Chapter 29

Seasonal and Pandemic Influenza Surveillance and Disease Severity

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Core Message This chapter addresses the disease burden on the US population caused by the annual influenza epidemics or pandemic and the methods of influenza surveillance used to monitor and prevent the spread of the disease. The meaningful use of electronic health records for influenza research and surveillance are discussed with a focus on variations of influenza disease severity between seasons and between individual patients. Surveillance of severe disease cases can contribute to a more effective public health preparedness and response.

1 Introduction: Influenza Surveillance and Disease Burden

The recent influenza pandemic in 2009 caused by influenza A/H1N1 reassortant with high human-to-human transmissibility, demonstrated the unpredictable nature of emerging viruses and importance of continuous surveillance. During the 2009–2010 influenza season, the 2009 H1N1 virus infected approximately 61 million persons and caused an estimated 274,000 hospitalizations and 12,500 deaths in the USA [1]. This novel virus caused severe morbidity and mortality in pregnant women [2–4] and younger adults with 87 % of deaths occurring in persons younger than 65 years of age [5]. In addition to the human toll, annual influenza epidemics and pandemics carry substantial economic consequences in health-care utilization costs, intervention costs, and reduced productivity. The cost of annual influenza epidemics in the USA is estimated to range between $52 and $199 billion [6].

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Individual risk factors for severe outcomes of influenza infection vary between seasons and are associated with circulating influenza virus types and subtypes, as well as with individual demographic characteristics, such as age, ethnicity, and clinical conditions, such as asthma, diabetes, cardiovascular, lung, and neurological diseases [8–12]. Due to variations in influenza virus activity, the capacity to respond to seasonal epidemics and pandemics depends on the availability of accurate and timely information and swift and early identification of pandemic and epidemic strains.

The US national influenza surveillance systems include syndromic, clinical, and virologic monitoring. Information on influenza-like illness (ILI), influenza hospitalizations, influenza and pneumonia associated mortality, influenza-associated pediatric mortality, and laboratory testing of a subset of specimens from patients with ILI to characterize the circulating viruses are reported. These surveillance systems are resource-intensive [13, 14] and require sustained funding for epidemiologic and virologic information gathering at the national and local levels [15]. Enhanced and timely syndromic surveillance methods that use electronic health records (EHR) could improve the assessment of influenza medical and economic disease burden and associated risk factors leading to identification of at risk population groups, targeted and appropriate public health interventions, and estimates of economic burden associated with the disease [14, 16–18]. EHRs capturing information using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes lend themselves to efficient quantitative analyses and have been used in numerous epidemiologic studies and influenza surveillance [14, 17, 19–21].

With the growing focus of the US health care system on the meaningful use of electronic medical records, one of the practical applications is expanding biosurveillance and preparedness capabilities, such as surveillance of influenza severity and associated risk factors during seasonal epidemics and pandemics [18, 22]. Traditional influenza surveillance data are based on laboratory testing of a limited number of samples, case reporting by participating health care providers, hospital-based primary data, and deaths reported by statistics offices [24]. Data extracted from electronic medical records can enrich reporting of risk factors for disease severity or clinical diagnoses, even in the absence of laboratory testing, and augment the traditional surveillance. In addition, monitoring patients EHRs may enable detection of disease outbreaks for which no laboratory diagnostics were requested including emerging pathogens and biothreat events [25].

The timely reporting of information on circulating influenza viruses and the disease burden associated with seasonal and pandemic influenza is essential for optimal public health response, identification of vulnerable populations, and for prevention and patient management strategies. Large electronic datasets of hospital discharge records, such as the Nationwide Inpatient Sample (NIS), could provide information on risk factors for disease enhancing influenza surveillance methods [7, 21]. The use of much larger more representative national population repositories from existing electronic medical records can potentially augment or replace small hospital case series studies often employed for assessment of influenza severity.

2 Influenza Surveillance

Every year, emerging and reemerging influenza viruses lead to tens of millions of respiratory infections and up to 500,000 fatalities worldwide. Unpredictability of antigenic drift or antigenic shift leading to emergence of viral strains with limited or no immunity in human population results in variable disease spread and severity. A novel high pathogenicity virus adapted to human-to-human transmission could cause a global pandemic with millions of deaths [25]. Timely detection and reporting of disease in specific populations through an effective biosurveillance system is the most promising strategy for mitigating the impact from disease outbreaks caused by naturally occurring epidemics or bioterrorism events [26]. Influenza virus surveillance informs selection of the annual vaccine strains and guides antiviral therapy. Monitoring influenza outbreaks is of particular interest because they represent a proxy for research of potential biothreat surveillance systems. Early clinical symptoms of many biologic warfare agents such as aerosolized *B. anthracis*, tularemia, and smallpox resemble influenza like illness [17, 27].

Surveillance of infectious diseases can be conducted using passive or active approaches. Active methods based on laboratory testing and case reporting are usually resource intensive and require ongoing reporting by participating physicians, hospitals, and laboratories [14]. Only a subset of specimens can be tested [28] and cases are often underreported. Passive syndromic surveillance methods may be less accurate but they are also less expansive and enable assessment of the disease spread and severity in the population. Implementing syndromic surveillance based on signs and symptoms, diagnosis, and large volumes of other health related data for disease of interest can greatly improve the quality and timeliness of passive surveillance [29]. Information acquired integrating both methods can generate a more complete picture of an outbreak or an epidemic [14].

2.1 Active Influenza Surveillance

In the USA, the national influenza surveillance is lead by the CDC as a collaborative effort of state and local health departments and laboratories, health-care providers, hospitals, and clinical laboratories. The data on circulating influenza viruses and the disease activity including incidence, morbidity, and mortality is collected year round, compiled, and published weekly with a 1–2-week reporting delay [25]. Influenza virologic surveillance throughout the USA is conducted by approximately 140 laboratories comprising the WHO and National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratory networks. They collect information on the proportion of influenza A and B positive respiratory specimens and determine influenza A subtypes. A subset of the influenza positive samples, especially if the subtypes cannot be determined by standard diagnostic tests, are sent to CDC for further characterization by gene sequencing to monitor emergence of novel viruses and antiviral resistance [23]. The second component of the surveillance system is the Illness Surveillance Network (ILINet) comprised of approximately 3,000 health-care providers voluntarily reporting all outpatient visits and the number of visits due to influenza-like illness (ILI) stratified by age group. The percentage of weekly ILI visits weighted to reflect the population size of reporting states are compared to the national baseline of ILI visits outside of influenza season to monitor ILI activity levels in each state [23]. Vital statistics offices in 122 participating US cities report the total number of deaths and the number of deaths caused by pneumonia or influenza (P&I) stratified by age groups. Statistical methods are used to calculate the weekly level of P&I mortality above the seasonal baseline or epidemic threshold. In 2004, pediatric influenza-associated mortality for children 0–18 years of age became a nationally notifiable condition. Influenza Hospitalization Network comprised of hospitals in over 80 counties in 14 states collects information from hospital records and reports on laboratory-confirmed influenza hospitalizations for children and adults. The information on geographic spread of influenza activity is augmented by State and Territorial health department epidemiologists' reports [23].

In addition to the CDC surveillance systems, the armed forces operate the Global Emerging Infections Surveillance and Response System (GEIS) to protect military personnel and their families [30]. Respiratory Infections surveillance is one of the GEIS programs contributing to the global influenza surveillance network. The program leverages established laboratory and research facilities in host countries and collaborations with global partners. Its activities are coordinated and information regarding circulating influenza viruses, disease burden, and epidemiology is shared with CDC, WHO, and host countries. The data is also used in research and for development of vaccines and diagnostics [31]. International influenza surveillance is accomplished through the WHO Global Influenza Surveillance Network collaborating centers including the CDC. Global influenza surveillance information is shared through the WHO FluNet tool and it provides advance signals of influenza activity and trends, informs selection of annual vaccine strains, and enables member countries to better prepare for upcoming influenza season [32].

2.2 Alternative Surveillance Methods

In addition to the active surveillance efforts, alternative methods such as syndromic surveillance, electronic patient records from emergency room or ambulatory doctor visits, and hospital discharge records have been used for surveillance of influenza and other infectious diseases with growing frequency [19, 20, 27, 33]. Syndromic surveillance provides clues on disease patterns collected from multiple information sources such as emergency department visits, ambulatory health-care visits, calls to health information hotlines, Internet health information seeking, and over-the-counter medication purchases. Indication of potential disease outbreak from syndromic surveillance is usually available before laboratory test results are reported [14]. ESSENCE, the Electronic Surveillance System for the Early Notification of

Community-based Epidemics is an example of syndromic surveillance system implemented by the Department of Defense (DoD) to automatically download data from the electronic health records of military personnel and their families. The system captures information coded in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) standards from over 300,000 weekly outpatient visits to US military treatment facilities [17]. It monitors disease outbreaks based on health care utilization patterns and uses ICD-9-CM codes to group diagnosis into one of the eight disease syndromes. Another national electronic surveillance system, BioSense, launched in 2003 and operated by the CDC collects and analyzes ICD-9-CM coded data from outpatient visits to health-care facilities and emergency departments, hospitalized patients, laboratory tests, and information on over-the-counter medications sold in pharmacies [34]. Although different studies reported variable utility of syndromic disease surveillance systems for local disease outbreaks, the majority of them indicated that it was useful for monitoring respiratory disease activity and the annual influenza seasons [19, 35, 36]. Sensitivity of ICD-9-CM based detectors of acute respiratory disease and influenza epidemics varied from 44 to 79 % for acute respiratory disease to 100 % for influenza outbreak [37] and specificity ranged between 96 and 97 % [20, 27]. Sensitivity was found to be moderate and likely not sufficient to detect a small disease outbreak, e.g., in the event of a local bioterrorism incidence. However, ICD-9-CM coded data can be useful for influenza surveillance when accuracy, completeness, and timeliness are carefully considered [29] before using such data for decision making.

For a comprehensive influenza surveillance system, it is critical to include hospitals that would collect epidemiological and virological information on severe cases. This data enables characterization of severe ILI, identification of at risk population groups, tracking of genetic changes in the circulating viruses, and serve as a monitoring tool for emerging pandemics [38]. Hospital based case series studies yield valuable information on risk factors for sever influenza during an ongoing or past influenza seasons. Although these studies can inform vaccination and therapy decisions, majority of them have a limited sample size, are recourse intensive, and the results are not generalizable on the national level. The lack of this data became especially apparent during the 2009 H1N1 pandemic when the disease incidence rate was very high resulting in declaration of phase 6 pandemic while the disease severity on a national level was not ascertained [28]. Hospital-based electronic surveillance is a cost-effective approach to identify influenza season-specific populations at high risk for ILI complications and fatal outcomes. Detailed clinical information on each individual case is coded in patients' records and can be used to augment active surveillance in public health response planning and implementation [16].

Advances in information technologies enabled new global and national surveillance methods and real time information sharing among multiple stakeholders. Monitoring indicators other than the traditional information captured by health-care providers can be a cost effective approach to augment respiratory disease surveillance. Rise in purchases of over-the-counter cold medications, school absenteeism, Internet health information searches, and utilization of health advice phone lines were shown to correlate with increased influenza activity [14]. The rise in health information seeking preceded doctors' visits by about 1 week and was also correlated with media coverage of the health concern [39].

An approach to influenza surveillance monitoring ILI health-seeking Internet queries was launched by Google and CDC during the 2007–2008 influenza season. The system analyzed logs of Web searches related to ILI information and reported data with only 1 day lag instead of the usual delay of 1–2 weeks. The accuracy of the ILI estimates was 85–96 % as compared to the actual disease incidence reported by CDC influenza surveillance [25]. A Health Map Web based data collection system was employed during the 2009 H1N1 pandemic to monitor the Internet, compile, and report influenza activity in geographically diverse locations through an interactive map. Data was collected from news media, blogs, and other nontraditional sources as well as from the WHO, CDC, and the public health agency of Canada. The median lag between reported and confirmed cases ranged from 9 to 18 days with considerable variations between the countries influenced by public health infrastructure, political system restricting information, and media coverage. The nontraditional information sources may enable earlier detection of outbreaks and epidemics, expand population coverage, improve sensitivity of emerging diseases detection, and place the epidemic or pandemic in the context of the affected population [40].

2.3 Utilization of Electronic Health Records in Influenza Research and Surveillance

While electronic surveillance based on nonclinical data such as over-the-counter medication sales, school absenteeism, and health information seeking may provide preliminary signs of potential infection spread, prompt release of electronic health records (EHR) containing diagnosis and clinical outcomes can lead to a more informative and timely disease surveillance [20]. Increasing utilization of patient electronic records could play an important role in attaining public health objectives and complimenting other information sources.

Information from electronic medical records captured through surveillance platforms or stored in local or centralized databases has been used in numerous studies for monitoring disease incidence, prevalence, severity, risk factors, and medical care decisions. Analyses of electronic medical records were employed to augment the traditional approaches [17, 18] during respiratory seasons in the USA. Standard surveillance was not sufficient during the recent influenza 2009 H1N1 pandemic when several states, including New York [41], Wisconsin [42], and California [43] implemented additional information gathering methods based on electronic medical records to gain a more complete understanding of the ongoing pandemic severity. EHR-based surveillance systems such as Electronic Medical Record Support for Public Health (ESP) implemented in Ohio and Massachusetts and BioSense were successfully used for analyzing ICD-9 diagnosis codes, reporting notifiable disease cases, surveillance of ILI, identification of influenza or upper respiratory infection risk factors among hospitalized patients, and for monitoring diabetes prevalence, risk factors, and disease severity [13, 19]. The results of influenza risk factor analyses based on ICD-9 coded data overall agreed with earlier observations based on primary data collected through the Emerging Infections Program during 2005–2008 influenza seasons [44] and in Manitoba, Canada during 2009 H1N1 pandemic [45] as well as with laboratory confirmed influenza hospitalizations reported to the CDC during the 2009 pandemic [17, 46, 47] demonstrated that optimally selected ICD-9 code groups can be used in an automated surveillance system drawing information from electronic medical records for accurate monitoring of influenza activity. In this study of the US Air Force personnel and their dependents outpatient visits the syndromic surveillance results correlated with the results of sentinel ILI surveillance conducted by the CDC. Placzek and Madoff (2011) used administrative hospital discharge records to estimate the hospitalization rates and characterize patients hospitalized with ILI during the seasonal flu epidemics and the 2009 H1N1 pandemic in Massachusetts. They evaluated two sets ("maximum" and "minimum") of ICD-9 diagnosis codes for their relevance and accuracy in identifying influenza-associated hospitalizations and disease severity and concluded the proposed minimum ICD-9 criteria more accurately reflected the actual influenza cases. ICD-9 coded diagnosis alone or in conjunction with other electronic health data were used in monitoring of ILI severity and risk factors [18, 48, 49], and for modeling early detection of local respiratory disease outbreak [24]. This approach was adopted for other disease surveillance, such as SARS [50], diabetes incidence and management [13], and pertussis [51]. The study results suggest that timely ILI surveillance is feasible using ICD-9-CM coded electronic medical records and emphasized the importance of the appropriate ICD-9-CM code selection for case definition for accurate assessment of disease activity and severity [18, 20].

Current influenza surveillance systems are resource intensive and provide limited information on patients at-risk for severe influenza. To date, no study has been conducted using a large sample of electronic health records (EHR) to examine the risk factors for influenza in hospitalized patients across the USA. Larger data sets of EHRs will enable the creation of statistically significant age-specific models of influenza severity and predict more representative influenza risk factors and vulnerable groups. A recent study utilized the Nationwide Inpatient Sample (NIS) which is a repository of eight million electronic hospital discharge records from 1,000 participating hospitals in over 43 states representing approximately 20 % of all US hospitalizations [7]. This data source is maintained by the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ). Results from the retrospective unmatched case–control study of NIS patients hospitalized with influenza during the 2009 H1N1 pandemic and severe A/H3N2 2007–2008 epidemic seasons confirmed the utility of using an existing electronic resource to identify comorbidities and demographic risk factors for severity of clinical outcomes associated with pandemic and epidemic influenza viruses [21]. The use of primary diagnosis ICD-9-CM codes 487.xx–488.xx to correctly identify influenza hospitalizations from NIS was verified by comparing

Table 29.1 Number of influenza cases reported in NIS and CDC surveillance systems during the 2007–2008 season and 2009 pandemic

Surveillance system	2007–2008	2009
WHO/NREVSS	41,809	177,814
FluSurv-NET	3,933	8,278
NIS	17,767	30,613

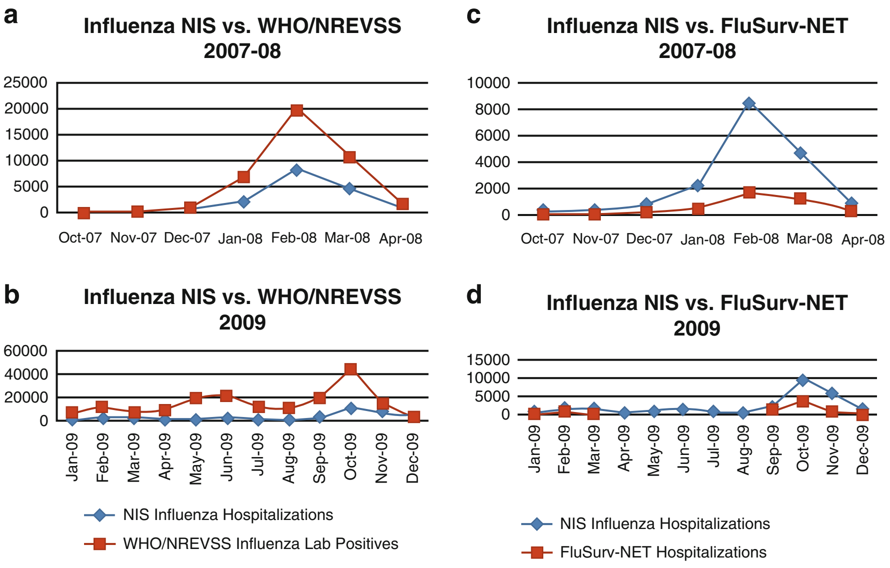

Fig. 29.1 Number of monthly influenza hospitalizations in NIS compared with WHO/NREVSS reported laboratory confirmed influenza infections during October 2007–April 2008 (Panel **a**) and January to December 2009 (Panel **b**) and FluSurv-NET during October 2007 to April 2008 (Panel **c**) and January to December 2009 (Panel **d**)

the temporal trends of monthly hospitalization counts identified in NIS records (Table 29.1) with influenza cases reported by the National Respiratory and Enteric Virus Surveillance System WHO/NREVSS and Hospitalization Surveillance Network (FluSurv-NET) during the 2007–2008 and 2009 influenza seasons (Fig. 29.1).

Findings from these studies demonstrate that large datasets of electronic medical records are an essential component of influenza epidemic surveillance. Integration of ICD-9 diagnosis codes into more complex disease detection algorithms can further improve the sensitivity and specificity of surveillance systems based on electronic medical records [52]. However, this approach is limited if electronic records are fragmented between different providers using different disease algorithms whereas the ICD-9 codes even though potentially less specific are standardized among all users and may be more applicable to nationwide surveillance [13]. Further standardization of data coding and selection criteria, and interoperability among private and government surveillance efforts has the potential to enhance the electronic data quality and timeliness [14, 18]. This methodology can be especially advantageous for public health applications as it uses routinely collected data and requires modest investments for maintenance and operation [50].

3 Influenza Virus

Influenza virus is a zoonotic pathogen causing annual epidemics and pandemics resulting in human toll and economic losses all over the world. Influenza-associated morbidity and mortality are especially high among persons with chronic health conditions and usually among the very old or the very young [53]. Although the virus was identified and isolated only 80 years ago, influenza disease outbreaks can be traced back to Middle Ages and identified by signs and symptoms, sudden start of the epidemic, and excess mortality in historical sources dating to 1650 [54]. Shope demonstrated in 1930s that the infectious agent causing flu in humans could adapt to other species and cause similar disease in swine. The influenza virus adaptability to the host immune system enables sustained human-to-human transmission and the emergence of novel viral strains [55]. It also poses a challenge to the public health efforts to predict and control the annual influenza epidemics and pandemics.

3.1 Pathophysiology

Influenza viruses belong to the *Orthomyxoviridae* family and are divided into three genera or types, Influenza virus A, B, and C [56]. Influenza A viruses are further classified into subtypes defined by one of the 18 hemagglutinin and one of the ten neuraminidase subtypes present in the virus [57]. Influenza B viruses are not classified into distinct subtypes but are divided into two genetic lineages, Yamagata and Victoria [58].

It is an enveloped single stranded RNA virus with a genome fragmented into eight segments encoding 11 proteins. The surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) play the most important role in viral infection and transmission. HA attaches the virus to the target cell's sialic acids receptors facilitating the viral RNA entry into the cell. The NA enzymatic activity cleaves the sialic acid releasing the newly produced viral particles [53, 59].

The annual epidemics are caused by influenza A and influenza B, but only influenza A can adapt to multiple hosts and emerge as a novel virus causing pandemics. Antigenic drift due to mutations in HA and NA genes allows the virus to evade preexisting antibodies in the human immune system conferring the pathogenicity and virulence. Antigenic shift occurs when influenza viruses containing diverse HA and NA subtypes coinfect the same host, triggering a reassortment event and producing progeny with genomic segments from both parental viral subtypes [53]. Wild birds are the natural reservoir for influenza viruses. Sixteen hemagglutinin and nine neuraminidase influenza A subtypes were isolated from aquatic birds and only the most recent HA17 was isolated from fruit bats [60]. According to the mixing vessel theory, pigs are considered the main mammalian host where the adaptation of an avian influenza viruses to human host and reassortment events occur [61]. Pigs' cell-receptors match both human and avian influenza, rendering them susceptible to infection with viruses from both hosts [53]. Influenza A viruses have been also isolated from other animals, including a horse, dog, cat, tiger, and leopard [59]. Influenza Type B and C is rarely found in hosts other than humans, although influenza B has been found in seals and influenza C has been reported in swine and dogs [53].

3.2 *Epidemiology*

Despite the investments in influenza research, surveillance, and prevention efforts, influenza virus remains a cause of respiratory infection in the USA and in the world. Annual influenza-associated deaths in the USA range between 3,349 and 48,614 [62] and, on the average, 200,000 are hospitalized due to severe disease [63]. The variations in mortality can be attributed to difference in the circulating viral types and subtypes. The average mortality rates are 2.7 times higher during the seasons when influenza A(H3N2) subtype is predominant as compared to seasons when influenza B or other influenza A subtypes are the predominantly circulating viruses. During a typical influenza season, severe illness and death occur most frequently among individuals 65 years and older (89.4 %) or children younger than 2 years of age [62]. Persons of any age with underlying health conditions are also at a greater risk for severe outcomes associated with influenza infections [64].

Influenza viruses are transmissible among humans via the respiratory rout. During seasonal epidemics and pandemics, each case transmits the virus at 2–3 day interval to 1.1–1.8 and 1.5–5.5 individuals respectively [65]. The human-to-human transmission occurs in one of the three ways: direct contact with infected persons, touching object contaminated with the virus and then transferring it from hands to mucus surfaces of the nose or eyes, and inhaling virus-containing droplets produced by infected person when coughing or sneezing [66, 67]. The efficiency of influenza transmission aerosolized in droplets depends on the size of the droplet, viral concentration, and humidity. Yang and Marr (2011) demonstrated that the concentration of infectious influenza virus in cough droplets is inversely related to the relative humidity (RH) in indoor settings, while the droplet size is directly related to relative humidity. In a dryer environment, the smaller droplets tend to stay in the air longer, infecting larger number of sensitive hosts. In a humid environment, the virus in large droplets settles on objects (fomites) and can survive for several days. Viable influenza viruses in mucus were detected on paper money bills after 48 h and in some cases up to 17 days [68].

In temperate climates, influenza epidemics occur in a seasonal pattern during the colder months of the year, while in the tropical climates, influenza circulates all year round with patterns associated with rainy seasons. Multiple reasons for this periodicity such as sunlight, temperature, humidity, human mobility, and contact rates, and functions of the immune system have been explored without arriving at a definitive conclusion [69, 70]. Yang and Marr (2011) suggested that the winter seasonality can be partially explained by higher concentration of droplet-suspended influenza viruses in heated buildings due to lower humidity. Other environmental factors, such as colder temperature and reduced ultraviolet radiation, are also independently associated with virus survival and seasonality. Temperature and humidity also effect the human immune system, diminishing the blood flow and leukocyte supply in low temperatures while increasing viral shedding [69]. Lowen and Palese (2011) confirmed that cold and dry conditions facilitated viral transmission through aerosolized droplets, while warm or humid environment (30 °C, 80 % RH) prevented the viral spread. They proposed that seasonal pattern of influenza epidemics in temperate climate occurs due to viral transmission by aerosolized droplets, while year-round infections occur through fomites or direct contacts in tropical climate. The exception to this pattern was the 2009 spring outbreak of the swine-origin influenza A H1N1, which possibly could be explained by the increased frequency of transmission via direct contact due to the absence of human immunity to the novel antigenic strain. Variations in temperature and humidity did not affect viral spread by direct contact [66].

Influenza pandemics are caused by novel viruses for which the world population has no immunity [54, 72]. Each of the six pandemics in the last 120 years were caused by a different novel influenza A virus that has undergone antigenic shift, reassortment of gene segments encoding HA and/or NA, and successfully adapted to the human host [53]. However, of the multiple possible combinations between 17 HA genes and 10 NA genes, influenza viruses with only three combinations (H1N1, H2N2, and H3N2) have adapted to enable human-to-human transmission suggesting the presence of inherent limitations in viral ability to adapt [72, 73].

Of the documented pandemics, the most devastating occurred in 1918–1919 (the Spanish influenza), causing more than 500,000 deaths in the USA and over 50 million deaths in the world [74]. The avian origin influenza A H1N1 virus which caused the pandemic had a case-fatality rate of 2.5 %, with the majority of the deaths occurring among otherwise healthy young adults 20–40 years of age [130]. The high mortality appeared to be associated with pneumonia caused by bacterial coinfection [72]. World War I potentially contributed to the spread and severity of the pandemic. Crowded conditions, increased stress, and malnutrition could have weakened the immune system of the troops while increased travel of the armed forces and civilians facilitated the spread of the virus throughout the world [75].

The sequence data of the 1918 influenza a H1N1 virus suggest that the virus was not a reassortant but rather all eight viral segments were novel with no prior immunity in the human population. In contrast, the viruses that caused the 1957 (H2N2) and 1968 (H3N2) pandemics were direct descendants of the 1918 influenza and evolved from the existing strains through reassortment events with genes from avian influenza viruses [76]. The H2N2 virus with two surface proteins new to humans caused the Asian pandemic, resulting in approximately 70,000 deaths in the USA and two million deaths worldwide. The 1968 H3N2 "Hong Kong'" virus was associated with 34,000 deaths in the USA and approximately 1,000,000 excess deaths globally. The disease caused by the pandemic H3N2 was relatively mild and the virus became seasonal and is circulating to date [53, 77].

Predictions that high pathogenicity avian influenza (HPAI) H5N1 would be the next pandemic strain were the subject of public health concern. The H5N1 continues to spread, causing disease in poultry and occasional human infections through direct contacts with infected poultry. Data pertaining to the H5N1 IAV strain adaptation to human host is limited, but it appears that human-to-human transmission has not occurred. Meanwhile, a fourth generation swine origin descendant of the 1918 virus caused a pandemic in 2009 [53, 72]. Three strains of viruses, derived from birds, pigs, and humans, gave rise to the pandemic virus by antigenic shift, reassortment, and recombination in pigs [78]. Human infections with the novel triple reassortment swine origin virus pdm2009H1N1 were first detected in Mexico and then in California in April of 2009, followed by the declaration of public health emergency in the USA [79]. Due to the fast spread of the virus worldwide, the WHO declared influenza pandemic in June 2009 [78].

Despite the high transmissibility, the disease severity was moderate which is not typical of most pandemic strains [79]. A distinguishing feature of the 2009 H1N1 virus, also observed in previous pandemics, was the off-season timing for the start of the pandemic and young age prevalence among influenza cases, hospitalizations, and deaths. In Mexico in the early stage of the pandemic, 87 % of deaths were reported for patients 5- to 59-years-old [80]. In the Northern Hemisphere, the majority of deaths, 65.5–91.7 %, occurred among adults 25–64 years and only 4.2–20.7 % of deaths were reported in adults older than 65 years [81] compared to a typical influenza season when estimated 90 % of deaths occur in this age group [82]. Among hospitalized patients 68.8 % of fatalities occurred among adults 19–64 years of age during the 2009 pandemic while 74.9 % fatalities occurred among patients 65 years and older during the preceding influenza season [21]. Underlying medical conditions contributed to disease severity in all age groups. Cross-reactive immunity was found more frequently among persons older than 60 years of age due to earlier exposure to influenza A/H1N1 strains derived from the 1918 pandemic virus [83, 84].

4 Influenza Disease

The impact of influenza epidemics or pandemics on the affected population has been associated with predominantly circulating viral types and subtypes and their relation to the preexisting immunity of the human host [62, 72]. Influenza infections may cause especially severe disease in populations already burdened with a high prevalence of chronic pulmonary conditions [85]. Galiano et al. (2012) suggested that the major determinant of influenza disease severity was host-related and included immune response, individual genetic background, and likely environmental factors surrounding human host and the virus. They based their hypothesis on the fact that a complete sequence of the A/Fujian/411/2002-like H3N2 virus isolates from cases that died and those who survived did not reveal any genetic differences that could be associated with disease severity or increased mortality [64]. Because the mechanisms by which viruses evolve and adapt to human hosts remain undetermined and the seasonal influenza disease continues to cause substantial public health threat, identifying the most vulnerable population groups in a timely manner remains a critical component of public health response.

Interventions to prevent or mitigate the impact of epidemics and pandemics include vaccination, antiviral drug therapies, and non-pharmaceutical methods. Vaccination is considered the most effective prevention method because it creates herd immunity by protecting not only the vaccinated individual but also precluding the viral transmission to those who did not receive the vaccine. However, effective protection can be achieved only if the vaccine strains antigenically match the circulating viral strains [86]. Antiviral therapy is beneficial, especially when a new viral strain emerges for which there is no vaccine. Novel therapeutic technologies against influenza offer great promise such as the use of siRNA and ribozymes delivered by intranasal spray or retroviral carriage [79]. Non-pharmaceutical methods include social distancing to reduce crowding and personal interactions and travel restrictions [71].

4.1 Clinical Symptoms and Patient Management

Influenza symptoms range from mild upper respiratory ailment to severe complications resulting in patient hospitalizations and in extreme cases, death [87]. The symptoms of influenza-like-illness (ILI) include fever, chills, sore throat, or cough [46, 88]. Depending on the circulating viral strains, diarrhea or vomiting may also be associated with influenza infection, especially in children [47]. Influenza may be difficult to diagnose based on clinical symptoms alone because the clinical presentation may be similar to other respiratory viral and some bacterial infections [90]. Presence of influenza virus can be confirmed by laboratory testing. The disease severity can be characterized by outcome indicators such as hospitalizations, admissions to intensive care units, length of hospital stay (LOS), utilization of mechanical ventilators, and flu-associated mortality [8, 42, 90, 91].

On the average, the frequency of severe cases requiring hospitalization or resulting in death is higher during the seasons when A(H3N2) viruses are predominant [62, 92]. During the 2009 pandemic, an estimated 0.45 % of the pdmH1N1 influenza cases required hospitalization and could be characterized as severe; approximately 12,500 of the cases or 0.02 % died [93]. In a review of studies characterizing the disease severity in the beginning of the 2009 H1N1 pandemic, Falagas et al. (2010) found a wide range of hospitalization rates (0–93.8 %), ICU admission rates (0–36.4 %), and fatality rates (0–38.5 %) among influenza cases. The fatality rate was significantly higher (25–41.4 %) among patients admitted to the ICU. A prospective study in Canadian population measured the outcomes of severe 2009 influenza A (H1N1) cases as mortality, length of stay (LOS) in an ICU, and duration of mechanical ventilation. In this study of 215 critically ill patients, 81 % required mechanical ventilation, the median ICU stay was 12 days, and 17.3 % died within 90 days [94].

Annual influenza vaccination is universally recommended in the USA as the most effective prevention method for children older than 6 months of age and for all adults [95]. Vaccinating in advance 70 % of the US population even with low-efficacy vaccine in combination with school closure could be a cost-effective approach to reducing the disease burden [71].

4.2 Influenza Risk Factors and Vulnerable Population Groups

Susceptibility to influenza and severity of the disease is affected by multiple factors including characteristics of the circulating virus strain, genetics of the host, prior infection history, comorbidities, age, and environmental factors [87, 96]. Higher proportion of younger adults aged 20–50 [97] were more frequently infected during the 2009 H1N1 pandemic than traditionally more vulnerable age group 65 years or older during the seasonal influenza epidemics while pediatric mortality and morbidity was of a greater concern during the 2003–2004 season [90, 98]. This unpredictability of the virus–host interactions and consequences to population's health underscores the need for continuous timely and informative influenza surveillance.

Multiple studies conducted during different influenza seasons demonstrated increased severity of influenza when chronic conditions such as asthma, diabetes, neurologic disorders, obesity, and cardiovascular disease are present in children and adults [42, 47, 89, 99]. Underlying health conditions, especially chronic lung and heart disease [12] were more prevalent among the cases admitted to ICU or those who died compared to other hospitalized patients diagnosed with influenza [100]. In an international study of more than 70,000 hospitalized patients with laboratory confirmed H1N1pdm influenza proportion of patients with underlying chronic conditions increased with disease severity and constituted 52.3 % of those admitted into ICU and 61.8 % of those who died [99]. During the 2009 pandemic, mortality was higher among individuals with underlying medical conditions regardless of their age [83]. The presence of any chronic disease was also associated with influenza severity among hospitalized cases in the USA during the 2009 pandemic and preceding seasonal epidemics [21, 101].

4.2.1 Clinical Influenza Risk Factors

Underlying health conditions including HIV, cancer, heart disease, lung and respiratory conditions, diabetes, neuromuscular and neurological disorders, obesity, and pregnancy were reported to be associated with increased risk for influenza infection or disease severity. However, results were often controversial or not confirmed to be statistically significant.

Slightly more than half of a sample from the NIS hospitalization records (54.4 % in 2007–2008 and 53 % in 2009) reported at least one underlying health condition assessed (Fig. 29.2) [21]. For both the 2009 H1N1 pandemic and A/H3N2 2007–2008 epidemic seasons, the proportion of records with comorbidities among severe cases (64.7 % and 62.9 % respectively) and among those who died in the hospital (62 and 63.4 %) was similar and significantly higher than among the hospitalizations with moderate disease (45.4 and 46.2 % respectively). The hospitalized patients with any comorbidity had greater odds of severe seasonal and pandemic influenza (OR = 2.21 and 1.97 respectively) and inpatient death (OR = 1.96 and 2.02 respectively) [21].

During the 2009 H1N1 pandemic, a greater proportion of immunocompromised HIV-positive persons were hospitalized with influenza compared to HIV prevalence in general population but the H1N1pdm-associated disease severity and mortality were not substantially affected. In a US study of hospitalized patients with confirmed 2009 pandemic influenza A H1N1, there was no statistically significant difference between the proportion of immunosuppressed patients among those with pneumonia (10 %) compared to patients without pneumonia (14 %) [102]. In low prevalence settings the severity of seasonal influenza does not appear to change significantly in adults infected with HIV. However, in high HIV prevalence populations, influenza may pose a higher morbidity and mortality risk due to compromised immune functions and the presence of tuberculosis, hepatitis, and other comorbidities [103]. In South African population with high prevalence of HIV among patients with confirmed influenza A (H1N1) infection referred to ICU, 31.5 % were immunosuppressed due to either HIV or immunosuppressive therapy [85].

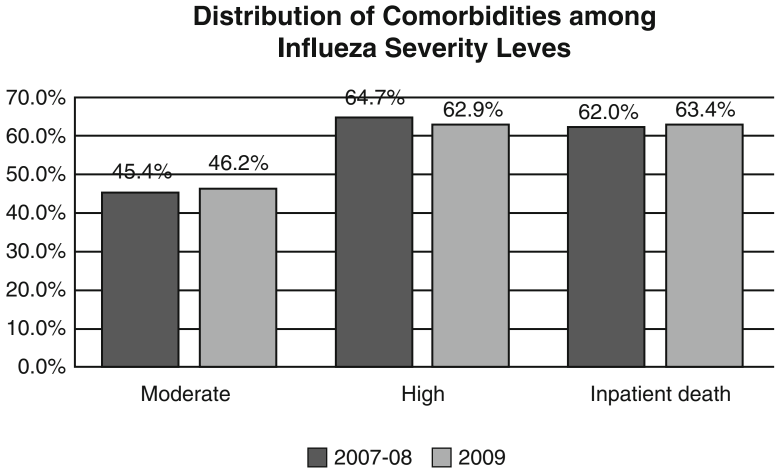

Fig. 29.2 Distribution of cases in the influenza severity groups among hospitalizations with at least one underlying medical condition during the 2007–2008 epidemic and 2009 pandemic

Cancer patients receiving chemotherapy or after hematopoietic cell transplant (HCT) have suppressed immune functions and are susceptible to infections including seasonal or pandemic influenza viruses. Influenza infection outcomes in HCT recipients vary depending on the influenza virus type and subtype [104]. Studies comparing seasonal and pandemic influenza disease in children and adults undergoing cancer therapy found significant differences in clinical symptoms at presentation and in clinical outcomes [105–107]. Although children infected with 2009 H1N1 were healthier at presentation and had fewer comorbidities they more frequently had pneumonia, stayed longer in the hospital, were more frequently admitted to ICU [106], and experienced higher mortality (10 % vs. 0 %) due to complications compared to children with seasonal influenza infections. Males were especially at high risk for developing pneumonia. Timely antiviral therapy mitigated the influenza disease severity in children and adult recipients of HCT [104, 107].

Chronic heart disease is a known risk factor for severe outcomes among persons with influenza-like illness. During the 2009 H1N1 pandemic, heart disease was the second most prevalent medical comorbidity present in approximately 25 % of reported deaths among adults and in almost 50 % of fatalities among persons 65 years or older [83]. Heart and lung disease were also frequent comorbidities with diabetes and kidney disease among the influenza case fatalities. In a dataset pooled from multiple countries in Europe, Asia, and America chronic heart disease was present in 7.1 % of all hospitalized patients with pH1N1 infection, 10.9 % of ICU admissions, and 12.1 % of deaths [99].

Lung diseases were the most frequently reported chronic conditions for the 2009 H1N1 influenza case fatalities with the chronic obstructive pulmonary disease (COPD) most prevalent in adults and asthma in children [83]. Regardless of asthma severity, its prevalence tends to grow with escalating influenza disease severity [99]. Influenza virus infection is known to exacerbate asthma and asthma is a known risk factor for influenza infection. It was the most frequently reported underlying medical condition in pediatric deaths associated with influenza A/2009 H1N [83]. The impact of asthma may also depend on the circulating influenza viruses. In a Canadian studies of pediatric population hospitalized with influenza, children with pandemic H1N1 influenza in 2009 were significantly more likely to have asthma (22 %) than those with seasonal influenza during the 2004–2009 seasons (6 %) although there were no difference in severity or clinical presentation of asthma between the pandemic and seasonal pediatric influenza cases [108]. Asthma was also more prevalent among the children admitted to ICU with pH1N1 and developing pH1N1-associated pneumonia compared with seasonal influenza in 2006–2009 [109]. Patients with chronic lung and airways diseases such as COPD are at a greater risk for severe morbidity and mortality associated with influenza infection. Evidence suggests that bacterial coinfections in COPD cases may further impact the disease severity. In a study of patients hospitalized with severe COPD in Italy, viral infection was detected in 23.4 % and viral-bacterial coinfection in 25 % of patients hospitalized with COPD exacerbation. Influenza was one of the most frequently identified infections adversely effecting lung function and extending hospital stay [110]. Although many national guidelines recommend influenza vaccination, there is only limited evidence that vaccine is effective in COPD patients. However, some observational studies suggest that vaccine reduces both hospitalizations and mortality [111].

The association between diabetes Type1 and Type 2 and a greater risk for influenza associated complications may be explained by adverse impact of excessive blood glucose on immunity, as well as heart, kidney, and lung functions [112]. Influenza surveillance data in Wisconsin and New Mexico during the 2009 H1N1 pandemic indicated that diabetes was the second most frequent comorbidity following asthma and was present in 16–20 % of hospitalized influenza cases [42, 105]. Van Kerkhove et al. (2011) reported that diabetes was an underlying chronic condition in 9 % of influenza-associated hospitalizations and 13.6 % of cases admitted to the ICU in a sample representing 19 countries with diverse populations and healthcare systems. Diabetes was present in 8 % of influenza A/H1N1 associated fatalities in England [113], 14.4 % fatalities in a large international sample [99], and 29 % of fatalities in New Mexico [105]. The higher proportion of diabetes in New Mexico potentially could be due to a higher than 50 % obesity among hospitalized patients older than 18 years. Diabetes prevalence is on the rise in the USA, especially among the aging population, reaching almost 27 % prevalence among persons 65 years of age or older [114]. Influenza surveillance and timely characterization of clinical disease course are important for potential prevention and treatment of diabetic influenza cases [112].

Neurological and neuromuscular disorders (NNMD) are risk factors for influenza infections possibly due to difficulty clearing secretions from respiratory tract due to impaired or reduced muscle tone and lung function could lead to severe disease [9]. Persons with NNMD also may have an increased susceptibility to recurrent respiratory infection due to diminished ability to protect airways through cough [90] and a higher risk (OR, 5.6) of influenza-related neurologic complications such as seizures [115].

In a study of influenza-associated pediatric deaths during the 2003–2004 influenza season, 33 % of the children had neuromuscular or neurologic disorder [116]. Louie et al. (2006) further confirmed that neurologic diseases with the potential to compromise respiratory function were present in more than 25 % of severe influenza cases among children. NNMD were the most prevalent chronic diseases associated with respiratory failure in hospitalized children with laboratory-confirmed influenza diagnosis followed by chronic lung and chronic heart conditions [9]. A study of pediatric deaths reported to CDC during the 2009 H1N1 pandemic showed that 43 % of case fatalities had neurologic disorders. Majority of the children also had additional comorbidities such as heart disease [117]. Adult patients who developed pneumonia as a consequence of influenza 2009 H1N1 infection were more than twice as likely to have a neurological disease compared to patients who had no complications [102]. Neurological disorders found among patients hospitalized due to influenza included Down syndrome, cerebral palsy, developmental delay, history of stroke [102], seizures, spinal cord injuries [90], neuromuscular disorders, hydrocephalus, and epilepsy [117]. Pediatric deaths due to pandemic influenza five times exceeded the annual average number of deaths caused by seasonal influenza viruses during the five proceeding seasons. Neurologic disorders were the most frequent comorbidities found in influenza-associated pediatric deaths [117] underscoring the importance of continues surveillance of disease severity and the need for timely characterization of risk factors during an ongoing influenza season.

During the 2009 H1N1 pandemic, obese individuals with body mass index (BMI) exceeding 30 kg/m^2 were at a higher risk for influenza infection; they were more likely to be hospitalized and were disproportionately represented among the patients in ICUs, those with longer duration of mechanical ventilation, longer hospital stay, and those who died compared with those who were not obese [99, 118, 119]. In a study of California adults the prevalence of obesity and extreme obesity among influenza cases was 1.5 and 2.8 times higher respectively than the US population average. The odds ratio (OR) for fatality among the extremely obese (BMI > 40) patients was 2.8–4.2 [120]. These findings corroborated the results of Kwong, Campitelli, and Rosella (2011) suggesting that obese individuals were at a greater risk for hospitalization than persons with normal weight during 12 prepandemic influenza seasons with OR = 1.45 and 2.1, for individuals with BMI 30-34.9 and ≥35 respectively.

The association between obesity and infection can be explained by impaired immune response or by strain of infection on respiratory system and reduced mechanical function of lungs and airways. Obese persons consume high percentage of oxygen to maintain normal respiratory function; they have increased airway resistance and may suffer from hypoventilation and chronic inflammation of the respiratory tract altering the immune function and the ability to respond to challenges to respiratory system [119, 120]. The role of obesity as an independent risk factor may be difficult to ascertain, especially in studies with a limited sample size, as it is often directly correlated with other underlying health conditions (e.g., diabetes and heart disease) known to increase risk for influenza infections and severe outcomes [118]. However, because more than 35 % of adults in the USA [121] and 500 million worldwide [122] are obese it may be a major contributor to excess morbidity and mortality associated with influenza and warrants further investigation.

Pregnancy has been reported as a risk factor for seasonal and pandemic influenza infections and severe disease outcomes using historical and current data. About 50 % of pregnant women infected with influenza developed pneumonia during the 1918 and 1957 pandemics [123]. Pregnancy was reported to be a risk factor for infection with influenza and severe disease outcome during the influenza A/2009 H1N1 pandemic as well. In a review of publications on 2009 H1N1 pandemic epidemiology in the Northern Hemisphere, Falagas et al. (2010) reported that 4.5–17.4 % of hospitalized cases were pregnant women and they comprised 11.5–18.2 % of ICU admissions. Compared to nonpregnant women diagnosed with influenza, they were seven times more likely to be hospitalized and twice more likely to have fatal outcomes [99]. In a UK study of a population with an estimated 6 % prevalence of pregnancy, 21 % of patients hospitalized with laboratory confirmed influenza 2009 H1N1 were pregnant and the majority of them were in the second or third trimester. The case fatality rate ranged between 1 and 6 % [2]. The rate of respiratory hospitalizations among pregnant women in Nova Scotia during non-pandemic influenza seasons between 1990 and 2002 was almost 8 times higher for pregnant women than the year before they became pregnant [124]. Pregnant women with comorbidities such as asthma, anemia, and heart or renal disease were at the greatest risk for influenza-associated hospitalization.

The findings on influenza severity association with pregnancy were not consistent. In several countries as the level of disease severity increased the proportion of pregnant women diminished and the odds ratio for death among hospitalized pregnant women was <1 [99]. Interestingly, in a study of ILI hospitalized patients during the 2007–2010 influenza seasons, pregnancy was protective against pneumonia (OR 0.4), possibly due higher likelihood of hospitalizing pregnant women with severe respiratory infection [125]. This observation was supported by a UK study reporting that maternal outcomes were no more severe that for nonpregnant women of similar age hospitalized for influenza [2]. An increased susceptibility to influenza infection and severe disease among pregnant women could be partially explained by changes in immune response due to lower plasma levels of adiponectin regulating macrophage activity [119]. An additional explanation could be psychosocial changes that may occur during pregnancy such as perceived increased stress, anxiety, and negative mood which also were shown to alter the immune functions and increase the risk for respiratory tract infections [126].

4.2.2 Demographic Influenza Risk Factors

In addition to clinical comorbidities demographic characteristics and socioeconomic conditions also can increase the risk for influenza infections. Close human contacts in crowded housing during the influenza season, influenza vaccine uptake in a community, awareness of influenza transmission routs, and following the nonpharmaceutical prevention practices effect influenza virus spread and attack rates in population. The risk for influenza infection may also vary in individuals from different racial/ethnic backgrounds and age groups.

Historically, higher attack rates and more severe disease outcomes were observed among minorities since 1900s including during the 1918 influenza pandemic [45, 127]. In an analysis of influenza 2009 H1N1 cases pooled from 19 countries, Van Kerkhove et al. (2011) reported that indigenous populations and minority groups were disproportionately represented among hospitalized influenza cases and fatalities in Canada, Australia, and New Zealand, while in Mexico and Thailand minority groups did not carry excess disease burden. In a Canadian case–control study of laboratory-confirmed pH1N1 cases, 37 % were represented by the First Nation residents. The odds ratio was 6.52 for the First Nation individuals being admitted to the ICU compared to other ethnic groups even when controlling for socioeconomic status, age, residency settings, comorbidities, and time to treatment [45]. Similar results for influenza severity were observed in the USA where the risk for pH1N1 influenza hospitalization in New Mexico was 2.6 times higher among American Indians, 1.7 times higher for Blacks, and 1.8 times higher for Hispanics compared to non-Hispanic Whites [105]. Surveillance data from 12 states showed that the rate of mortality attributed to pH1N1 was four times higher among the American Indians and Alaska Natives (AI/AN) and they had the highest rate (81.0 %) of underlying health conditions than all other ethnic groups [128]. Higher proportion of pediatric hospitalizations among minorities was observed during the pre-pandemic seasons as well, including the 2000–2001 season [129] and 2003–2004 when influenza A/ Fujiian was the prevalent circulating virus [116].

Although the reasons for disparities in influenza susceptibility and severity among the racial and ethnic populations are not fully identified several explanations have been proposed including socioeconomic status and resulting differences in living conditions, crowding, health behaviors, and access to medical care [96]. Cultural differences may affect utilization of available health care or vaccination uptake. Difference in genetic susceptibility and higher prevalence of chronic conditions associated with increased risk for influenza disease severity may also impact the attack rates and the disease outcome in ethnic minority communities [99].

Traditionally populations at the extremes of the age spectrum, young children and older adults are the most vulnerable groups during seasonal influenza epidemics while pandemics exhibit a characteristic shift towards younger adults in influenza-related deaths [65, 80, 130]. Persons younger than 65 years of age accounted for a greater proportion of deaths during all three pandemics in the twentieth century as well as during the 2009 H1N1 pandemic when young adults were at an increased risk for morbidity and mortality. Age was an independent risk factor for severe disease outcomes and death. In a study of hospitalized influenza cases in Washington State the odds of ICU admission or death were 4.4 and 5.9 times greater among adults 18–49 years and 50–64 years of age respectively compared with children younger than 18 years when controlling for other risk factors [11]. The lower influenza incidence rate and mortality among adults over 64 years observed during pandemics could be explained by antigen recycling mechanism, a partial protection due to earlier exposure to a similar virus [65]. However, if infected, this age group had the highest mortality rate among the hospitalized patients [99] potentially due to the presence of comorbidities, effect of medications, and bacterial coinfections. Explanations for severe disease among young adults included antibody-dependent enhanced infection and strong inflammatory response in the lungs leading to lung injury and ARDS [11]. Once infected with a novel influenza virus younger persons may retain long-lasting immunity better than older persons [130].

During the seasonal influenza epidemics older adults and young children are usually at a higher risk for severe disease and death. The proportion of influenza-attributable deaths during the 1994–2000 influenza seasons in Canada increased with age from 2 % in 65–69 age group to 5 % in persons 90 years and older. The case fatality rate for influenza hospitalized patients increased from 4 to 30 % for population 50–64 years to 90 years or older respectively and over 90 % of deaths occurred in persons older than 65 years of age [12]. During the 2003–2004 season when Influenza A Fujian strain was predominantly circulating virus increased morbidity and mortality was observed among children younger than 5 years of age [90, 98] while children hospitalized due to severe influenza during the 2009 H1N1 pandemic were significantly older with a larger proportion older than 5 years of age as compared to pediatric admissions during the pre-pandemic influenza seasons [108]. Developing immune system and absence of immunity to circulating viruses in young children and weakened immune response to vaccination among the older adults renders both groups especially susceptible to seasonal influenza infection [11, 12, 99].

Although the health conditions described in this chapter contribute to influenza virus susceptibility and severity of the disease, their prevalence and impact may vary during different influenza seasons. During the 2009 influenza pandemic, only one third of the 70,000 hospitalized cases representing 19 countries had an identified chronic clinical comorbidity while approximately two thirds of hospitalized cases and 40 % of fatal cases did not have any identified preexisting disease. For the 2009 influenza pandemic, the overall difference in demographic and clinical factors between the disease severity groups and moderate disease controls suggests that age, sex, race, and all clinical conditions of interest showed overall statistically significant association with influenza severity. However, pregnancy was not associated with influenza severity for women of childbearing age [21]. The differences of risk factors and clinical outcomes in different countries further highlighted the need for country-specific and global surveillance as well as data sharing internationally [99].

5 Conclusion

Timely information on circulating influenza viruses and the disease burden associated with seasonal and pandemic influenza is essential for optimal public health response, identification of vulnerable populations, and for prevention and patient management strategies. Susceptibility to influenza and severity of the disease is affected by multiple factors including characteristics of the circulating virus strain, genetics of the host, prior infection history, comorbidities, age, and environmental factors. The unpredictability of the virus–host interactions and consequences to population's health underscores the need for continuous timely and informative influenza surveillance. Clinical surveillance is critical for identification of at risk population groups which also may change depending on the circulating virus as well as for monitoring the disease spread in the population and severity. Syndromic surveillance based on nonclinical indicators may contribute to a signal of epidemic spread and increase of cases. To better predict viral strains for effective vaccines and monitor novel emerging viral strains that could cause epidemics it is critical to continue and expand viral surveillance on an International level. While electronic surveillance based on nonclinical data such as over-the-counter medication sales, school absenteeism, and health information seeking may provide preliminary signs of potential infection spread, prompt release of electronic health records (EHR) containing diagnosis and clinical outcomes can lead to a more informative and timely disease surveillance. Increasing utilization of patient electronic records could play an important role in attaining public health objectives and complimenting other information sources.

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