be reassorted between influenza A variants (*antigenic shift*); and (3) their extensive mammalian and avian reservoirs, in which multiple variants with distinct hemagglutinin and neuraminidase genes lie in wait.
- As a result of all of these factors, influenza A virus has the ability, particularly after an antigenic shift, to cause a worldwide epidemic (*pandemic*).
- The most severe influenza A pandemic in modern history took place in 1918; ~50 million deaths were attributed to the culpable influenza A H1N1 virus in the years surrounding 1918.

ETIOLOGIC AGENTS

- The influenza A viruses are further classified by their surface glycoproteins (H and N), the geographic location of their isolation, their sequential number among isolated viruses, and their year of isolation.
- Thus, the influenza vaccine for the 2017–2018 season in the Northern Hemisphere was formulated to provide protection against influenza A/Michigan/45/2015 (H1N1)pdm09–like virus, influenza A/Hong Kong/4801/2014 (H3N2)–like virus, and two lineages in the influenza B family: B/Brisbane/60/2008–like virus (Victoria lineage) and B/ Phuket/3073/2013–like virus (Yamagata lineage).

EPIDEMIOLOGY

- Influenza virus causes outbreaks during the cooler months of the year and thus has a mirror-image season in the antipodes compared with that in the Northern Hemisphere.
- The circulation of strains in the Southern Hemisphere has some predictive value for vaccine composition in the Northern Hemisphere, and vice versa.
- This information is important as the degree of antigenic drift is one determinate of vaccine efficacy.
- Vaccine composition typically must change in at least one component yearly in anticipation of the predicted circulating strains.

EPIDEMIOLOGY

- A typical outbreak begins in early winter and lasts 4–5 weeks in a given community, although its impact on the country as a whole will be of considerably longer duration.
- When excess mortality occurs, an influenza outbreak is classified as an *epidemic*.
- Influenza's impact is reflected in increased school and work absenteeism, increased visits to emergency rooms and primary care physicians, and increased hospitalizations, particularly of elderly patients and individuals with underlying cardiopulmonary disease.
- The impact often is most easily recognized in the pediatric population, whose school absenteeism quickly peaks.

EPIDEMIOLOGY

- Influenza’s global spread and causative strain(s) in a given year are well documented by the surveillance networks of the World Health Organization (WHO) and the CDC.
- The severity of an epidemic depends on the transmissibility and virulence of the viral strain, the susceptibility of the population, the adaptation of the virus to its human host, and the degree of antigenic match to the recommended vaccine.
- None of these parameters is totally predictable for influenza A.

EPIDEMIOLOGY

- Influenza is largely spread by small- and large-particle droplets; spread is undoubtedly facilitated by the coughing and sneezing that accompany the illness. Within families, the illness is often introduced by a preschool or school-aged child.

EPIDEMIOLOGY

- In the United States, influenza virus circulation in first-quarter 2020 declined sharply within 2 weeks of the COVID-19 emergency declaration and widespread implementation of community mitigation measures and travel restrictions.
- The decline occurred in other Northern Hemisphere countries and the tropics.
- In 2020, Southern Hemisphere temperate climates had virtually no influenza circulation.
- Influenza activity remained at low levels at the start of the 2020–2021 Northern Hemisphere season.
- While changes in health care–seeking behavior and testing priorities during the pandemic may have contributed, such declines in influenza detection were noted even in areas with continued or increased testing, implicating community mitigation measures as the most likely reason.

EPIDEMIOLOGY

- Despite efforts to limit influenza spread through vaccination, cohorting, use of masks, and hand washing, long-term-care facilities house another sentinel population, including many elderly patients who are at increased risk of complicated disease.

Influenza A Viruses

- When a major shift in the hemagglutinin and/or the neuraminidase occurs, with introduction of a new serotype from an animal or avian reservoir, an influenza A strain has the potential to cause a pandemic.
- In modern influenza history, such shifts occurred in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), 1977 (H1N1), and 2009 (H1N1pdm) .
- On the basis of seroarchaeology (the analysis of serum antibody profiles in the elderly), epidemics that took place in the 1890s have been attributed to H3N2 and H2N2 viruses.
- Epidemics typical of influenza have been documented throughout recorded history.

EPIDEMIOLOGY

- In some epidemics, a younger age group proves especially susceptible.
- This is the case with current H1N1 epidemics, where individuals born before 1968 had likely been exposed to related viral strains and thus were relatively protected against the current strain.
- The 1918 epidemic was striking in this regard: the most severely infected individuals were infants and previously healthy young adults—the latter being a group not typically found to have high influenza mortality .

EPIDEMIOLOGY

- The 1918 epidemic increased all-cause mortality and led to more deaths than all military losses in World War I.
- In spite of the attention paid to the risk and impact of pandemic disease, it is generally appreciated that—with the exception of 1918—cumulatively more illness occurs during yearly epidemics combined than in pandemics.

EPIDEMIOLOGY

- All of the annual influenza A epidemics in the past 50 years have been caused by H1N1 and/or H3N2 strains.
- H2N2 strains circulated between 1957 and 1968, and H1N1 strains circulated prior to that, including in 1918. However, potentially pandemic viruses continue to emerge, mostly in Asia, with higher-numbered hemagglutinins (e.g., H5, H6, H7, H9) reflecting some of the 16 distinct H and 9 distinct N subtypes in avian reservoirs.

EPIDEMIOLOGY

- Most cases of these potentially pandemic illnesses have occurred in individuals who have had direct contact with domesticated birds or who have visited live-bird markets, which are common in Asia.
- In addition to the global aeronautic movement of infected people, bird migration is one mechanism for rapid global spread.
- It is not clear why higher-numbered avian hemagglutinin strains have not acquired the degree of transmissibility necessary to cause pandemic disease.

Avian and Swine Influenza Viruses

- The full panoply of influenza viruses is found in domestic and migratory wild birds.
- It is postulated that epithelial cells in the swine respiratory tract may play a specific role as a “mixing vessel,” allowing the reassortment of genes from avian and human sources and thereby permitting the transition of avian viruses to humans.
- The nature of the sialic acid receptors for influenza virus hemagglutinin partially accounts for host preference.

Avian and Swine Influenza Viruses

- Humans have largely α-2,6-galactose receptors, while birds have α-2,3-galactose receptors.
- Swine have both types of receptors on their respiratory epithelial cells—hence their postulated role in facilitating reassortment and host adaptation of avian strains to growth in humans.
- Strains such as 2009 H1N1pdm (pandemic) had genes of avian, swine, and human origin.
- Some avian strains—notably H5 strains—are highly pathogenic in humans, as was the 1918 strain.
- The reasons for the high pathogenicity of certain strains are not entirely clear.
- Virulence and transmissibility often appear to be separate genetic traits.

Avian and Swine Influenza Viruses

- After the sequencing of the 1918 virus recovered from the lungs of bodies buried in the Arctic permafrost, the virus was genetically reconstructed under carefully controlled isolation conditions.
- In animal studies of this viable 1918 virus, both the hemagglutinin and the ribonucleoprotein contributed to high levels of replication accompanied by an abnormally enhanced innate immune response characterized by proinflammatory cytokines. Perhaps this “cytokine storm” is the best explanation for the enhanced illness occurring in young, immunologically vigorous individuals in the 1918 pandemic.

Avian and Swine Influenza Viruses

- Sequencing demonstrated that the 1918 virus was of avian origin.
- Although the 1918 virus was first identified in military camps in the United States, its impact cannot be attributed to the disruption of war: the illness was well documented in countries such as Iceland that were not directly involved in World War I.

Avian and Swine Influenza Viruses

- The same concerns about a “cytokine storm” have been raised with regard to the H5N1 viruses that first emerged in Hong Kong in 1996.
- These viruses exhibited high pathogenicity in individuals who had direct contact with domestic fowl, with mortality rates close to 50%, but also displayed poor human-to-human transmissibility.
- Pathogenicity appears to be a function not just of the viruses’ surface proteins, but also of an optimal gene constellation including all eight segmented influenza genes.
- However, unlike the 1918 strain, the H5N1 viruses have, to date, caused only sporadic disease, as have other limited clusters of a highly pathogenic H7N9 virus.

Influenza B and C Viruses

- The influenza B viruses are more genetically stable than the influenza A viruses and have no animal reservoirs.
- Two lineages of influenza B have circulated for the past 40 years (B/Yamagata-like and B/Victoria-like viruses), and it has proven very difficult to predict which strain will be dominant in a given year.
- This issue has led to the incorporation of representatives of both influenza B lineages plus influenza A/H1N1 and H3N2 viruses into a quadrivalent vaccine.
- Influenza C viruses cause intermittent mild disease and have attracted little attention.
- These viruses have been the subject of fewer than 10 publications annually since the year 2000.

Influenza-Associated Morbidity and Mortality

- Although epidemics vary in severity and in the age groups most affected, certain high-risk groups are seen in all epidemics.
- These groups are assigned the highest priority for vaccination and other preventive and therapeutic measures. Their caregivers and close contacts are also prioritized targets of interventions.
- A generalization is that the relative impact of an epidemic is seen in the youngest age group with the least prior exposure—and therefore the least immunity—to influenza.

Influenza-Associated Morbidity and Mortality

- The impact of influenza can be depicted as a pyramid of illnesses, medical visits, hospitalizations, and deaths .
- Pneumonia and influenza mortality, reported as excess over the anticipated sine-wave curve of deaths during the year, is seen in the CDC's data for 2012–2017 .
- In addition to excess respiratory deaths directly attributed to influenza, an increase in circulatory deaths also occurs during an influenza epidemic.

Influenza-Associated Morbidity and Mortality

- Influenza virus infects people of all ages and causes mild to severe illness, and even death in some cases.
- The impact of influenza is highly variable from year to year and can be depicted as a pyramid of illnesses, medical visits, hospitalizations, and deaths .
- Infection rates are highest among children, with complications and hospitalizations from seasonal influenza being greatest among certain high-risk groups during most epidemics.
- These groups are assigned the highest priority for vaccination and other preventive and therapeutic measures.
- Their caregivers and close contacts are also prioritized targets of interventions .

Influenza-Associated Morbidity and Mortality

- Mortality attributable to influenza, reported as excess over the anticipated sine-wave curve of pneumonia and influenza deaths during the year, has been between 12,000 to 61,000 deaths annually over the past decade.
- The dramatic effect of the COVID-19 pandemic on excess pneumonia and influenza mortality data is evident from the comparison of 2020 data with data from the prior three seasons .
- Influenza-associated pediatric mortality is based on laboratory confirmation rather than modeling estimates.
- During the 2015−2020 influenza seasons, an estimated 95 to 195 children have died annually from influenza disease.

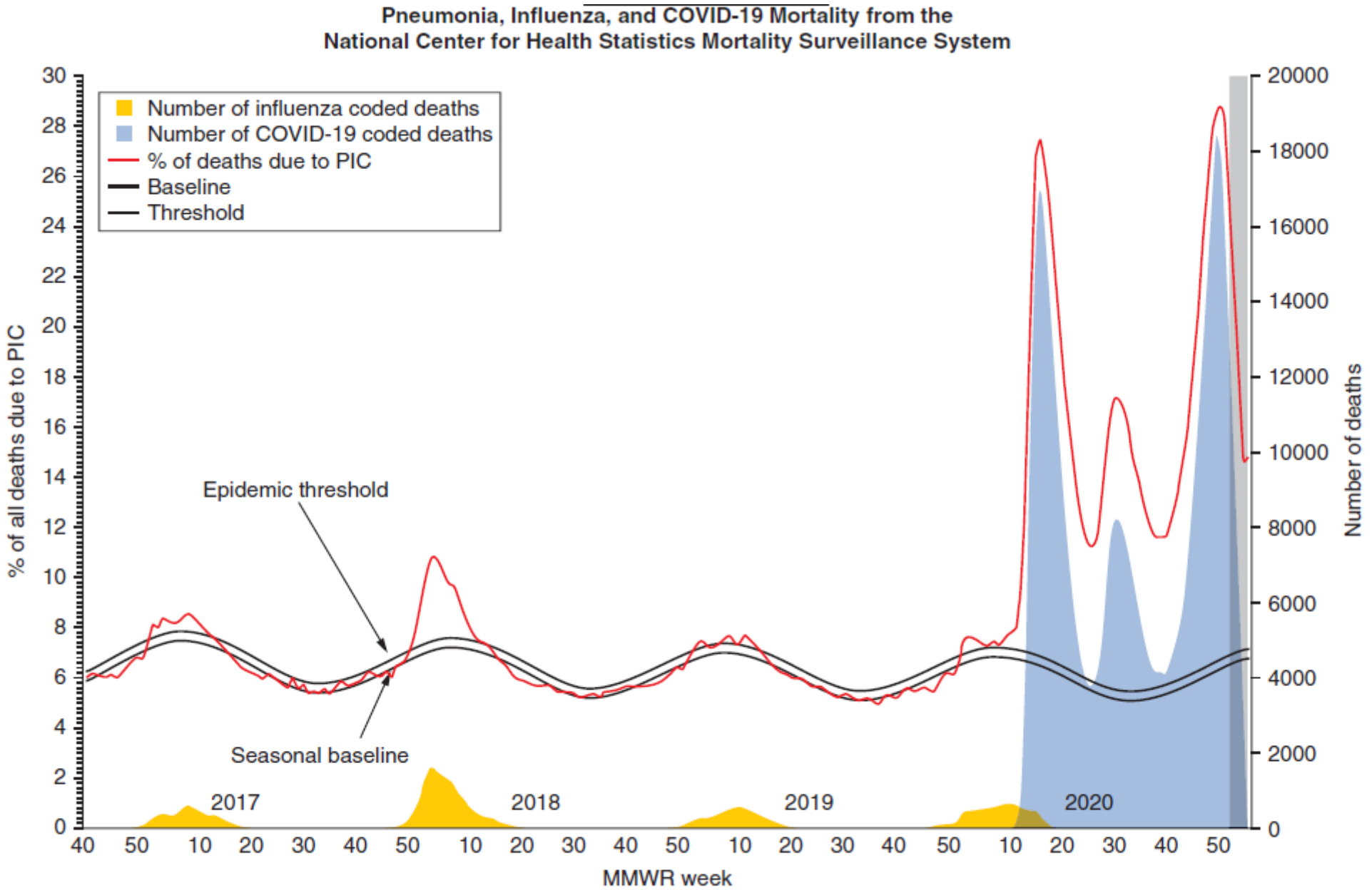

FIGURE 200-4 Pneumonia, Influenza, and COVID-19 Mortality; MMWR, *Morbidity and Mortality Weekly Report*; PIC, pneumonia, influenza, COVID-19. Data through the week ending January 23, 2021, as of January 28, 2021. *(From https://www.cdc.gov/flu/weekly/index.htm.)*

PATHOGENESIS AND IMMUNITY

- At a cellular level, influenza virus binds to sialic acid receptors and enters the epithelial cell through receptor-mediated endocytosis.
- The virus then enters an endosome, where acidification promotes proteolytic cleavage of the hemagglutinin, exposing a fusion domain.
- The influenza hemagglutinin undergoes a marked structural reorganization in this cleavage step.
- Hemagglutinin cleavage may be one of the factors that restrict viral growth to epithelial cells, as a unique protease in the respiratory milieu is required for this cleavage to occur.

PATHOGENESIS AND IMMUNITY

- The fusion domain allows the viral RNA to enter the cytoplasm.
- The nucleoprotein is transported into the nucleus of the cell, where transcription to a positive-sense RNA and replication take place.
- Viral proteins then assemble on the apical surface of the infected cell and, after incorporation of cellular membrane, bud from the membrane back into the mucosal milieu.

PATHOGENESIS AND IMMUNITY

- Influenza infection is initiated in the upper respiratory tract via aerosolized virus.
- The cells infected with influenza virus are primarily the ciliated cells of the respiratory tract.
- Denudation of the superficial epithelium probably accounts for much of the symptomatology and may predispose to secondary bacterial infections.
- The onset of symptoms follows an incubation period that, for a viral illness, is very short: 48–72 h.
- The infection spreads to the lungs but, even there, remains confined to the epithelial layer.

PATHOGENESIS AND IMMUNITY

- Uniquely among respiratory viruses, influenza virus is associated with systemic symptoms of fever, malaise, and myalgia.
- These manifestations are presumed to be mediated by cytokines, and excess cytokine production has been implicated in the acute toxicity of H5N1 and other highly pathogenic influenza viruses.
- The immune response to influenza virus occurs at the systemic and mucosal levels and involves both T and B cells.
- The B cell responses are directed primarily toward antigenic epitopes on the two surface glycoproteins—i.e., hemagglutinin and neuraminidase.
- At a structural level, the four recognized epitopes on the hemagglutinin are largely confined to the globular head of the protein, which collectively constitute the targets for hemagglutination inhibition (HAI) antibodies.

PATHOGENESIS AND IMMUNITY

- HAI and neutralizing antibodies are highly correlated; HAI antibody levels are used as a measure of susceptibility to clinical infection and thus as a measure of vaccine-induced protection.
- In a child or an adult without prior vaccination or with the emergence of a distinctly new strain, serum HAI antibody is a surrogate for protection.
- However, in individuals with both vaccine-induced and natural immunity, the protective efficacy of a vaccine based on serum HAI antibody is more difficult to predict.

PATHOGENESIS AND IMMUNITY

- Studies with improved collection methods and assays that more sensitively and reproducibly measure mucosal antibody suggest that mucosal neutralizing IgA antibody more accurately reflects susceptibility to infection.
- Perhaps the patterns of immune protection are best shown in a murine model, in which passively administered IgA antibody to influenza virus protects animals from initiation of infection and epithelial damage in the upper respiratory tract, while infused IgG antibody to the virus is protective in the lungs.

PATHOGENESIS AND IMMUNITY

- There is now considerable research interest in the induction and protective role of broadly neutralizing antibodies that recognize less antigenically variable regions on the stalk of the hemagglutinin.
- The results of these studies have led to talk of a universal influenza vaccine, although no such vaccines are yet available in clinical practice.
- The role of T-cell immunity, which primarily recognizes internal protein epitopes, remains unclear in humans.
- However, T-cell immunity is thought to play a role in clearance of an influenza infection that quite reproducibly develops 8–10 days after exposure.
- A role for T cells in protection against acquisition of infection has also been proposed.

High-Risk Groups Who Should Be Assigned a High Priority for Influenza Immunization and Treatment High-Risk Group

- Children 6–59 months of age
- Adults ≥50 years of age
- Persons with chronic disorders
- Persons who are immunocompromised
- Women who are or plan to be pregnant during the influenza season
- Children and adolescents (6 months through 18 years of age) who are receiving aspirin
- Residents of nursing homes
- Native Americans, including Alaska Natives
- Persons who are extremely obese (BMI ≥40)


Thank
you!