Ann Allergy Asthma Immunol xxx (2020) 1–7

Contents lists available at ScienceDirect

Review

Influenza epidemics

The role of allergists-immunologists

Arnaud J. Wautlet, MD [*]; Payal D. Patel, MD [†]; Patricia Chavez, MLIS [‡]; Christopher D. Codispoti, MD, PhD [†]

[*] Departments of Internal Medicine and Pediatrics, Rush University Medical Center, Chicago, Illinois
[†] Division of Allergy/Immunology, Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois
[‡] Library of Rush University Medical Center, Chicago, Illinois

Key Messages:

- Influenza epidemics have plagued the world repeatedly.
- The influenza virus can make small changes that can lead to seasonal influenza epidemics or make drastic changes that can lead to pandemics.
- Allergists care for high-risk groups including patients with asthma and immunodeficiencies.
- Vaccination is a key tool to prevent epidemics and pandemics.
- Allergists can help improve influenza vaccination coverage.

ARTICLE INFO

Article history:
Received for publication September 23, 2020.
Received in revised form November 15, 2020.
Accepted for publication November 23, 2020.

ABSTRACT

Objective: To review influenza epidemics and pandemics for practicing allergists-immunologists.
Data Sources: English-language articles published in PubMed from 1990 to present with relevance to allergic disorders and articles cited by or similar to these articles.
Study Selections: A total of 472 articles were identified from PubMed. Two independent reviewers appraised the titles for relevance.
Results: A total of 212 relevant articles were selected. Additional articles and government websites increased the number to 295 relevant citations.
Conclusion: Influenza epidemics and pandemics have recurred throughout history. Patients with asthma and immunodeficiency are at an increased risk. Nonpharmaceutical interventions, vaccination, and neuraminidase inhibitors are key strategies for the prevention and treatment of influenza epidemics/pandemics. Allergists play a vital role in protecting high-risk groups and increasing influenza vaccination coverage.

Introduction

Influenza epidemics have occurred throughout recorded history and are likely to recur. Reviewing the history of influenza epidemics and pandemics is important for practicing allergists because we care for high-risk patients, including those with asthma and immunodeficiencies.

Our objective is to review influenza epidemics and pandemics for practicing allergists-immunologists. We searched for English-language articles published in PubMed from 1990 to present with relevance to allergic disorders and articles cited by or similar to these. We used the Medical Subject Headings (MESH) terms ((“Influenza, Human”[Mesh] OR “Influenza Pandemic, 1918-1919”[Mesh] OR influenza*[tiab] OR flu[tiab]) AND (“Epidemics”[Mesh] OR epidemic*[tiab] OR pandemic*[tiab])) AND (“Hypersensitivity”[Mesh] OR allergy[tiab] OR allergies[tiab] OR “allergic reaction”[tiab] OR “allergic reactions”[tiab] OR “Rhinitis,

Reprints: Christopher D. Codispoti, MD, PhD, Division of Allergy/Immunology, Department of Internal Medicine, Rush University Medical Center, 1725 W Harrison Street, Suite 117, Chicago, IL 60612; E-mail: Christopher_D_Codispoti@rush.edu.
Disclosures: The authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.

https://doi.org/10.1016/j.anai.2020.11.012
1081-1206/

Allergic"[Mesh] OR rhinitis[tiab] OR "Asthma"[Mesh] OR asthma* [tiab] OR "Sinusitis"[Mesh] OR sinusitis[tiab] OR "sinus infection"[tiab] OR "sinus infections"[tiab] OR "Allergy and Immunology"[Mesh] OR immunology[tiab]). A total of 472 articles were identified from PubMed. Two independent reviewers appraised the titles for relevance. A third independent reviewer resolved any discrepancies between the reviewers. A total of 212 relevant articles were selected. Additional articles and government websites increased the number to 295 relevant citations that were reviewed in detail.

The Influenza Virus

Classification of Influenza Virus

Influenza viruses belong to a family of RNA viruses called *Orthomyxoviridae*. Influenza tends to be classified into 3 types of viruses—A, B, and C—each with different natural hosts and unique serologic responses to their internal proteins. Birds tend to be the natural host for influenza A, whereas influenza B and C are mostly restricted to humans.[1] Type C tends to cause much less severe disease in humans, with mild symptoms similar to those found with the common cold.[2]

Influenza A, owing to its antigenic variability, has caused the most serious illness in humans. Influenza A is further classified based on the hemagglutinin (HA) and neuraminidase (NA) surface antigens found on its surface. HA attaches virions to cells by binding terminal sialic acid residues on cellular surfaces, which allows for the initiation of the infectious cycle, whereas NA cleaves terminal sialic acids, leading to the release of the virion and allowing for the completion of the infectious cycle. There are currently 18 HA and 11 NA subtypes known to exist in nature.[2] Although many combinations of these subtypes are possible, only the following 3 seem to circulate in humans: A/H1N1, A/H2N2, and A/H3N2.[1] The influenza genome undergoes a rapid rate of mutation owing to the low fidelity of the virion's RNA-dependent RNA polymerase, which lacks proofreading capacity. As a result, the genes encoding NA and HA undergo frequent mutations, eventually mutating enough that host antibodies can no longer neutralize the virus.[3] This concept refers to antigenic drift and will be discussed subsequently in this review.

The Role of HA and NA in Viral Evolution

Because HA allows the virus to attach to the surface of host cells, it is also the primary target of the host adaptive immune response to influenza. The HA protein contains the following 2 components: a globular head (HA1) and a stalk (HA2) domain (Fig 1). Because the globular head is more accessible to host antibodies than the stalk, it is most often the target of the immune response.[1,4] Given the frequent and rapid mutation potential of these proteins, one would expect that new genetic variants would appear extremely frequently; however, new H3N2 variants only appear every 3 to 5 years, whereas new A/H1N1 and influenza B variants appear less frequently.[1] Mapping of the antigenic evolution of the influenza virus reveals a punctuated, rather than linear, antigenic evolution, with antigenic clusters developing over time.[5] An explanation for this clustered evolution is likely multifactorial, with both viral and host factors playing a role in preventing a more linear antigenic evolution of the virus. The virus must walk a fine line when mutating to escape the targeted response of the host's antibodies. Mutations in the HA protein can allow the virus to escape the host antibodies, but they may also compromise function. A review of the molecular construction of HA of human influenza A/H3N2 virus from 1968 to 2003 revealed that antigenic change was mainly caused by single amino acid substitutions found at only 7 positions in HA.[6] The amino acid substitution was always located in proximity to the receptor-binding site, suggesting that the mechanism involved in slowing the antigenic evolution of the virus could involve a reduction in the receptor-binding function.[6] Thus, only a small subset of mutations seems to be able to achieve both antigenic changes while also retaining receptor-binding functions of HA that are necessary for viral infection.

Innate and Adaptive Immunities Limit Antigenic Variance

Host immunity also plays a role in antigenic variance by exerting selection pressure on the virus. Previous infection, or vaccination, leads to the extinction of some antigenic variants and the emergence of new ones. In murine models, the adaptive immune response allows the host to quickly deploy immunoglobulin A antibodies in the upper respiratory tract to bind and neutralize the influenza virus.[7] This response provides effective protection from previously encountered antigenic variants of the virus, but it also leads to evolutionary selection of any new, previously unencountered antigenic variants that are present in a population to propagate.[1]

In a naive host, the innate immune system plays a vital role in the body's response to infection. Mucus produced by the body's mucosal barrier is rich in sialic acid, which binds the viral HA protein and traps it before it can reach host cells and infect them.[8] Only a small number of virus particles will actually make it past this barrier to infect host cells. Infected host cells will trigger interferon (IFN)-mediated responses establishing antiviral state. Murine studies revealed the importance of interferon lambda (IFN-λ) in promoting innate immunity against viral pathogens by decreasing viral replication and inducing an antiviral state in epithelial cells.[9] IFN-λ plays a role in regulating cytotoxic activity of neutrophils, another crucial player in the innate immunity response to viral infection.[9] IFN-λ also seems to play a role in improving the adaptive immunity response by triggering the release of immunoregulatory cytokines from epithelial cells.[9]

The innate and adaptive immune responses of the host play a large role in explaining relatively slower-than-expected rate of antigenic variation found with influenza. The process of transmission has been described as a "bottleneck," which reduces both the viral load and the new antigenic variants that can propagate within recipient cells.[1] Similarly, most virus diversity that arises from a host will be lost when transmitted to a new host, making antigenic variation more difficult to achieve.

A Brief History of Influenza Epidemics

Influenza Outbreaks before the 20th Century

The influenza virus has caused epidemics and pandemics for many centuries. Although pandemics lead to virus spread on a global scale, epidemics are found when there is a spike in infection rates at the local level, often after seasonal patterns of infection. The influenza virus was not identified and isolated until the 20th century; however, there is little doubt that numerous outbreaks occurred for centuries before that. An outbreak in 1580 is often referred to as the first influenza pandemic.[10] In that year, the strain seems to have emerged from Asia and spread via land to North Africa, Europe, and North America, leading to wide reports of illness and death.

The 18th century brought 2 major influenza pandemics. The first occurred in 1729, originating in Russia and spreading around the globe over the ensuing 3 years.[11] The 1781 pandemic started in China and then spread to Europe and Russia over 8 months.[11]

The first pandemic of the 19th century began in winter of 1830 in China and spread throughout Asia, Russia, and North America by 1831. The second pandemic started in Russia in 1889. This pandemic was important for the speed with which it spread and its high number of casualties (estimated to be approximately 1

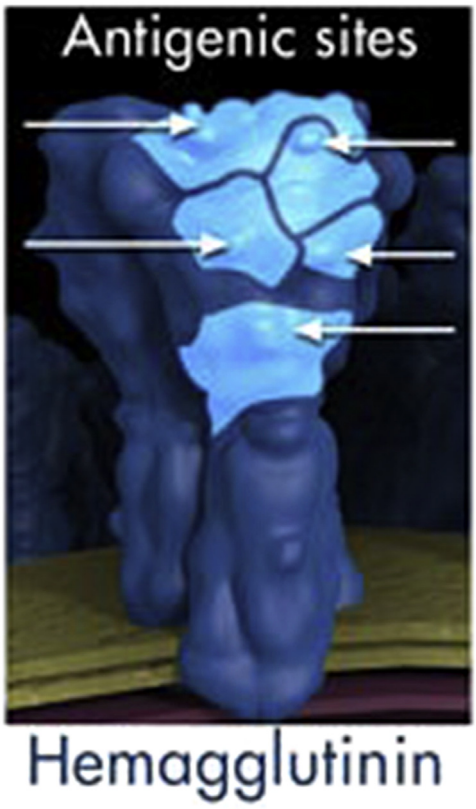

Figure 1. Structure of influenza hemagglutinin.[70]

million), representing an early indication of the effects of technological advances brought by the industrial revolution on influenza outbreaks.[12] Whereas earlier pandemics were often contained to spreading along commercial trading routes, the advent of the steam engine meant that the virus could spread more broadly and rapidly throughout the world.[11]

Influenza in the Modern Age—The Spanish Flu

The 20th century brought many technological advances that allowed for the isolation of the influenza virus from infected pigs in the laboratory for the first time in 1931 by Richard Shope.[13] Before this discovery, however, the influenza had already ravaged the world with its most deadly pandemic to date: the Spanish Flu of 1918. This pandemic, caused by an H1N1 strain, ravaged much of the world and caused up to 40 to 50 million deaths, with most of these casualties occurring in the fall of 1918.[11] It is believed that more than half of the world's population became infected. World War I led to poor sanitary conditions, overcrowding, lack of medical services, and the interaction of many nations that allowed for the virus to spread rapidly and globally.[11] Because influenza itself had yet to be isolated, let alone the discovery of a vaccine against the virus, the outbreak had to be controlled through nonpharmaceutical interventions (NPIs), such as school closures, quarantines, and banning of public gatherings.[14] The implementation of NPIs in the United States was found to have a significant association with reduction in mortality. NPIs that were implemented earlier and for longer duration proved to have greater impact.[14]

Post—World War II Outbreaks

The first influenza vaccines were developed in the late 1930s/early 1940s. Government agencies tasked to deal with public health formed in countries around the world, with the Communicable Disease Center (now Centers for Disease Control and Prevention, CDC) formed in 1946 in the United States.[15] The post—World War II period saw a sharp increase in the global population and international travelers and a growth in global trade. In 1957, a new H2N2 strain of influenza was discovered in China. Only those more than 65 years old seemed to have immunity to this strain, indicating that it may have been in circulation in the late 19th and early 20th centuries.[11] This strain spread across the world over the next year and became known as the Asian Flu. For the first time, scientists were able to study the response of an immunologically naive population to the influenza vaccination.[16,17] However, only 30 million doses of the vaccine were able to be distributed globally, preventing vaccination from having a significant impact on the spread of the virus.[16] The fatality rate was relatively low at 0.67%, but it led to 1 to 2 million deaths worldwide.[11,18] In 1968, another new strain of the influenza virus was discovered, this time in Hong Kong. The H3N2 strain led to a pandemic that came to be known as the Hong Kong Flu. Despite being highly transmissible, it was even milder than the Asian Flu, possibly in the setting of preexisting immunity to the NA antigen (N2) that was also present in the Asian Flu.[11,19]

Influenza in the 21st Century

No major influenza pandemic would occur until 2009. Known as the pH1N1/09 virus or swine flu, it emerged from Mexico and the United States in April 2009. The emergence of this pandemic has been traced to reassortments of 2 viruses that had been circulating in swine.[20] The virus spread throughout the world and exhibited a wave pattern behavior that varied based on geographic location. The World Health Organization declared the pandemic over in August 2010. By that time, 18,500 laboratory-confirmed deaths had been declared; however, mathematical modeling suggests that the mortality of the virus was up to 10-fold higher than the laboratory-confirmed cases.[21] The swine flu pandemic also marked the first time healthcare providers were able to use both vaccination and antiviral therapy to combat the virus and try to stem its propagation.[11]

Effects of Influenza on Allergy-Immunology Patients

Effects of Influenza on Asthma

Asthma affects 339 million people of all ages worldwide and is the leading cause of chronic disease in children.[22] It has long been understood that viral infections can lead to asthma exacerbations in all age ranges. Influenza is detected in up to 20% of acute wheezing illnesses in pediatrics and up to 25% in acute asthma exacerbations in adults.[23] In addition to exacerbations, influenza increases hospitalization rate in patients with asthma. In a study of 6- to 23-month-old children, the rate of hospitalization was significantly higher in those with asthma than in those without asthma (2.8 vs 0.6 cases per 1000 children, respectively; $P < .05$).[24] The mortality rate owing to influenza in patients with asthma was evaluated in an epidemiologic study spanning 8 years within the pediatric population using the national influenza-associated pediatric mortality surveillance system. A total of 830 influenza-related deaths occurred with 16% having asthma.[25] These studies emphasize the impact of seasonal influenza on asthma.

The effects of influenza on asthma were even more pronounced during the 2009 influenza A (H1N1) pandemic. A pediatric study found a significantly higher risk of infection of H1N1 in children with asthma than in those without asthma in a multivariate model (adjusted odds ratio [aOR] 4.0; 95% confidence interval [CI] 1.8-9.0; $P < .001$). This difference between these 2 groups was not found with other viral infections of rhinovirus, adenovirus, and enterovirus, indicating the profound role of H1N1 in asthma.[26] Asthma was also the most common underlying condition found in adults

and pregnant women hospitalized with H1N1.[27] Pediatric patients with asthma with H1N1 had increased odds of intensive care unit (ICU) admission (aOR 4.56; 95% CI 1.16-17.89).[28] The mortality in a pediatric ICU study of patients with H1N1 was 47%, with asthma being associated with higher mortality (aOR 1.34; 95% CI 1.20-2.91).[29] A CDC study characterizing patients with H1N1 who were hospitalized revealed that asthma was the most common comorbidity in both pediatric and adults.[30]

The current primary prevention of influenza includes vaccination. The efficacy of the influenza vaccine on asthma has been summarized in a recent meta-analysis that included 1 randomized controlled trial (RCT) and 3 observational studies.[31] An initial population-based retrospective cohort study of 1- to 6-year old children conducted by the CDC during 1993 to 1996 influenza seasons found the incidence rate ratio of asthma exacerbations after vaccination to be lower in 3 seasons when adjusted for asthma severity.[32] In contrast, a randomized, double-blinded, placebo-controlled study of pediatric patients aged 6 to 18 years revealed that there were greater number of influenza positive asthma exacerbations in the vaccinated group; 24 in the vaccine group and 18 in the placebo group (difference of 31% after adjustment for confounders; 95% CI −34% to 161%).[33] A Cochrane review analyzing the efficacy of influenza vaccine in patients with asthma concluded that there is a lack of significant reduction in asthma exacerbations owing to influenza exposure based on current available trials.[34] Despite this, there may still be a role for influenza vaccination. In a randomized, double-blinded placebo trial of 696 children with asthma aged 6 to 18 years, influenza vaccination improved quality of life scores ($P = .02$) during the weeks of an influenza-detected illness, which was not found in other respiratory illnesses.[35]

Influenza vaccination in asthma seems to be safe and is recommended. Trivalent inactivated influenza vaccine (TIV) is safe in older children and adults without evidence of inducing asthma exacerbations after vaccination.[32] Compared with TIV, a randomized open-label study in population of 6- to 17-year-old patients found the rate of influenza to be lower in those receiving live attenuated influenza vaccine (LAIV) than in those receiving TIV (4.1% vs 6.2%, respectively; 95% CI 3.9%-56.0%) without significant incidence of asthma exacerbations suggesting superior efficacy and safety.[36] In infants aged 6 to 11 months, an increase in medically significant wheezing in the first 42 days after LAIV (2.3%) compared with TIV (1.5%) indicating a possible age-based limitation in the safety of LAIV was noted.[32] Another study also revealed a trend for more frequent wheezing episodes in infants younger than 12 months who were given LAIV (3.8%) compared with inactivated influenza vaccine (IIV) (2.1%).[37] These studies form the basis of current CDC recommendations.

Effects of Influenza on Primary Immunodeficiency

Acquiring influenza in the setting of primary immunodeficiency can lead to a more severe course and an increase in mortality and morbidity. Data on hospitalization rate and death due to influenza in those with cellular and humoral deficiencies are lacking. However, a recent survey conducted in the 2016-2017 influenza season was able to capture some data on prevalence rates within patients with primary antibody deficiency.[38] A total of 1009 pediatric and adult patients had X-linked agammaglobulinemia (XLA), common variable immunodeficiency (CVID), or hypogammaglobinemia; physician-diagnosed influenza was reported in 30% (30) of children and 15% (139) in adults. Comparing the rate of influenza in patients with XLA, CVID, and hypogammaglobinemia on and off of immunoglobulin therapy, fewer patients receiving immunoglobulin developed influenza. Within the XLA group, influenza in those receiving immunoglobulin vs those not receiving immunoglobulin was 5% compared with 50% ($P < .05$), respectively. This trend was found in those with CVID in whom 16% receiving immunoglobulin developed influenza compared with 41% in those not on immunoglobulin therapy ($P < .001$). Within the hypogammaglobinemia group, 14% on immunoglobulin therapy developed influenza compared with 50% not on therapy ($P < .001$). This may indicate the presence of some influenza-neutralizing antibodies within immunoglobulin therapy.

Looking into predicative markers that allow a positive response from TIV vaccination in patients with CVID, Gardulf et al[39] reported 16.7% response rate in their cohort of 48 patients when given the influenza A (H1N1) Pandemrix vaccine. Responders had higher proportions of enteropathies, higher levels of plasmablasts, and lower $CD21^{low}$ B cells, whereas nonresponders had bronchiectasis and autoimmune cytopenias, lower mean serum immunoglobulin G1, and higher mean serum immunoglobulin M.

Beyond antibody deficiency, patients with particular defects within the innate immune system can succumb to influenza. Two unrelated children with life-threatening influenza were found to have mutations within interferon regulatory factor 7 and 9 (IRF7 and IRF9).[40,41] A 41-year-old previously healthy man who developed a severe course of H1N1pdm09 was found to have a genetic variant within retinoic acid-inducible 1 (RIG-1) gene.[42] Similarly, a variant within IRF3 was found in a 55-year-old man with severe life-threatening influenza illness.[43] These defects highlight the importance of an intact innate signaling system that allows appropriate induction of type I and III interferons.

Prevention and Treatment of Influenza

The influenza virus has the potential to cause annual epidemics and global pandemics. Antigenic drift results from the accumulation of minor mutations in the genes that encode some of the antibody-binding sites located on the influenza virus. A virus strain can develop several of these minor mutations, allowing it to evade the immune system and cause annual epidemics. In contrast, the influenza virus also has the potential to undergo a more rapid and radical change in viral antigenicity, most often by combining with other existing strains and leading to the development of a new viral subtype. When this sudden transformation occurs, a pandemic may develop, because previously infected individuals do not have any immunity to the new strain. This process is referred to as an antigenic shift.

Immunization: Primary Prevention

Given the potential for epidemics and pandemics to develop, preventing influenza infections is crucial. Vaccination has proved to be the most effective means of preventing influenza and its complications. However, antigenic drift, antigenic shift, and waning immunity all complicate annual vaccination efforts, leading to the need to vaccinate individuals yearly. Despite the wide availability of the influenza vaccine in the United States, from 2010-2011 to 2015-2016, the influenza virus is estimated to infect between 9.2 and 35.6 million people annually in the United States alone, leading to 12,000 to 56,000 deaths.[44] It has been observed that IIVs tend to have few adverse effects, with the most common being soreness at the site of injection.[45] Pain, low-grade fever, and fatigue are less common. Use of the IIV in pregnant women has also been found to be safe, with no identified adverse pregnancy or fetal outcomes.[46] Importantly, anaphylaxis after influenza vaccination is extremely rare. A 2010 study of 830 individuals with a confirmed egg allergy revealed no cases of anaphylaxis after the administration of the H1N1 influenza vaccine.[47] Despite its robust safety profile, in the past 10 years, the annual influenza vaccination rates in the US population ranged from 41.7%, in the 2017-2018 influenza season, to 49.2%, in the 2018-2019 influenza season (Fig 2).[48]

Low adherence to influenza vaccination is multifactorial, with psychological, physical, and sociodemographic barriers all playing a

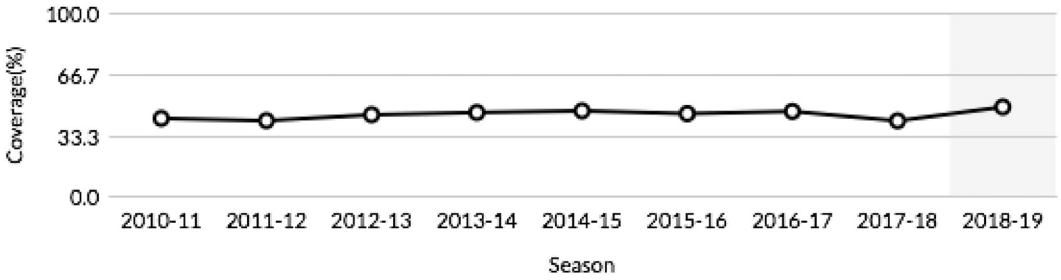

Figure 2. Influenza vaccination coverage by season.[48]

role. A 2017 review of influenza hesitancy from 2005 to 2016 identified that having a negative attitude toward vaccines (ie, perceived low effectiveness and lack of trust in health authorities) was the most frequently reported barrier to vaccination.[49] Other factors included low perceived risk of the disease, knowledge gaps, such as belief that the vaccine can cause influenza, lack of recommendations from medical professionals, and low frequency of interaction with health services. Another study noted that among older individuals, the older, ethnically White, higher-income individuals with access to health insurance coverage with a regular care provider were most likely to receive influenza vaccination, again indicating the socioeconomic impact on vaccination adherence.[50] Further efforts are therefore needed to address each of these barriers. At a population level, improving education on the benefits of vaccination, along with limiting the spread of misinformation regarding the influenza vaccine, which can now rapidly spread through social media use, is crucial. Continuing to lower barriers to access to health care by making influenza vaccine cheap and readily available is also necessary. On an individual level, strategies also include using each patient encounter as an opportunity to vaccinate and educate patients by providing up-to-date, clear recommendations. These efforts are necessary to reduce vaccine hesitancy. One of the common myths is that influenza can be contracted from the influenza vaccine, a belief held by 43% of participants of a national survey. Providing corrective information from the CDC reduced belief in this myth, but among participants who had a high concern about adverse effects of vaccines, receiving this information significantly reduced their intent to receive influenza vaccination.[51] Further research is needed in this area to effectively address each individual's concern to increase influenza rates.

Recent estimates from the 2018-2019 influenza season revealed that influenza vaccination has prevented 4.4 million illnesses, 58,000 hospitalizations, and 3500 deaths.[52] Furthermore, several studies have revealed the effectiveness of the influenza vaccine in reducing illness severity, in-hospital mortality, and ICU admissions when compared with unvaccinated individuals.[53,54] For instance, 1 study determined that influenza vaccination reduces the risk of ICU admission and death in older patients (≥65 years) who were hospitalized.[53] Another study concluded that influenza vaccination led to reduction in in-hospital deaths for patients of any age, along with reducing ICU admission rates in patients aged 18 to 49 years and greater than or equal to 65 years. The ICU length of stay was also reduced in half in patients aged 50 to 64 years compared with unvaccinated patients.[54] A study in Spain described vaccine effectiveness (VE) in preventing both outpatient and hospital-associated influenza cases, with a VE of 89% in preventing severe cases. Furthermore, inpatient cases were associated with a lower risk of severe influenza.[55]

Although the standard-dose influenza vaccines have proved effective in younger patients, decreased immunogenicity and effectiveness of standard-dose vaccines is found in persons aged 65 years and older. Among adults 65 years and older, high-dose (HD) trivalent IIV provided greater protection against laboratory-confirmed influenza illness compared with standard-dose trivalent IIV.[56] In addition, adjuvant vaccines with up to 4 times the antigen concentration of standard-dose vaccines have been developed for patients aged 65 years or older. A recent RCT described that a recombinant HD quadrivalent influenza vaccine provided better protection than an egg-grown standard-dose quadrivalent vaccine in older adults.[57] Another study reported that an HD vaccine significantly reduced respiratory-related hospitalizations compared with standard-dose vaccine in elderly nursing home residents.[58]

Although the evidence for HD influenza vaccination accumulates at a time of immune senescence in the elderly, few randomized trials have investigated the efficacy of influenza vaccination at time of immune immaturity during infancy. This evidence gap is starting to be addressed. A recent phase III multicenter RCT of children aged 6 to 36 months revealed that quadrivalent IIV was safe and effective in preventing influenza illness.[59]

Novel Immunization Strategies

Antigenic mismatches and relatively low vaccination rates have prevented even further decrease in disease burden, leading to the search for the development of a more broadly cross-protective vaccine. Several approaches to creating a "universal" influenza vaccine are currently underway. Although current seasonal vaccines target the variable regions on the HA head, new approaches are investigating the possibility to target the HA stem instead, a region that exhibits much stronger conservation.[60] Other approaches include developing a vaccine that elicits NA antibodies that target an epitope that is key for NA function, along with targeting internal antigens that have higher conservation across viral strains.[60]

Antiviral Therapy: Secondary Prevention

Antiviral therapy can provide treatment of the influenza virus. Currently, Food and Drug Administration–approved antiviral medications in the treatment of influenza include NA inhibitors (eg, oseltamivir), cap-dependent endonuclease inhibitors (baloxavir marboxil), and adamantanes (amantadine, rimantadine).[61] Initiation of these medications needs to occur as soon as possible after illness onset for maximal efficacy, with greatest clinical benefit when antivirals are started within 2 days of symptom onset.[62] A meta-analysis of the efficacy of oseltamivir in the treatment of influenza found faster time to symptom alleviation and decreased risk of lower respiratory tract complications.[63] Similar findings regarding decreased duration of illness were noted in children.[64] Oseltamivir did lead to increased nausea and vomiting in treated individuals.[53] An increase in psychiatric adverse events, such as

confusion, depression, and hallucinations, has also been reported.[65] Therefore, careful consideration of the risks and benefits of antiviral drugs needs to be weighed before their initiation.

Role of the Allergist-Immunologist in Preventing Influenza Epidemics

The role of the allergist-immunologist in influenza epidemics is a unique one in that it entails expertise in asthma and immune deficiencies, thereby playing a crucial role in upholding the health status of 2 of the most vulnerable populations to influenza illnesses.

The CDC recommends vaccinating all patients with asthma above the age of 6 months. Influenza vaccination rates among people with asthma range widely in varying parts of the world. It has been reported below 50% in adults and children in the United States.[48] Racial disparities on vaccination rates have been noted, with lower rates among Black children (45%) and those of lower socioeconomic class (47%) than White children (51%) and those of higher socioeconomic class (54%).[66] Several interventions have been studied to increase the rate of vaccination. Positive effects have been found with use of convenient vaccination services, notification of importance of vaccination, availability of vaccines within a medical facility conducive to vaccination, and providing motivation to patients and their families. These efforts increased vaccination across different racial groups in a statistically significant manner and higher than the national average by 11%.[66] Using technology to remind patients by electronic letters followed by autodial recall telephone message has also proved to increase vaccination rate.[67] Finally, evaluation of patients with egg allergy within an allergy practice can further increase rates of vaccination because several studies now have proved safety of IIV and LAIV in patients with egg allergy.[68,69] Implementing evidence-based interventional methods within the allergy-immunology office can greatly enhance immunization efforts toward influenza and thereby provide some protection to our patients with allergy and those who are immunocompromised.

Conclusion

Influenza virus is under constant pressure to evade immune responses. In evading the immune response, small changes in influenza lead to determining the major prevalent seasonal strain. Bigger changes in influenza can lead to epidemics and pandemics. Allergists are in a unique position to protect vulnerable patients, including those with asthma and immunodeficiencies, with the use of vaccinations and NA inhibitors that can prevent and treat influenza infections. Allergists can increase vaccination rates by reminder techniques and communicating the safety of influenza vaccines in patients with egg allergy.[48,70]

References

1. Petrova VN, Russell CA. The evolution of seasonal influenza viruses. *Nat Rev Microbiol*. 2018;16(1):47–60.
2. Centers for Disease Control and Prevention. Types of influenza viruses. Available at: https://www.cdc.gov/flu/about/viruses/types.htm. Accessed September 15, 2020.
3. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases. How the flu virus can change: "drift" and "shift". Available at: https://www.cdc.gov/flu/about/viruses/change.htm. Accessed September 7, 2020.
4. Bizebard T, Gigant B, Rigolet P, et al. Structure of influenza virus haemagglutinin complexed with a neutralizing antibody. *Nature*. 1995;376(6535):92–94.
5. Smith DJ, Lapedes AS, de Jong JC, et al. Mapping the antigenic and genetic evolution of influenza virus. *Science*. 2004;305(5682):371–376.
6. Koel BF, Burke DF, Bestebroer TM, et al. Substitutions near the receptor binding site determine major antigenic change during influenza virus evolution. *Science*. 2013;342(6161):976–979.
7. Renegar KB, Small Jr PA, Boykins LG, Wright PF. Role of IgA versus IgG in the control of influenza viral infection in the murine respiratory tract. *J Immunol*. 2004;173(3):1978–1986.
8. Cohen M, Zhang XQ, Senaati HP, et al. Influenza A penetrates host mucus by cleaving sialic acids with neuraminidase. *Virol J*. 2013;10:321.
9. Ye L, Schnepf D, Staeheli P. Interferon-λ orchestrates innate and adaptive mucosal immune responses. *Nat Rev Immunol*. 2019;19(10):614–625.
10. Potter CW. A history of influenza. *J Appl Microbiol*. 2001;91(4):572–579.
11. Saunders-Hastings PR, Krewski D. Reviewing the history of pandemic influenza: understanding patterns of emergence and transmission. *Pathogens*. 2016;5(4):66.
12. Valleron AJ, Cori A, Valtat S, Meurisse S, Carrat F, Boelle PY. Transmissibility and geographic spread of the 1889 influenza pandemic. *Proc Natl Acad Sci USA*. 2010;107(19):8778–8781.
13. Shope RE. Swine influenza: III. Filtration experiments and etiology. *J Exp Med*. 1931;54(3):373–385.
14. Markel H, Stern AM, Navarro JA, Michalsen JR, Monto AS, DiGiovanni C. Nonpharmaceutical influenza mitigation strategies, US communities, 1918-1920 pandemic. *Emerg Infect Dis*. 2006;12(12):1961–1964.
15. Henderson DA. The development of surveillance systems. *Am J Epidemiol*. 2016;183(5):381–386.
16. Jackson C. History lessons: the Asian flu pandemic. *Br J Gen Pract*. 2009;59(565):622–623.
17. Kilbourne ED. Influenza pandemics of the 20th century. *Emerg Infect Dis*. 2006;12(1):9–14.
18. Viboud C, Simonsen L, Fuentes R, Flores J, Miller MA, Chowell G. Global mortality impact of the 1957-1959 influenza pandemic. *J Infect Dis*. 2016;213(5):738–745.
19. Morens DM, Taubenberger JK, Fauci AS. The persistent legacy of the 1918 influenza virus. *N Engl J Med*. 2009;361(3):225–229.
20. Smith GJ, Vijaykrishna D, Bahl J, et al. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature*. 2009;459(7250):1122–1125.
21. Dawood FS, Iuliano AD, Reed C, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. *Lancet Infect Dis*. 2012;12(9):687–695.
22. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1211–1259.
23. Coverstone AM, Wang L, Sumino K. Beyond respiratory syncytial virus and rhinovirus in the pathogenesis and exacerbation of asthma: the role of metapneumovirus, bocavirus and influenza virus. *Immunol Allergy Clin North Am*. 2019;39(3):391–401.
24. Miller EK, Griffin MR, Edwards KM, et al. Influenza burden for children with asthma. *Pediatrics*. 2008;121(1):1–8.
25. Wong KK, Jain S, Blanton L, et al. Influenza-associated pediatric deaths in the United States, 2004-2012. *Pediatrics*. 2013;132(5):796–804.
26. Kloepfer KM, Olenec JP, Lee WM, et al. Increased H1N1 infection rate in children with asthma. *Am J Respir Crit Care Med*. 2012;185(12):1275–1279.
27. Schwarze J, Openshaw P, Jha A, et al. Influenza burden, prevention, and treatment in asthma—a scoping review by the EAACI Influenza in asthma task force. *Allergy*. 2018;73(6):1151–1181.
28. Morris SK, Parkin P, Science M, et al. A retrospective cross-sectional study of risk factors and clinical spectrum of children admitted to hospital with pandemic H1N1 influenza as compared to influenza A. *BMJ Open*. 2012;2(2):e000310.
29. Torres SF, Iolster T, Schnitzler EJ, et al. High mortality in patients with influenza A pH1N1 2009 admitted to a pediatric intensive care unit: a predictive model of mortality. *Pediatr Crit Care Med*. 2012;13(2):e78–e83.
30. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med*. 2009;361(20):1935–1944.
31. Vasileiou E, Sheikh A, Butler C, et al. Effectiveness of influenza vaccines in asthma: a systematic review and meta-analysis. *Clin Infect Dis*. 2017;65(8):1388–1395.
32. Kramarz P, Destefano F, Gargiullo PM, et al. Does influenza vaccination prevent asthma exacerbations in children? *J Pediatr*. 2001;138(3):306–310.
33. Bueving HJ, Bernsen RM, de Jongste JC, et al. Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. *Am J Respir Crit Care Med*. 2004;169(4):488–493.
34. Cates CJ, Rowe BH. Vaccines for preventing influenza in people with asthma. *Cochrane Database Syst Rev*. 2013;2013(2):CD000364.
35. Bueving HJ, van der Wouden JC, Raat H, et al. Influenza vaccination in asthmatic children: effects on quality of life and symptoms. *Eur Respir J*. 2004;24(6):925–931.
36. Fleming DM, Crovari P, Wahn U, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. *Pediatr Infect Dis J*. 2006;25(10):860–869.
37. Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med*. 2007;356(7):685–696.
38. Ballow M, Henderson T, Scalchunes C, Blaese RM. Seasonal viral influenza among persons with primary antibody immunodeficiency. *J Allergy Clin Immunol Pract*. 2019;7(3):1058–1060.e3.
39. Gardulf A, Abolhassani H, Gustafson R, Eriksson LE, Hammarstrom L. Predictive markers for humoral influenza vaccine response in patients with common variable immunodeficiency. *J Allergy Clin Immunol*. 2018;142(6):1922–1931.e2.

40. Hernandez N, Melki I, Jing H, et al. Life-threatening influenza pneumonitis in a child with inherited IRF9 deficiency. *J Exp Med*. 2018;215(10):2567–2585.
41. Ciancanelli MJ, Huang SX, Luthra P, et al. Infectious disease. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. *Science*. 2015;348(6233):448–453.
42. Jørgensen SE, Christiansen M, Ryø LB, et al. Defective RNA sensing by RIG-I in severe influenza virus infection. *Clin Exp Immunol*. 2018;192(3):366–376.
43. Thomsen MM, Jørgensen SE, Storgaard M, et al. Identification of an IRF3 variant and defective antiviral interferon responses in a patient with severe influenza. *Eur J Immunol*. 2019;49(11):2111–2114.
44. Rolfes MA, Foppa IM, Garg S, et al. Annual estimates of the burden of seasonal influenza in the United States: a tool for strengthening influenza surveillance and preparedness. *Influenza Other Respir Viruses*. 2018;12(1):132–137.
45. Uyeki TM. Influenza. *Ann Intern Med*. 2017;167(5):ITC33–ITC48.
46. Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices - United States, 2020-21 influenza season. *MMWR Recomm Rep*. 2020;69(8):1–24.
47. Gagnon R, Primeau MN, Des Roches A, et al. Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. *J Allergy Clin Immunol*. 2010;126(2):317–323.
48. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases. 2010-11 through 2019-20 Influenza Seasons Vaccination Coverage Trend Report. Available at: https://www.cdc.gov/flu/fluvaxview/reportshtml/trends/index.html. Accessed September 11, 2020.
49. Schmid P, Rauber D, Betsch C, Lidolt G, Denker ML. Barriers of influenza vaccination intention and behavior - a systematic review of influenza vaccine hesitancy, 2005 - 2016. *PLoS One*. 2017;12(1):e0170550.
50. Okoli GN, Abou-Setta AM, Neilson CJ, Chit A, Thommes E, Mahmud SM. Determinants of seasonal influenza vaccine uptake among the elderly in the United States: a systematic review and meta-analysis. *Gerontol Geriatr Med*. 2019;5:2333721419870345.
51. Nyhan B, Reifler J. Does correcting myths about the flu vaccine work? An experimental evaluation of the effects of corrective information. *Vaccine*. 2015;33(3):459–464.
52. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases. 2018–19 Influenza illnesses, medical visits, hospitalizations, and deaths averted by vaccination. Available at: https://www.cdc.gov/flu/about/burden-averted/2018-2019.htm. Accessed September 11, 2020.
53. Casado I, Dominguez A, Toledo D, et al. Effect of influenza vaccination on the prognosis of hospitalized influenza patients. *Expert Rev Vaccines*. 2016;15(3):425–432.
54. Arriola C, Garg S, Anderson EJ, et al. Influenza vaccination modifies disease severity among community-dwelling adults hospitalized with influenza. *Clin Infect Dis*. 2017;65(8):1289–1297.
55. Castilla J, Godoy P, Dominguez A, et al. Influenza vaccine effectiveness in preventing outpatient, inpatient, and severe cases of laboratory-confirmed influenza. *Clin Infect Dis*. 2013;57(2):167–175.
56. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med*. 2014;371(7):635–645.
57. Dunkle LM, Izikson R, Patriarca P, et al. Efficacy of recombinant influenza vaccine in adults 50 years of age or older. *N Engl J Med*. 2017;376(25):2427–2436.
58. Gravenstein S, Davidson HE, Taljaard M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. *Lancet Respir Med*. 2017;5(9):738–746.
59. Pepin S, Dupuy M, Borja-Tabora CFC, et al. Efficacy, immunogenicity, and safety of a quadrivalent inactivated influenza vaccine in children aged 6-35 months: a multi-season randomised placebo-controlled trial in the Northern and Southern Hemispheres. *Vaccine*. 2019;37(13):1876–1884.
60. Saad-Roy CM, McDermott AB, Grenfell BT. Dynamic perspectives on the search for a universal influenza vaccine. *J Infect Dis*. 2019;219(suppl 1):S46–S56.
61. Chow EJ, Doyle JD, Uyeki TM. Influenza virus-related critical illness: prevention, diagnosis, treatment. *Crit Care*. 2019;23(1):214.
62. Katzen J, Kohn R, Houk JL, Ison MG. Early oseltamivir after hospital admission is associated with shortened hospitalization: a 5-year analysis of oseltamivir timing and clinical outcomes. *Clin Infect Dis*. 2019;69(1):52–58.
63. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet*. 2015;385(9979):1729–1737.
64. Malosh RE, Martin ET, Heikkinen T, Brooks WA, Whitley RJ, Monto AS. Efficacy and safety of oseltamivir in children: systematic review and individual patient data meta-analysis of randomized controlled trials. *Clin Infect Dis*. 2018;66(10):1492–1500.
65. Heneghan CJ, Onakpoya I, Jones MA, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. *Health Technol Assess*. 2016;20(42):1–242.
66. Lin CJ, Nowalk MP, Zimmerman RK, et al. Reducing racial disparities in influenza vaccination among children with asthma. *J Pediatr Health Care*. 2016;30(3):208–215.
67. Gaglani M, Riggs M, Kamenicky C, Glezen WP. A computerized reminder strategy is effective for annual influenza immunization of children with asthma or reactive airway disease. *Pediatr Infect Dis J*. 2001;20(12):1155–1160.
68. Greenhawt MJ, Spergel JM, Rank MA, et al. Safe administration of the seasonal trivalent influenza vaccine to children with severe egg allergy. *Ann Allergy Asthma Immunol*. 2012;109(6):426–430.
69. Turner PJ, Southern J, Andrews NJ, Miller E, Erlewyn-Lajeunesse M, SNIFFLE Study Investigators. Safety of live attenuated influenza vaccine in atopic children with egg allergy. *J Allergy Clin Immunol*. 2015;136(2):376–381.
70. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases. Understanding influenza (flu) infection: an influenza virus binds to a respiratory tract cell. Available at: https://www.cdc.gov/flu/resource-center/freeresources/graphics/images.htm. Accessed September 15, 2020.