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Review Article

Influenza: A Persistent Public Health Concern

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Abstract

The aim of this paper is to gain a better understanding of the impact Influenza presents to public health, to ascertain the risk factors associated with severe outcomes and review current literature on the benefits of the influenza vaccine. In addition, this paper will assess various preventive measures that can reduce the risk of transmission or emergence of a new pandemic strain and discuss the implications that these findings present to the field of public health.

Keywords: *Influenza; Public Health; Vaccine*

Introduction

Influenza is a viral illness caused by the various strains of the influenza virus, an RNA virus part of the Orthomyxoviruses family. Influenza has three predominant strains; the influenza A viral subtypes, the influenza B, and the rare influenza C viruses [1]. The influenza A and B viral subtypes are the predominant viral strains that precipitate the seasonal influenza outbreaks, whereas the influenza A subtypes can also result in a pandemic outbreak. The virus is known to spread through 3 recognized modes of transmission; (1) large respiratory droplets (2) aerosolized smaller particle, and (3) direct contact with secretions or contaminated objects (such as fomites). The infective period will begin from 1 day prior to symptom onset and lasts for up 7 days after the initial symptoms manifested. Influenza is typically a self-resolving illness with patients commonly being asymptomatic or presenting with minor upper respiratory tract symptoms, (along with myalgia or headaches) for 5 - 7 days [2]. However, certain groups within the population are at risk of severe symptoms and further complications from these common viral infections. Therefore, influenza is considered a persistent public health concern with the potential to places a significant burden on both the health of people as well as contributing to a significant burden on health care resources.

Seasonal Influenza

Influenza is a disease prone to outbreaks, epidemics and, in rare instances, pandemics. The incidence of these events will depend on which strain currently in circulation. However, every season there are slight variations and mutations introduced within these strains that alter their recognition by our immune system. As such, the seasonal vaccine from prior years will not be effective against these new alterations. These mutations can be primarily attributed to capacity of influenza A and B viruses to undergo antigenic drift, which allows for small mutations that alter its composition and allows it to no longer be effectively recognized by our immune system [3]. Seasonal influenza has been shown to infect nearly 9.2 to 60.8 million persons annually since 2010. Nearly 140,000 - 710,000 of those annual cases result in hospitalizations of which 12,000 - 56,000 patients will die from severe complications [4]. As such the role of a public health practitioner should be to properly educate and promote proper annual vaccinations schedules to the general population to prevent severe complications from influenza.

Pandemic Influenza

Pandemic influenza occurs when there is an antigenic shift within the Influenza A virus subtypes resulting in increased virulence of that particular strain or an entirely new immunogenically naive viral strain. Historically, pandemic influenza occurs when the initial outbreak shows greater than the expected attack rates and expands beyond the original nation's borders. The most recognized influenza pandemic is the 1918 "Spanish Flu" pandemic, which introduced the H1N1 strain into seasonal circulation. This pandemic resulted in nearly 20 - 50 million deaths worldwide, primarily due to secondary bacterial pneumonia infections [5]. Since then, there have been other instances of pandemic outbreaks, but none as severe as the 1918 Spanish flu pandemic. The second pandemic outbreak resulted from an H2N2 strain of Avian Influenza A that resulted in the "Asian Flu" pandemic lasting from 1957 - 1958. This pandemic resulted in less deaths than the 1918 outbreak but showed primarily more deaths from viral Influenza pneumonia rather than secondary bacterial infections. Similarly, in 1968 a variant strain of the 1957 influenza virus underwent an antigenic shift resulting in the "Hong Kong Influenza" pandemic, which resulted in nearly 1 to 4 million deaths worldwide [5]. This instance introduced the Influenza a H3N2 viral strain which is still predominantly circulating in the seasonal winter influenza strains. More recently, in 2009 a new pandemic strain of the Influenza a H1N1 virus termed "A [6] pdm09", emerged as a zoonosis from swine in Mexico and South America. This spread rapidly from 2009 to 2010, causing an estimated 200 000 respiratory deaths and 83 000 cardiovascular deaths during the first 12 months of circulation [7].

Zoonotic variant influenza

In addition, certain animal influenza viruses have been shown the potential to transmit outside their host animal species to infect humans. The two most common influenza strains come from the avian influenza virus subtypes (i.e. H5N1 and H9N2) and the swine influenza viruses [6,8]. Usually these zoonotic infections can occur from either direct contact with infected animals or through contact with environment of the animal. Although these viral strains present novel antigen properties, they often lack the virulence to spread far within the human population. However, there are sporadic instances when a zoonotic infection can arise from a more virulent strain which can precipitate an epidemic or pandemic outbreak. As such there should strong consideration in controlling the influenza infection rates among those commonly anticipated host animals, (i.e. poultry, aquatic birds, and swine) [8].

Severe Complications

To construct the proper guidelines and plans to prevent the spread and transmission of influenza it is imperative to first understand what the possible complications from these influenza infections, along with who will be at the highest risk of developing a severe outcome from these infections. Historically, most cases of influenza infections result in asymptomatic or minor upper respiratory tract presentations such as fever and chills, coughing, runny nose, sore throat [1]. However certain groups within the population can be at risk of developing complications or severe outcomes from these minor influenza infections leading to prolonged hospitalization, ICU stays, or even death [9]. The most common complication is a pneumonia caused by a secondary bacterial co-infection or as a direct result from the influenza virus causing alveolar damage or pulmonary edema [10]. Typically, the most common bacterial pathogens were found to be streptococcus pneumonia and staphylococcus aureus, although several other microbes have been shown to have an increased frequency following influenza infections, such as pseudomonas aeruginosa, Haemophilus influenza and etc [10. Patients would thus require hospitalization and proper treatment with both anti-viral and broad-based antibiotic coverage. However, most hospitalized patients were reported to have only received antibiotic medication and thus the underlying viral process remained unresolved [10]. As a result, the most common causes of mortality in these patients is often because of these bacterial superinfections leading to Acute Respiratory distress syndrome (ARDS), airway aspiration, or septic shock (associated with multi-organ failure) [6]. Furthermore, this viral infection has been shown to place undue stress on the body which can result in exacerbation of symptoms from any co-morbid or pre-existing chronic disease in those affected individuals. As such patients with pre-existing heart, respiratory, or renal conditions are at risk of exacerbation of their symptoms [11].

Children are particularly susceptible to developing neurological complications from H1N1 strains of influenza including encephalitis and febrile seizures; especially if they have been on long-term aspirin therapy (i.e. Reye's Syndrome) [12]. Furthermore, studies have shown that children affected by the influenza virus, (particularly those afflicted by the H1N1 pandemic strain) have a higher risk of developing lifelong neurological conditions that can affect their development and learning abilities [12]. This further highlight the necessity for proper surveillance, recognition and prevention of those afflicted by these circulating influenza viruses.

High Risk Groups

Although most cases of influenza are asymptomatic or present with self-resolving minor upper respiratory infections, certain groups can be at a high risk of developing those previously mentioned severe outcomes from influenza, or at risk of hospitalization or death from these infections. Current research and reviews of available literature has consistently demonstrated 4 main risk factors for the development of complications or severe outcomes of influenza; Age, Pregnancy, Immunosuppression, Co-morbid/pre-existing conditions [11]. A study by Mertz., *et al*. [9] in 2013 suggested that people over 65 years old were shown to have a higher risk of hospitalization rates and death because of infections from either seasonal influenza or pandemic influenza strains. Children aged 5 years old or younger were found to be particularly susceptible to developing pneumonia but showed less mortality rates from either seasonal or pandemic influenza. Interestingly, pregnant women (particularly in the 3rd trimester) were found to be at increased risk of hospitalization, with lesser mortality rates, whereas women up to 4 weeks post-partum had less rates of hospitalization but were at an increased risk of a severe complication and mortality [9]. The presence of any pre-existing chronic medical condition, (such as asthma, COPD, diabetes mellitus, or any immunosuppressive condition) doubled the risk of hospitalization, ICU stays, and mortality from both pandemic and seasonal influenza, regardless of any other existing risk factors. This same study also demonstrated that obesity, (BMI > 30) was considered an independent risk factor that increased the likelihood of mortality in both pandemic and seasonal influenza strains [9].

A recent study by Coleman., *et al* [11] compared the onset of these complications between higher income nations and low-to-middle income countries. Interestingly, they demonstrated that younger children (less than 5 years old) had nearly a 50% higher risk of developing severe complications compared to children in higher income countries. Similarly, children with pre-existing neurological or metabolic conditions in low/middle income countries was a particular risk factor for developing severe outcomes as compared to adults with similar pre-existing conditions, and similar children from high income countries. Pregnant women in these lower income countries had a much higher risk of severe complications compared to pregnant women in high income countries [11]. Lastly, immunosuppressed patients living in high income countries had similar rates of severe complications as non-immunosuppressed patients; whereas those same patients in lower income countries often had greater than 50% risk of hospitalization and mortality from influenza complications [11]. Although the study did not elaborate on the specific causes of these rates, these findings may reflect different cultural health-seeking behavior, unequal access to health care, and the economic burden shared among households due to productive loss in lower- and middle-income countries [13].

Influenza Vaccine

Worldwide health agencies recognize that the annual influenza vaccine is still the best preventive strategy against the seasonal influenza [3]. The influenza vaccine is typically a trivalent formulation of the 3 most likely anticipated strains to be in circulation for the upcoming seasons [2]. For the 2017 - 2018 season, the trivalent vaccine is composed of a variant of the pandemic Influenza a H1N1 strain (A/Michigan/45/2015 (H1N1) pdm09-like virus), the common H3N2 strain, (A/Hong Kong/4801/2014 (H3N2)-like virus); along with an influenza B strain (B/Brisbane/60/2008-like virus). A quadrivalent vaccine is also available which includes a 2nd influenza B virus (B/Phuket/3073/2013-like virus) [1]. These vaccines are recommended for all people over 6 months of age, and those without any significant contraindications to the flu vaccine. In addition, the WHO and CDC strongly recommend that all healthcare workers, along with nursing home/long-term care residents and workers receive the annual vaccines to avoid spreading the infection to their contacts [1]. Although considered the best prevention method against influenza, the efficacy of the vaccine will often vary with unexpected results each influenza season. Prior to the 2009 H1N1 pandemic, the average efficacy of the trivalent vaccine ranged annually from 60 to 80% in young adults and children older than 2 years but offered less protection against the elderly [14]. Since then improvements in the formulation process has yield better protection against the H1N1 pandemic influenza virus, the previous H1N1 [6] (pre-2009) virus, and the variant influenza B viruses, although it has shown less protection against the more common H3N2 variants [15]. The annual influenza vaccine was shown to have only 33 - 53% efficacy from 2010 - 2015 when the circulating H3N2 strains were antigenically similar to the vaccine H3N2 strain, and roughly 3 - 30% efficacy when other dissimilar variants of the H3N2 virus were circulating [16]. Yet despite the variable efficacy of the vaccine, studies have shown that there are still significant benefits for those elderly and other high-risk patients that still warrant an annual influenza vaccination.

Benefits of the Seasonal Influenza Vaccine:

One of the expected benefits from the influenza vaccine is the reduced rate of complications and severe outcomes from influenza infections [17]. Studies have shown that the vaccines can offer moderate protection (37% - 51%) against hospitalization from complications of influenza, with a higher efficacy offered towards patients aged 18 - 64 years old [16]. In the same study, elderly patients (over 65 years old) did not show the same efficacy with the trivalent vaccine as the younger patients except during season when the H3N2 vaccine strain was more antigenically similar to the circulating H3N2 seasonal strains [16]. A similar study in 2017, demonstrated that hospitalized patients in 2013 - 2014 who had received the flu vaccine experienced shorter hospitalizations, ICU stays and lower mortality rates; particularly among the elderly population over 65 years of age [18]. Thus, vaccinations can also help mitigate the infections among those who may still get exposed to influenza; particularly those with severe risk factors. A 2013 study by Ferdinands., *et al*. showed that the influenza vaccine had moderate results in reducing rates of community acquired pneumonia by reducing potential secondary bacterial superinfection and by preventing viral influenza pneumonia within an outpatient setting [19]. Studies have also shown that the seasonal vaccine can significantly reduce incidences of influenza infections among pregnant women, including pregnant women who were immunosuppressed (i.e. HIV/AIDS infections). This also provided passive immunity to their infants for up to 24 weeks after birth [20]. Similarly, vaccinations were noted to reduce the incidence of severe cardiac complications for patients with previous cardiac history and risk factors for cardiac disease [21]. Lastly, seasonal vaccinations were shown to present an economical advantage in both high and lower- and middle-income countries as this limited productivity losses and averted medical costs, especially with older populations (> 65 years old) and those at risk of premature death [22].

Prevention of Pandemic and Zoonotic Influenza Viruses

While the annual influenza vaccine is considered a strong preventive tool for seasonal influenza, there is unfortunately no real prophylactic vaccination that can anticipate and protect against any new pandemic influenza strains. The CDC and WHO suggest implementing infection control practices (including handwashing and proper sanitization of equipment and tools) to limit the spread of disease during both seasonal and pandemic outbreaks [3]. Similarly, the neuraminidase inhibitors, such as Oseltamivir and Zanamivir, typically used as treatment for acute influenza infections, have shown potential to be used as prophylactic treatment along with the influenza vaccine [23].

Another important consideration is the potential of a zoonotic transmission of influenza from an animal influenza strain, (such as the Avian H5N1 Influenza). As such, there is a strong need for prevention strategies for agricultural or livestock facilities to limit the potential for transmission to humans. Some current practices in controlling the spread of avian influenza include (1) surveillance in endemic regions to carry out limited or widespread culling of the known infected poultry, (2) vaccination of poultry in endemic regions to limit the circulating virus and reduce the chance of spreading to humans [24]. In addition, studies have found that (3) improving biosecurity measures can serve to limit any interaction between livestock poultry and infected wild birds [24]. Some biosecurity measures currently in place include the reducing sales of live birds in markets, preventing keeping live birds overnight in open-markets, and preventing extensive backyard farming of livestock [25]. These recommendations were shown to have great effects in controlling the spread of avian influenza in many parts of Asia, South America and other regions of endemic outbreaks [24].

Discussion

Although the efficacy of the vaccine varies annually with lower than expected rates observed in recent years, the benefits from the influenza vaccine in reducing severe complications, hospitalizations or even mortality in elderly and high-risk patients confers a significant advantage that should let clinicals continue recommendations for the annual vaccine. Clinicians and public health practitioners should also recognize the need for preventive strategies such as proper hygiene and sanitation practices to reduce the transmission of the virus. In addition, there is a significant risk present for possible zoonotic influenza transmissions which require better agricultural and livestock practices to control the spread and transmission of those viral strains.

As previously mentioned, the seasonal influenza vaccine is formulated based on an estimation of the most anticipated strains for the upcoming flu season, and the greatest vaccine efficacy was appropriately seen when the season's circulating viral strains (especially the H3N2 strain) was antigenically matched to the vaccine strains. It was noted that although the seasonal influenza vaccine was found to have the lowest efficacy among the elderly (> 65 years old) population, this population was also shown to have the greatest vaccine coverage, or compliance compared to other younger adults. Similarly, studies have shown following the 2009 Influenza A H1N1 pandemic, seasonal influenza A H1N1 viruses more commonly infected younger adults, while elderly patients (> 65 years old) more often had influenza A H3N2 strain infections [6]. This indicated that although the elderly had higher infection rates, they also showed less severe complications compared to younger unvaccinated adults [6]. This finding implicates a present need for clinicians and public health officers to promote increased vaccination rates among younger adults especially within those in the high-risk groups.

Conclusion

Overall, influenza is persistent disease that results in significant burden to the health care system and economy of any country. These viruses present a constant risk for a new pandemic outbreak which imposes a need for persistent surveillance and vigilance from clinicians, public health practitioners, and the general public. Through proper prevention control, vaccinations, surveillance and research, we may be able to mitigate the effects of these viruses and reduce the burden they place on our nations.

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