From antigenic drift to algorithmic prediction: Emerging paradigms in influenza vaccine design and global effectiveness (Review)

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Abstract. Despite widespread annual vaccination efforts, seasonal influenza continues to represent a substantial global public health burden. The present comprehensive review critically discusses the virological, immunological and epidemiological determinants that constrain the effectiveness of contemporary influenza vaccines. A major challenge lies in the rapid evolutionary dynamics of the influenza virus, particularly through antigenic drift and, less frequently, antigenic shift, which frequently result in mismatches between vaccine strains and the circulating variant. The prolonged lead time required for vaccine production, based on early strain prediction, further increases the likelihood of such mismatches. Host-related factors, including an advanced age, immunosenescence, obesity, comorbid conditions and immunological imprinting, contribute to marked variability in vaccine responsiveness across populations. Furthermore, the majority of currently available influenza vaccines predominantly elicit humoral immune responses, with the comparatively limited induction of cellular immunity, which is essential for durable and broad protection. The virus also employs multiple immune-evasion strategies, including glycosylation masking and the suppression of interferon responses, further complicating vaccine effectiveness. Beyond biological constraints, factors such as vaccine hesitancy, inequitable access, and limitations in public health communication hinder vaccine uptake and the development of herd immunity. The present review further discusses emerging strategies, including mRNA vaccine platforms, broadly neutralizing antibodies, universal vaccine candidates targeting conserved viral epitopes and artificial-intelligence0driven models for improved strain prediction. In conclusion, reducing the global burden of seasonal influenza will require an integrated approach that combines advances in vaccine technology with strengthened public health strategies, enhanced global surveillance and equitable vaccine access.

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Abbreviations: WHO, World Health Organization; NA, neuraminidase; HA, hemagglutinin; H3N2, hemagglutinin type 3 and neuraminidase type 2; AI, artificial intelligence; mRNA, messenger ribonucleic acid; CRISPR, clustered regularly interspaced short palindromic repeats

Key words: seasonal influenza, vaccine effectiveness, antigenic drift, host immune system, viral evolution, artificial intelligence, vaccine hesitancy

Contents

1. Introduction

Influenza is an acute viral respiratory infection that occurs annually and is primarily caused by influenza A and B viruses. It continues to impose a substantial global public health burden, affecting millions of individuals annually and

contributing to significant morbidity and mortality worldwide. According to the World Health Organization (WHO), influenza is responsible for ~290,000 to 650,000 respiratory-related deaths globally each year (1,2). The impact of influenza varies considerably from year to year, largely due to rapid viral evolution that results in frequent antigenic changes. This continuous viral evolution, combined with heterogeneity in population immunity, contributes to unpredictable and sometimes highly variable severity of seasonal influenza outbreaks (3,4).

Vaccination remains the primary strategy for the prevention of seasonal influenza. Influenza vaccines are designed to elicit immune responses against the strains most likely to predominate during a given influenza season. These vaccines primarily target the viral surface glycoproteins hemagglutinin (HA) and neuraminidase (NA), which are essential for viral entry into host cells and subsequent propagation within the respiratory tract. Vaccine composition is determined based on predictions of circulating seasonal strains generated through coordinated surveillance by the WHO and national health authorities (5,6). However, the effectiveness of influenza vaccines demonstrates considerable inter-seasonal variability, typically ranging between 40 and 60% (7,8). This variability is attributable to factors, such as antigenic mismatch, ongoing viral evolution and heterogeneity in host immune responses. The rapid pace of genetic alterations in influenza viruses represents one of the principal barriers to achieving consistently high vaccine effectiveness. Influenza viruses are subject to continuous genetic variation through antigenic drift, characterized by the accumulation of point mutations in the HA and NA genes. These mutations alter surface proteins, enabling the virus to evade immunity acquired through prior infection or vaccination (9,10). Consequently, vaccinated individuals may remain susceptible to infection when circulating strains differ substantially from vaccine strains. Antigenic drift becomes particularly problematic during seasons in which vaccine strains are poorly matched to circulating variants. Evidence indicates that vaccine-virus mismatch significantly reduces vaccine effectiveness and increases the likelihood of breakthrough infections (11,12). For example, during the 2014-2015 influenza season, a substantial genetic mismatch between the vaccine and circulating HA type 3 and NA type 2 (H3N2) strains resulted in markedly reduced vaccine effectiveness (13). In addition to the antigenic drift, influenza viruses may undergo an antigenic shift, a process involving major genetic reassortment that can generate novel viral subtypes. Such shifts may lead to pandemic strains capable of evading existing seasonal vaccines and spreading rapidly within populations. Pandemic strains can evade seasonal vaccines; however, the method through which they function indicates how the virus can spread rapidly within populations despite this (14,15). Annual influenza vaccines are formulated based on strain predictions issued by the WHO and national surveillance systems. As vaccine production requires substantial lead time, these predictions are typically made 6 to 9 months prior to the influenza season. This interval increases the risk of mismatch between vaccine strains and circulating viruses due to ongoing antigenic drift (16,17). Furthermore, the majority of influenza vaccines contain inactivated or attenuated forms of only three or four viral strains, thereby limiting the breadth of protection (18,19). Although quadrivalent vaccines have expanded coverage to include an additional influenza B lineage, protection remains restricted in scope. Ongoing research is focused on the development of broader or universal influenza vaccines capable of conferring cross-strain protection (20,21); however, such vaccines are not yet available to the public. Vaccine effectiveness is also strongly influenced by host-related factors. Age, health status and prior influenza exposure can substantially influence vaccine-induced immune responses. Certain populations, particularly older adults and immunocompromised individuals, may exhibit a reduced responsiveness to vaccination (22,23). The phenomenon known as 'original antigenic sin', or immune imprinting, may bias immune responses toward previously encountered strains rather than newly emerging variants (24). The present review therefore discusses the roles of viral evolution, vaccine design, host immune responses and epidemiological determinants in explaining the persistence of influenza infections despite widespread vaccination.

The present review aimed to: i) Examine the factors that limit influenza vaccine effectiveness; ii) synthesize recent evidence explaining breakthrough infections; and iii) discuss emerging strategies to enhance vaccine performance and global influenza control.

2. Literature search

The present study was conducted as a structured narrative review to synthesize current evidence on influenza virus evolution, vaccine effectiveness, host-related determinants of vaccine response, and emerging strategies in influenza vaccine design and prediction. The present review aimed to integrate findings from virology, immunology, epidemiology and public-health research to provide a comprehensive and critical overview of factors influencing the global effectiveness of influenza vaccination. Although not designed as a formal systematic review, the study followed a transparent and reproducible search approach to ensure scholarly rigor and breadth of coverage.

A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science and Google Scholar databases to identify relevant publications between January, 2000 and February, 2025. Earlier landmark studies were included where necessary to provide historical context. Search terms combined Medical Subject Headings and keywords related to influenza vaccination and viral evolution, including 'influenza', 'influenza vaccine', 'vaccine effectiveness', 'antigenic drift', 'antigenic shift', 'immune response', 'immunosenescence', 'vaccine hesitancy', 'universal influenza vaccine', 'mRNA vaccine', 'genomic surveillance', and 'artificial intelligence'. Boolean operators were applied to refine results, and reference lists of relevant articles were screened manually to identify additional sources.

Studies were included if they addressed influenza vaccine effectiveness, immune responses, viral evolution, vaccine technologies, or public-health determinants of vaccine uptake. Clinical, epidemiological, laboratory and review studies published in the English language were considered. Articles lacking sufficient methodological detail or unrelated to influenza vaccination were excluded. Titles and abstracts were screened for relevance, followed by full-text review of eligible

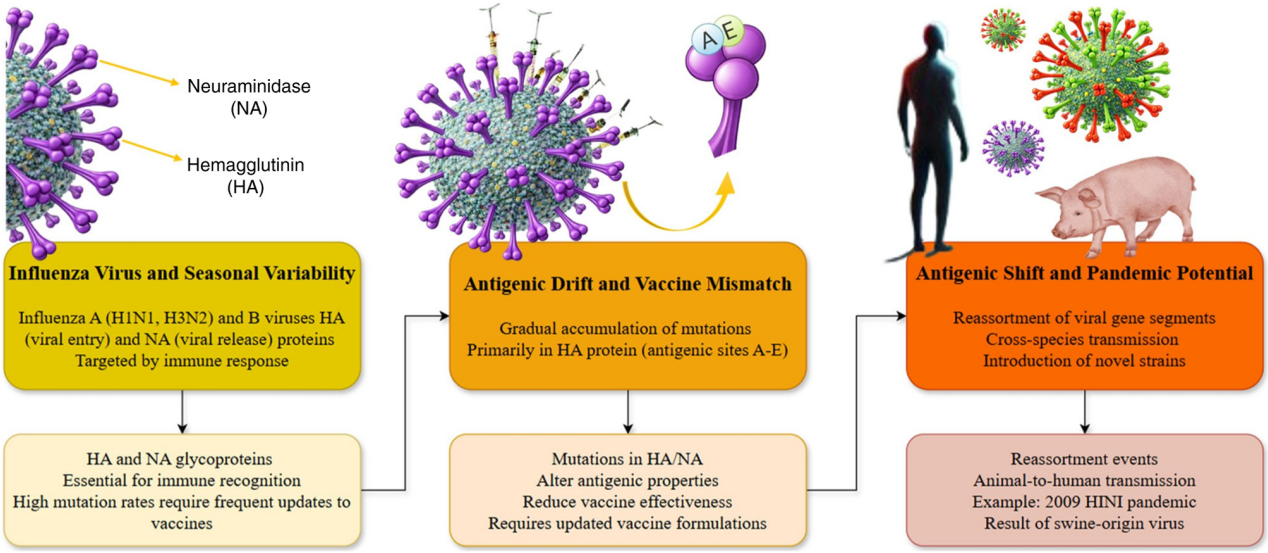

Figure 1. Influenza virus variability and pandemic potential: antigenic drift and shift. The image illustrates the evolution of the influenza viruses through antigenic drift and antigenic shift. (Left panel) Influenza virus and seasonal variability: The image depicts influenza A (H1N1 and H3N2) and B viruses, highlighting their key proteins, HA and NA, which are targeted by the immune response. These proteins have high mutation rates, necessitating frequent updates to vaccines. (Middle panel) Antigenic drift and vaccine mismatch: This process involves gradual mutations in the HA protein, particularly in antigenic sites A-E, which can lead to mismatches between circulating strains and vaccine strains, reducing vaccine effectiveness. (Right panel) Antigenic shift and pandemic potential: Antigenic shift occurs when the reassortment of viral genes leads to the emergence of novel strains with the potential for cross-species transmission, such as the swine-origin virus from the 2009 H1N1 pandemic. This process increases the risk of pandemics. NA, neuraminidase; HA, hemagglutinin.

studies. Evidence was synthesized narratively due to the heterogeneity of study designs and outcomes, with emphasis on key themes and emerging trends in vaccine performance, immunological mechanisms, and future vaccine development. Priority was given to peer-reviewed studies, systematic reviews and reports from major public-health organizations to ensure reliability and scientific validity.

3. Influenza virus evolution and vaccine mismatch

Influenza virus evolution is primarily driven by two mechanisms: Antigenic drift and antigenic shift. These processes result in continuous alterations of viral surface proteins, frequently leading to vaccine mismatch when circulating strains differ from those selected for vaccine production (9). Such mismatches reduce vaccine effectiveness because viral evolution remains unpredictable while vaccine production timelines are fixed. Consequently, robust global surveillance and regular updates to vaccine formulations are essential to mitigate this challenge. As illustrated in Fig. 1, influenza viruses evolve through gradual mutations (antigenic drift) and major genetic reassortment events (antigenic shift). These mechanisms necessitate frequent vaccine reformulation and, in some cases, facilitate zoonotic transmission events that increase pandemic risk (9).

Influenza virus and seasonal variability. Seasonal variation in influenza viruses is sufficiently pronounced to require annual reformulation of vaccines (25). Influenza A and B viruses possess segmented RNA genomes encoding multiple proteins essential for viral replication and immune evasion (26). The viral envelope is characterized by surface glycoproteins, HA and NA, which are central to viral infectivity (27). These glycoproteins form the basis of the influenza subtype classification system; for example, 'H1N1' denotes a virus with HA subtype 1 and NA subtype 1. HA mediates viral entry through receptor binding, whereas neuraminidase facilitates viral release by cleaving sialic acid residues. As illustrated in Fig. 1, HA comprises two subunits: The HA1 globular head responsible for receptor binding and the HA2 stalk region that mediates membrane fusion (28,29).

Annual vaccine composition is determined through WHO-coordinated surveillance and may require modifications each year. The HA head contains five principal antigenic sites (A-E), which are the primary targets of neutralizing antibodies (30-32). Mutations within these antigenic sites, and within key positions in the stalk region, enable the virus to evade immune recognition, posing substantial challenges for vaccine development (33,34). Influenza B viruses exhibit less genetic diversity than influenza A viruses and are categorized into two lineages: Yamagata and Victoria. Current quadrivalent vaccines include antigens from both influenza B lineages alongside H1N1 and H3N2 strains to broaden protection (35). The WHO monitors global influenza evolution through the Global Influenza Surveillance and Response System (GISRS), established in 1952 (36). This system provides biannual recommendations for vaccine composition in both the Northern and Southern Hemispheres (37). Historically, the emergence of novel influenza subtypes underscores the importance of continuous surveillance and rapid vaccine adaptation. For example, the A/H2N2 virus responsible for the 1957 Asian influenza pandemic emerged following earlier H1N1 circulation, illustrating the dynamic nature of influenza evolution (38,39).

Antigenic drift and vaccine mismatch. Antigenic drift refers to the gradual accumulation of amino acid substitutions in the HA and NA surface glycoproteins, particularly within antigenic

epitopes (40). This continuous process enables influenza viruses to alter their antigenicity, thereby evading pre-existing host immune responses. Beneficial mutations allow dominant seasonal variants to emerge and replace previously circulating strains (41,42). Although detailed evolutionary tracking is complex due to the large volume of viral samples, modern genomic technologies now enable high-resolution phylogenetic analysis of viral diversification (43).

In addition to point mutations, genetic reassortment substantially contributes to viral diversification, particularly when multiple influenza subtypes co-circulate. Reassortment between related strains increases genomic variability and enhances viral adaptability (44,45). Intra-subtype reassortment can transfer a drifted HA gene onto a genetically advantageous viral background, as observed during the severe epidemics in the 1946-1947 and 2003-2004 seasons (46,47). Similarly, the emergence of reassortant H1N2 viruses during the 2001-2002 season, which predominated in 41 countries, highlighted the global impact of such events (48,49). Surveillance programs rely on hemagglutination inhibition assays and viral RNA sequencing to monitor antigenic drift in HA and NA (50). Surveillance programs rely on hemagglutination inhibition assays and viral RNA sequencing to monitor these incremental mutations in HA and NA. Greater attention to neuraminidase antigenic drift, assessed through neuraminidase inhibition assays, may improve vaccine-virus matching and enhance vaccine effectiveness (21,51).

Antigenic shift and pandemic potential. In contrast to antigenic drift, antigenic shift involves abrupt and substantial changes in the antigenic properties of influenza A viruses. Such shifts frequently result in the emergence of antigenically novel viruses capable of causing pandemics (52). Pandemic influenza viruses often acquire HA and NA genes from animal reservoirs that are antigenically distinct from circulating human strains (53,54). These shifts may lead to the replacement of previously circulating strains, as observed during the 1957 H2N2 pandemic, which displaced the earlier H1N1 lineage (55).

The 2009 H1N1 pandemic virus provides a contemporary example, having emerged through reassortment among avian, human, and swine influenza viruses (56,57). As illustrated in Fig. 2, antigenic shift generates entirely new viral subtypes, whereas antigenic drift represents gradual genetic evolution that enables pandemic strains to persist as seasonal variants. The figure emphasizes the role of these processes in generating new viral subtypes and sustaining their circulation in humans. A comparison of the influenza A and B viruses is presented in Table I, highlighting the greater variability of influenza A, driven by both drift and shift, and its capacity to cause pandemics, in contrast to influenza B, which undergoes antigenic drift only. Its two lineages, Victoria and Yamagata, are included in quadrivalent vaccines for broader protection.

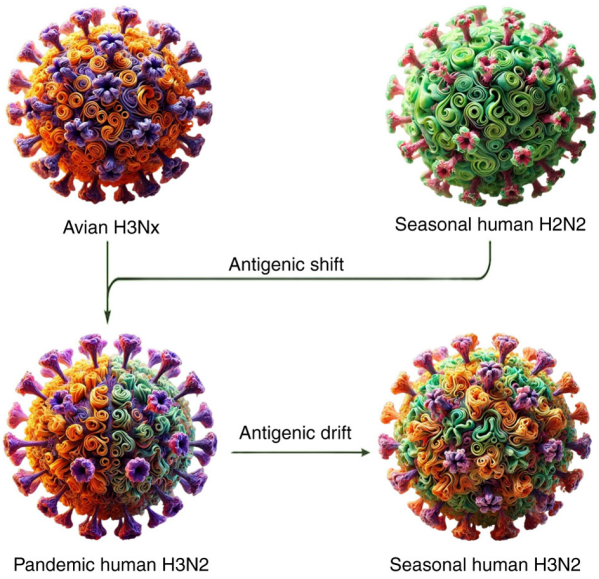

Figure 2. Genetic changes in influenza viruses: Antigenic drift and antigenic shift. The image illustrates the genetic changes in influenza A viruses through antigenic shift and antigenic drift. Avian H3Nx is a subtype of influenza A found in birds, characterized by the H3 hemagglutinin protein and a variety of neuraminidase (N) subtypes. It circulates in wild and domestic birds and occasionally crosses species, posing a potential risk to humans and other animals (160). Seasonal Human H2N2 refers to a subtype that caused the 1957 Asian flu pandemic. This strain, with H2 HA and N2 NA, circulated seasonally until it was replaced by H3N2 in 1968 (161,162). Pandemic human H3N2 emerged in 1968, causing the Hong Kong flu pandemic, and resulted from a reassortment event between avian and human influenza viruses. It continues to circulate seasonally. Seasonal human H3N2 evolved from the 1968 pandemic strain and continues to cause seasonal flu infections, especially affecting vulnerable populations (163,164). NA, neuraminidase; HA, hemagglutinin.

4. Host factors influencing vaccine response

Age-related immune response differences. Despite increasing vaccination coverage over recent decades, influenza-related mortality among older adults remains substantial. Age represents a critical determinant of vaccine responsiveness, particularly in older populations. Reduced vaccine effectiveness contributes to heightened susceptibility to infectious diseases among older adults, largely due to immunosenescence, the age-related decline in immune function (58). Immunosenescence substantially increases susceptibility to infection and disease severity in elderly populations. Age-associated immune deterioration leads to impaired responses to both pathogens and vaccination (59). Both the quantity and functional quality of the T-cell compartment decline with age, correlating with diminished vaccine-induced immune responses in older adults. Effective vaccine-induced recall immunity requires balanced T-cell responses that support both memory formation and high-affinity antibody production. With advancing age, T-cell responses tend to favor transient effector activity rather than durable memory or follicular helper T-cell responses. Consequently, the protective efficacy of vaccine-induced antibodies is often reduced in older adults (60,61). Declining immune integrity leads to reduced resistance to infectious diseases and diminished vaccine effectiveness. Immunosenescence also increases vulnerability to age-associated chronic conditions, including cardiovascular disease and autoimmune disorders (62,63). Age-related reductions in antibody responses to influenza vaccination are closely associated with alterations in T-cell function (64,65). Primary lymphoid organs, including the thymus and bone marrow, undergo involution with age,

Table I. Comparison of influenza A and B.

Feature/aspect	Influenza A (Refs.)	Influenza B (Refs.)
Subtypes/lineages	H1N1, H3N2 (main subtypes) (165)	Victoria lineage, Yamagata lineage (165)
Mechanism of change	- Antigenic drift: Gradual mutations in HA and NA proteins (166,167) - Antigenic shift: Genetic reassortment between strains (pandemics) (166,167)	- Antigenic drift only (166,167) - Lower variability compared to influenza A (165)
Pandemic potential	High due to antigenic shift (166,167) Examples: - 1918 H1N1 Pandemic (Spanish flu) (166) - 1957 H2N2 Pandemic (Asian flu) (166) - 1968 H3N2 Pandemic (Hong Kong flu) (166) - 2009 H1N1 Pandemic (swine flu) (166)	Low Antigenic shift does not occur; no history of pandemics (166,167)
Seasonal impact	Causes major seasonal epidemics with significant mortality and morbidity (165)	Causes seasonal outbreaks, generally milder than Influenza A (168)
Vaccine inclusion	Annual vaccines include: - H1N1 (2009 pandemic strain) - H3N2 subtype (169,170)	Included in quadrivalent vaccines: - Victoria lineage - Yamagata lineage (169-171)
Surveillance	WHO's GISRS monitors circulating strains globally (168,173) - Biannual updates for northern and southern hemispheres (169,172,173)	Part of GISRS monitoring; included to ensure broader protection in vaccines
Examples of reassortment	Genetic reassortment events drive pandemics and diversity (166,167) Example: 2009 H1N1 (swine-origin virus combining swine, human, and avian segments) (167)	Not applicable due to lack of antigenic shift
Historical examples	- 1918 Spanish flu (H1N1) (166) - 1957 Asian flu (H2N2) (166) - 1968 Hong Kong flu (H3N2) (166) - 2009 swine flu pandemic (H1N1) (166)	No historical pandemics; seasonal infections only (166,167)

resulting in reduced naïve lymphocyte production. Ageing is also associated with decreased phagocytic activity and reduced numbers of T- and B-cell progenitors. Chronic antigenic stimulation and increased synthesis of proinflammatory cytokines occur concurrently. Thymic involution significantly reduces the output of naïve T cells, limiting immune adaptability in older adults (66). Thymic activity declines progressively from early life, accompanied by structural changes in thymic epithelial cells (67,68). As a result, the number of naïve T cells entering peripheral circulation decreases with age, reducing immune repertoire diversity (69). Although influenza poses a risk across all age groups, children and older adults remain particularly vulnerable (70). Children may exhibit less mature immune responses, including reduced memory T-cell formation and antibody production compared with adults (71). Vaccinated infants often demonstrate lower vaccine-induced protection, while unvaccinated infants remain at greatest risk of severe influenza-related morbidity (72). Neonates possess relatively immature immune systems, characterized by reduced antigen-presenting cell activity and cytokine production compared with older children and adults (73).

Impact of comorbidities. In addition to immunosenescence, comorbid conditions can further impair immune responses to influenza vaccination (23,74). Comorbidities exert a substantial influence on vaccine-induced immune responses and overall vaccine effectiveness (75,76). Conditions, such as chronic kidney disease, cardiovascular disease, and diabetes mellitus are associated with reduced vaccine immunogenicity (77,78). These conditions can impair macrophage and lymphocyte function, thereby weakening post-vaccination immune responses (78).

Acute infections, including pneumococcal disease and seasonal influenza, are associated with increased morbidity and mortality rates in individuals with cardiovascular disease (79). Evidence suggests that individuals with cardiovascular disease should receive influenza vaccination as part of comprehensive secondary prevention strategies (80). Cardiovascular disease-related immune alterations may influence responses to vaccination and inflammatory stimuli. Influenza vaccination may elicit variable inflammatory responses in individuals with coronary artery disease (81). Influenza vaccination is generally safe in individuals with cardiovascular disease and typically induces protective antibody levels comparable to those in

healthy populations. However, individuals with congestive heart failure may exhibit lower post-vaccination antibody titers despite achieving similar seroconversion rates (80,82).

Obesity represents a key modifier of immune responses to influenza vaccination. Some studies suggest that individuals with overweight initially demonstrate higher serological responses following vaccination compared with individuals of normal weight (79). However, obese individuals may exhibit impaired CD8+ T-cell activation and reduced metabolic responses following vaccination (83). Although individuals with obesity may be more likely to receive influenza vaccination, immune responses may be less robust and less durable (84), however, many overweighed persons show decreased immune responses (innate and adaptive) to the vaccine and thus make the eventuality of vaccination less efficient (83). Obesity has also been shown to be associated with a diminished immune response to the influenza vaccine. Experimental models demonstrate that obesity is associated with reduced neutralizing antibody production and impaired viral clearance following vaccination (85).

Previous exposure and immunity imprinting. Influenza-related morbidity and mortality remain substantial despite repeated seasonal vaccination programs. The effects of repeated and imprinting seasonal influenza vaccinations were examined to assess the processes and immunological variables influencing influenza vaccine responses (86). Pre-existing immunity resulting from prior infection or vaccination can influence responses to subsequent influenza vaccination (87,88), which influences both the quantity and quality of antibodies generated later in life in response to influenza viruses. Antibody responses later in life are often shaped by early childhood exposure to influenza viruses. This phenomenon, currently commonly termed immune imprinting, reflects both beneficial and detrimental effects of immune history on vaccine effectiveness (24). Immune imprinting may preferentially stimulate memory B-cell responses to previously encountered strains while limiting responses to novel variants (23,24).

Repeated annual vaccination may also influence immune responses to subsequent influenza exposure. Some epidemiological studies suggest reduced vaccine effectiveness among individuals vaccinated across multiple consecutive seasons (89). However, other studies report sustained or comparable protection with repeated vaccination, indicating mixed evidence (90,91).

Vaccine immunogenicity remains a central determinant of vaccine effectiveness (92). Repeated immunization may alter the immunogenicity of a vaccine, according to previous research (93). As previously demonstrated, those who had received an influenza vaccine the year before were far less likely to experience seroconversion than those who did not (94). Repetition of the vaccine may reduce its immunogenicity, which may be one reason. Based on research conducted by Sherman *et al* (86), the immune response was found to have a lower fold change after many seasonal influenza vaccinations. Using three different vaccine platforms, researchers found that repeated immunizations had a negative impact on antibody binding, antibody affinity maturation, and hemagglutination inhibition responses to H1N1, H3N2 and B strains (93). Previous findings suggest that repeated vaccination may reduce antibody-secreting cell responses and impair effector B-cell function following subsequent vaccination (95). Proposed to explain the detrimental consequences of several vaccinations is the phenomena of antigenic imprinting.

5. Immunological and molecular mechanisms

Humoral vs. cellular immunity. Influenza vaccines primarily target the hemagglutinin and neuraminidase glycoproteins and function predominantly by eliciting humoral immune responses against these viral surface antigens. Vaccine-induced antibodies play a central role in preventing severe disease by blocking viral entry and enhancing immune clearance through mechanisms such as phagocytosis, complement activation, and antibody-dependent cellular cytotoxicity (96). However, influenza viruses can evade antibody-mediated immunity through rapid mutation, particularly within the receptor-binding region of hemagglutinin. Consequently, vaccine formulations must be updated annually to match circulating strains. Previous studies have indicated that inactivated influenza vaccines demonstrate reduced effectiveness when circulating viral strains differ antigenically from vaccine strains (96,97). By contrast, T-cell-mediated cellular immunity provides an additional layer of protection against influenza infection. $CD8^+$ T-cells contribute to viral clearance by eliminating infected cells, while $CD4^+$ T-cells support antibody production through cytokine-mediated activation of B-cells (98,99). Individuals with impaired humoral immunity, including older adults and immunocompromised patients, rely heavily on cellular immune responses for protection (99). Following natural infection, influenza-specific $CD8^+$ T-cell responses often serve as key correlates of protection due to their breadth and durability (96,98). Current influenza vaccines, however, often elicit relatively weak T-cell responses, limiting the development of robust cellular immunity in a number of recipients (100). Although humoral immunity is frequently prioritized due to the ease of measuring antibody titers, cellular immunity plays an equally critical role in cross-strain protection (97,98). Cellular immune responses target conserved viral epitopes, potentially providing broader and longer-lasting protection against diverse influenza strains (101). In summary, while current influenza vaccines predominantly stimulate humoral immunity, insufficient activation of cellular immunity may limit overall vaccine effectiveness. Future vaccine strategies should aim to induce balanced humoral and cellular responses to enhance durability and breadth of protection (96,97).

Immune evasion by the influenza virus. Influenza A viruses employ multiple strategies to evade detection and clearance by the host immune system (102-104). A defining feature of these viruses is their extensive genetic and antigenic diversity, driven primarily by antigenic drift and antigenic shift. These mechanisms alter viral antigens, reducing recognition by both innate and adaptive immune responses (101-103,105,106). Antigenic drift involves gradual accumulation of point mutations in genes encoding surface glycoproteins such as HA, resulting in reduced antibody binding while maintaining viral fitness. Antigenic shift involves the reassortment of gene

segments between different influenza strains, producing novel viruses with distinct antigenic properties (101,102,104).

The glycosylation of viral surface proteins represents another major immune-evasion mechanism. This process involves the addition of oligosaccharide chains to viral proteins, altering antigenic structure and immune recognition. Glycosylation is also crucial since it may affect HA and NA glycoprotein properties. These proteins are also involved in viral entry and escape. The increased glycosylation of HA, particularly within the globular head region, can mask neutralizing epitopes and reduce antibody binding (102,107). Recent H3N2 isolates demonstrate progressively increased HA glycosylation, suggesting selective pressure favoring enhanced immune evasion (102,107). Thus, by hiding critical regions from the immune system, glycosylation protects viruses from immune evasion.

The innate immune system constitutes the first line of defense against influenza infection, with interferon signaling playing a central role. Influenza viruses have evolved mechanisms to suppress interferon responses, primarily through the activity of the non-structural protein 1 (NS1). NS1 inhibits interferon production and disrupts host antiviral pathways, thereby enhancing viral replication and persistence. NS1 also blocks host gene expression due to pre-messenger ribonucleic acid (mRNA) processing and export of host mRNAs to the nucleus. Additionally, influenza viruses can inhibit protein kinase R and other antiviral signaling pathways, further weakening host defenses (105). At the adaptive immune level, the influenza A virus can avoid the human immune response by antigen drift and antigen shift (105,108). Mutations within viral epitopes recognized by $CD8^+$ T-cells also facilitate escape from cellular immune responses, contributing to sustained transmission (101).

Hypotheses on vaccine-induced immune modulation. Emerging research on vaccine-induced immune modulation highlights the importance of adjuvants and delivery systems in shaping immune memory, durability of protection, and responses to variant strains. Adjuvants can be defined as agents that, administered together with a vaccine, enhance the immune response. They improve immunogenicity and may enhance protection against antigenically variable viruses, such as influenza (109,110). Adjuvants range from simple mineral salts to complex lipid-based or particulate systems. The use of adjuvants in vaccination dates back to early observations that aluminum salts enhance antibody production when combined with antigens. Adjuvants are divided into provisors and delivery means. Adjuvants function by activating innate immune pathways, including Toll-like receptors and other pattern-recognition receptors, thereby promoting adaptive immune responses. Delivery systems improve antigen stability and facilitate targeting to antigen-presenting cells and lymphoid tissues (109).

The adjuvants of a delivery system incorporate the antigen in a carrier, which has a dual function of containing the antigen while also triggering a localized proinflammatory response. This response recruits immune cells to the site of injection, thus enhancing immune activation and memory consolidation. This combination of antigen and adjuvant activates pattern recognition receptor pathways, such as pathogen-associated molecular patterns that are negatively associated with self and positively associated with the production of numerous pro-inflammatory cytokines and chemokines, which in turn activate cells of the innate immune system (111).

Different delivery platforms, including emulsions, nanoparticles and virus-like particles, can substantially influence the magnitude and durability of immune responses. As an adjuvant, aluminum salts are frequently used to enhance immunological response, as well as aid in the retention of the antigen at the injection site, leading to prolonged immune activation. Emulsions like MF59 and AS03 increase the avidity of antigen for immune cells by enhancing their presentation and consequently, the activity of the immune cells, leading to more robust and durable memory of the immune system. The 'modeling' of viruses is crucial in virosomes and virus-like particles which help to amplify immune responses and increase protection against the subsequent infections (111).

As a result of antigenic drift, the surface proteins of the influenza virus are constantly modified. This dilutes the matching correlation between the virus prevalent in circulation and the strain used in the vaccine. This mismatch can diminish the effectiveness of the vaccine in preventing infection (110,112,113). The inclusion of some adjuvants and delivery systems into the vaccines has the potential to improve management of memory immune response, which can aid in controlling different strains of viruses and more generously reduce the chances of breakthrough infections. Thus, providing longer protection. Indeed, adjuvants or vaccination alone cannot guarantee no infection will occur. Despite ongoing challenges, seasonal influenza vaccination remains the most effective strategy for preventing influenza infection and its complications, particularly among high-risk populations (96).

6. Epidemiological and behavioral factors

Vaccine uptake and herd immunity. Influenza is a critical respiratory disease that substantially contributes to global morbidity and mortality. Timely and effective vaccination remains the primary strategy for reducing influenza-related illness and its complications (114). High vaccination coverage contributes to herd immunity, a key factor in controlling the spread of infectious diseases at the population level (115). When a sufficiently large proportion of the population acquires immunity through vaccination or prior infection, transmission can be significantly reduced. Although a precise herd immunity threshold for influenza is difficult to determine due to antigenic variation, a vaccination coverage of approximately 60-80% may be required to reduce transmission substantially (116). Emphasizing the societal benefits of vaccination has been associated with increased uptake. Achieving high vaccination coverage provides both individual protection and indirect protection for the broader community (117). It can also be considered a prosocial act, as it benefits others, by offering both personal and indirect benefits to unvaccinated individuals, including those who are too young, immunocompromised, or unable to be vaccinated (118). Vaccination behaviors are influenced by individual beliefs, perceived norms and the availability of accurate information. Public confidence

in vaccination programs is therefore essential for sustaining herd immunity and improving vaccination coverage (119).

Timing and availability of vaccination. Influenza affects millions of individuals annually and can result in severe complications, hospitalization and death, particularly among high-risk populations (120). In low- and middle-income countries, early vaccination has been shown to reduce influenza cases and associated mortality during pandemic simulations (121). However, the effectiveness of vaccination programs depends not only on timing, but also on distribution capacity, accessibility and healthcare infrastructure. In Europe, multiple manufacturers produce influenza vaccines, and the availability of specific formulations varies by region and procurement policies (122). Vaccine availability in a given location is influenced by licensing, national recommendations, procurement strategies and healthcare delivery systems (123).

As influenza seasonality varies geographically, vaccination schedules must be tailored to regional epidemiological patterns. Regional public health strategies should therefore focus on optimizing vaccination timing and improving access for local populations. To broaden the reach of the preventative strategy, regional protocols may emphasize the need of influenza vaccination in the local population's native language (124).

Of note, two main vaccination approaches are commonly used: Seasonal campaigns aligned with influenza peaks and year-round vaccination strategies in regions without clearly defined influenza seasons. Campaign-based vaccination programs often achieve rapid increases in coverage, particularly during initial implementation. Policymakers should consider local epidemiology, healthcare infrastructure, and population characteristics when selecting optimal vaccination strategies (125).

Vaccine hesitancy and misinformation. Vaccine hesitancy has been identified by the WHO as a major global health challenge (125). Vaccine hesitancy has been observed not only in the general population, but also among healthcare professionals. Healthcare workers play a crucial role in vaccine education, administration and the promotion of public confidence (126). In recent years, vaccine hesitancy has expanded globally, contributing to the resurgence of vaccine-preventable diseases (127). Factors contributing to hesitancy include misinformation, distrust in healthcare systems, and reliance on non-evidence-based information sources (128). Public concerns regarding vaccine safety and effectiveness often intensify during outbreaks and pandemics. This erosion of confidence, commonly termed vaccine hesitancy, represents a significant public health risk affecting both vaccinated and unvaccinated populations (129). Influenza vaccines are generally well tolerated, with the majority of adverse effects being mild and transient, such as injection-site reactions, low-grade fever and myalgia (6). Serious adverse reactions are rare, and extensive post-licensure safety evaluations have confirmed a favorable safety profile for seasonal influenza vaccines (130). Nevertheless, misinformation regarding vaccine safety continues to fuel public concern and reduce vaccination uptake.

7. Recent advances and future directions

Toward a universal influenza vaccine. The capacity of influenza viruses to evade immune responses through rapid mutation has intensified efforts to develop a universal influenza vaccine (128). Conventional vaccines provide limited protection when circulating strains differ antigenically from predicted strains. Universal vaccine strategies aim to confer durable protection against multiple influenza subtypes by targeting conserved viral regions. The HA protein, particularly its conserved stem region, represents a primary target for universal vaccine development (131). The HA stem evolves more slowly than the highly variable globular head, making it an attractive target for broadly neutralizing antibodies. Broadly neutralizing antibodies that bind conserved HA stem epitopes can inhibit viral fusion and provide cross-strain protection (132). Novel approaches, including epitope scaffolding and headless HA constructs, have demonstrated promise in eliciting broadly neutralizing antibodies (133).

Sequential vaccination strategies have also been explored to enhance immune responses to conserved viral epitopes. Incremental exposure to antigenically diverse strains may strengthen cross-protective immunity against multiple influenza subtypes (128,134).

Despite these advances, the development of a universal influenza vaccine remains challenging due to the immune system's tendency to prioritize responses to variable HA head epitopes. Redirecting immune responses toward conserved regions will likely require optimized adjuvants, innovative immunogen design and combinatorial vaccine strategies (135).

Artificial intelligence (AI) approaches are increasingly being applied to identify conserved epitopes and optimize vaccine antigen design. AI-driven models may enhance vaccine formulation and predict vaccine effectiveness across diverse populations. Advances in structural biology continue to reveal novel targets for universal vaccine development (136).

mRNA-based vaccines and adjuvant innovations. mRNA-based vaccines enable host cells to produce viral antigens, thereby stimulating targeted immune responses. Unlike traditional vaccines, mRNA vaccines can be rapidly developed and adapted to emerging viral strains. This flexibility makes mRNA platforms particularly well suited for influenza viruses characterized by rapid antigenic evolution (137,138).

mRNA vaccines have demonstrated the ability to induce both humoral and cellular immune responses, providing comprehensive protection. Experimental mRNA vaccines targeting conserved HA regions have generated broadly neutralizing antibodies capable of cross-protection against multiple strains (139).

Adjuvants are incorporated into vaccines to enhance immunogenicity and improve durability of immune responses. Novel adjuvants are being investigated to improve the magnitude and persistence of immune responses elicited by mRNA influenza vaccines. Lipid nanoparticles used for mRNA delivery also function as adjuvants by promoting cellular uptake and immune activation. Toll-like receptor agonists represent another class of adjuvants under investigation for their ability to enhance vaccine-induced immunity (109,140).

By allowing accurate genomic changes and improved antigen design, clustered regularly interspaced short palindromic repeats

(CRISPR)-Cas9 technology is emerging as a powerful tool for identifying conserved genomic regions and optimizing antigen design in influenza vaccine development. CRISPR-based approaches enable rapid identification of conserved viral targets and facilitate iterative vaccine optimization (141).

The integration of mRNA technology, advanced adjuvants and genome-editing tools provides a promising pathway for next-generation influenza vaccines. Future research is required however, to focus on improving durability of protection, expanding clinical trials across diverse populations and ensuring equitable global access (142).

Improved surveillance and prediction models. Advances in genomic sequencing technologies enable the rapid analysis of influenza virus evolution and mutation patterns. These technologies facilitate the early detection of emerging strains and provide real-time insights into antigenic changes (143,144).

AI models are increasingly used to predict influenza virus evolution and inform vaccine strain selection. Machine-learning algorithms analyze genomic, epidemiological and environmental data to forecast dominant strains for upcoming influenza seasons (145).

Deep-learning techniques can identify subtle genetic patterns associated with antigenic variation. In order to forecast HA and NA alterations that may evade existing vaccinations, convolutional neural networks have been applied as an example (146,147).

Integrating AI-based prediction with genomic surveillance can enhance vaccine strain matching and improve preparedness. Cloud-based technologies facilitate global collaboration by allowing genomic data to be shared among laboratories across the globe. When paired with real-time genetic data, predictive algorithms help bridge the gap between vaccine design and virus evolution (148).

CRISPR-Cas diagnostics facilitate the rapid identification and characterization of influenza viruses, hence aiding in flu surveillance. A CRISPR-based diagnostic instrument known as Specific High Sensitivity Enzymatic Reporter UnLOCKing (SHERLOCK) facilitates real-time monitoring and response strategies through precise detection of viral alterations (141,149).

Integrating real-time genetic data with international health networks is essential for influenza surveillance. Predictive models could be further improved by extending AI algorithms to incorporate more varied variables, such as social and environmental elements. Additionally, a promising path for quick strain identification and vaccine adaption is provided by integrating CRISPR techniques with AI-driven genomic surveillance (150,151). Sustained investment in genomic surveillance, artificial intelligence, and global data-sharing networks will be essential for improving influenza control and vaccine effectiveness.

Policy and public health interventions: Advanced strategies for influenza control. Policy initiatives and public health interventions remain critical for reducing the global burden of influenza. Recent developments in encouraging early immunization, overcoming vaccine reluctance and enhancing accessibility indicate great potential in reducing the prevalence of the flu.

Timely vaccination campaigns, improved accessibility, and targeted communication strategies are essential for preventing outbreaks. To guarantee early and extensive vaccine delivery, governments and health organizations are using measures such as 'flu shot days' and mobile immunization units. Research indicates that programs that offer free vaccines or financial incentives can boost uptake, particularly among underprivileged groups (152,153).

Vaccine hesitancy continues to pose a major barrier to achieving high vaccination coverage. Recent public health campaigns emphasize transparent communication and community engagement to build trust in vaccination programs. It has been demonstrated that using digital tools for public awareness, such as social media, can successfully refute anti-vaccine propaganda. Personalized reminders and encouragement constitute two behavioral science-based strategies that are becoming more popular for promoting vaccination (154,155).

Enhancing the public awareness of influenza risks and the advantages of vaccinations requires educational programs. Programs designed for neighborhood organizations, workplaces and schools to highlight the importance of vaccination in preventing high-risk persons. These approaches reduce logistical hurdles by frequently combining education with vaccine availability at the location of workplaces, schools, or educational institutions (156,157).

Ensuring equitable access to vaccines, particularly in underserved and remote communities, remains a key policy priority. Key steps include setting up immunization centers in remote and underserved locations and using technology to optimize vaccine distribution networks. Vaccines are delivered to disadvantaged and distant communities through collaborations with non-governmental organizations and local authorities (158,159).

Future strategies should integrate digital technologies, predictive modeling, and international collaboration to optimize vaccine distribution and uptake. Incorporating influenza vaccination into routine immunization programs may further normalize and increase coverage.

8. Limitations

The present review has several limitations. As a narrative synthesis, it may be subject to selection bias and does not include formal meta-analysis. Only English-language publications were included, and the rapidly evolving nature of influenza vaccine technologies and AI-based prediction models means that new evidence may emerge following publication. Nevertheless, efforts were made to include recent high-quality studies and authoritative public-health sources to provide a balanced overview of current knowledge.

9. Conclusion

The prevention of seasonal influenza through vaccination remains a complex challenge influenced by viral evolution, host-related factors, vaccine composition and epidemiological dynamics. Despite advances, such as quadrivalent vaccine formulations, the overall effectiveness of influenza vaccination programs remains constrained by the rapid and continuous evolution of influenza viruses.

Antigenic drift remains one of the most significant threats to vaccine performance, as structural changes in viral surface proteins, particularly HA and NA, can reduce the effectiveness of pre-existing immunity. Vaccine-induced protection is also influenced by host-related factors, including immunosenescence, comorbidities and immune imprinting, which contribute to heterogeneous immune responses across populations. The majority of currently available influenza vaccines predominantly induce humoral immune responses, with comparatively limited activation of cellular immunity, which is essential for broader and longer-lasting protection. Beyond biological constraints, vaccine uptake is negatively affected by misinformation, limited access and distrust in public health systems. Nevertheless, emerging technological innovations, including mRNA-based vaccines, novel adjuvants, AI-driven prediction models and universal vaccine strategies, provide promising opportunities to enhance influenza prevention. Achieving meaningful reductions in influenza burden will require coordinated global efforts involving technological innovation, equitable vaccine distribution, public trust, and sustained collaboration between governments, healthcare institutions and communities.

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DHMA and DHB conceptualized and designed the study. All authors (DHMA, DHB, HHK, BRA, SHS, AAA, SKA and RRQ) contributed to writing, literature review and manuscript revision. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

References

1. No authors listed: Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 48: 1-28, 1999.
2. Mancini P, Brandtner D, Veneri C, Bonanno Ferraro G, Iaconelli M, Puzelli S, Facchini M, Di Mario G, Stefanelli P, Lucentini L, *et al*: Evaluation of trends in influenza A and B viruses in wastewater and human surveillance data: Insights from the 2022-2023 season in Italy. Food Environ Virol 17: 6, 2024.
3. Weinberger DM, Harboe ZB, Viboud C, Krause TG, Miller M, Mølbak K and Konradsen HB: Pneumococcal disease seasonality: Incidence, severity and the role of influenza activity. Eur Respir J 43: 833-841, 2014.
4. Owuor DC, de Laurent ZR, Nyawanda BO, Emukule GO, Kondor R, Barnes JR, Nokes DJ, Agoti CN and Chaves SS: Genetic and potential antigenic evolution of influenza A (H1N1) pdm09 viruses circulating in Kenya during 2009-2018 influenza seasons. Sci Rep 13: 22342, 2023.
5. Wang X, Kulkarni D, Dozier M, Hartnup K, Paget J, Campbell H and Nair H; Usher Network for COVID-19 Evidence Reviews (UNCOVER) group: Influenza vaccination strategies for 2020-21 in the context of COVID-19. J Glob Health 10: 020310, 2020.
6. Grohskopf LA, Blanton LH, Ferdinands JM, Chung JR, Broder KR and Talbot HK: Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023-24 Influenza Season. MMWR Recomm Rep 72 (No. RR-2):1-25, 2023. DOI: http://dx.doi.org/10.15585/mmwr.rr7202a1.
7. Flannery B, Clippard J, Zimmerman RK, Nowalk MP, Jackson ML, Jackson LA, Monto AS, Petrie JG, McLean HQ, Belongia EA, *et al*: Early estimates of seasonal influenza vaccine effectiveness-United States, January 2015. MMWR Morb Mortal Wkly Rep 64: 10-15, 2015.
8. Huddleston J and Bedford T: Timely vaccine strain selection and genomic surveillance improves evolutionary forecast accuracy of seasonal influenza A/H3N2. medRxiv: doi: 10.1101/2024.09.11.24313489.
9. Kim H, Webster RG and Webby RJ: Influenza virus: Dealing with a drifting and shifting pathogen. Viral Immunol 31: 174-183, 2018.
10. Mosa AI: Antigenic variability. Front Immunol 11: 2057, 2020.
11. Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, Chen MH, Tashkandi M, Bauch CT and Loeb M: Comparing influenza vaccine efficacy against mismatched and matched strains: A systematic review and meta-analysis. BMC Med 11: 153, 2013.
12. Trombetta CM, Kistner O, Montomoli E, Viviani S and Marchi S: Influenza viruses and vaccines: The role of vaccine effectiveness studies for evaluation of the benefits of influenza vaccines. Vaccines (Basel) 10: 714, 2022.
13. Xie H, Wan XF, Ye Z, Plant EP, Zhao Y, Xu Y, Li X, Finch C, Zhao N, Kawano T, *et al*: H3N2 mismatch of 2014-15 Northern hemisphere influenza vaccines and head-to-head comparison between human and ferret antisera derived antigenic maps. Sci Rep 5: 15279, 2015.
14. Steel J and Lowen AC: Influenza A virus reassortment. Curr Top Microbiol Immunol 385: 377-401, 2014.
15. Harrington WN, Kackos CM and Webby RJ: The evolution and future of influenza pandemic preparedness. Exp Mol Med 53: 737-749, 2021.
16. Amorij JP, Huckriede A, Wilschut J, Frijlink HW and Hinrichs WL: Development of stable influenza vaccine powder formulations: Challenges and possibilities. Pharm Res 25: 1256-1273, 2008.
17. Wolk DM, Lanyado A, Tice AM, SherMohammed M, Kinar Y, Goren A, Chabris CF, Meyer MN, Shoshan A and Abedi V: Prediction of influenza complications: development and validation of a machine learning prediction model to improve and expand the identification of vaccine-hesitant patients at risk of severe influenza complications. J Clin Med 11: 4342, 2022.
18. Sparrow E, Wood JG, Chadwick C, Newall AT, Torvaldsen S, Moen A and Torelli G: Global production capacity of seasonal and pandemic influenza vaccines in 2019. Vaccine 39: 512-520, 2021.
19. Carregaro RL, Roscani ANCP, Raimundo ACS, Ferreira L, Vanni T, Da Graça Salomão M, Probst LF and Viscondi JYK: Immunogenicity and safety of inactivated quadrivalent influenza vaccine compared with the trivalent vaccine for influenza infection: an overview of systematic reviews. BMC Infect Dis 23: 563, 2023.
20. Osterhaus A, Fouchier R and Rimmelzwaan G: Towards universal influenza vaccines? Philos Trans R Soc Lond B Biol Sci 366: 2766-2773, 2011.

21. Wang Y, Tang CY and Wan XF: Antigenic characterization of influenza and SARS-CoV-2 viruses. Anal Bioanal Chem 414: 2841-2881, 2022.
22. Lord JM: The effect of aging of the immune system on vaccination responses. Hum Vaccin Immunother 9: 1364-1367, 2013.
23. Dhakal S and Klein SL: Host factors impact vaccine efficacy: Implications for seasonal and universal influenza vaccine programs. J Virol 93: e00797-19, 2019.
24. Henry C, Palm AK, Krammer F and Wilson PC: From original antigenic sin to the universal influenza virus vaccine. Trends Immunol 39: 70-79, 2018.
25. Nafziger AN and Pratt DS: Seasonal influenza vaccination and technologies. J Clin Pharmacol 54: 719-731, 2014.
26. Petrova VN and Russell CA: The evolution of seasonal influenza viruses. Nat Rev Microbiol 16: 47-60, 2018.
27. Gaymard A, Le Briand N, Frobert E, Lina B and Escuret V: Functional balance between neuraminidase and haemagglutinin in influenza viruses. Clin Microbiol Infect 22: 975-983, 2016.
28. De Vries E, Du W, Guo H and de Haan CAM: Influenza A virus hemagglutinin-neuraminidase-receptor balance: preserving virus motility. Trends Microbiol 28: 57-67, 2020.
29. Xu R and Wilson IA: Structural characterization of an early fusion intermediate of influenza virus hemagglutinin. J Virol 85: 5172-5182, 2011.
30. Swanson N: Characterization of in vitro fitness and antigenic drift differences between circulating H1N1 influenza clades (unpublished thesis). Johns Hopkins University, 2024.
31. Qiu Y, Stegalkina S, Zhang J, Boudanova E, Park A, Zhou Y, Prabakaran P, Pougatcheva S, Ustyugova IV, Vogel TU, *et al*: Mapping of a novel H3-specific broadly neutralizing monoclonal antibody targeting the hemagglutinin globular head isolated from an elite influenza virus-immunized donor exhibiting serological breadth. J Virol 94: e01035-19, 2020.
32. Tsuchiya E, Sugawara K, Hongo S, Matsuzaki Y, Muraki Y, Li ZN and Nakamura K: Antigenic structure of the haemagglutinin of human influenza A/H2N2 virus. J Gen Virol 82 (Pt 10): 2475-2484, 2001.
33. Wiley DC, Wilson IA and Skehel JJ: Structural identification of the antibody-binding sites of Hong Kong influenza haemagglutinin and their involvement in antigenic variation. Nature 289: 373-378, 1981.
34. Gerhard W, Yewdell J, Frankel ME and Webster R: Antigenic structure of influenza virus haemagglutinin defined by hybridoma antibodies. Nature 290: 713-717, 1981.
35. Baxter D: Evaluating the case for trivalent or quadrivalent influenza vaccines. Hum Vaccin Immunother 12: 2712-2717, 2016.
36. Daniels RS and McCauley JW: The health of influenza surveillance and pandemic preparedness in the wake of the COVID-19 pandemic. J Gen Virol 104: 001822, 2023.
37. World Health Organization (WHO): Sixth Meeting of National Influenza Centres and Influenza Surveillance in the Western Pacific and South-East Asia Regions, Hanoi, Viet Nam, 29-31 May 2012: Meeting report. WHO, Geneva, 2012.
38. Sánchez de Prada L: Humoral immune response after seasonal influenza vaccination (unpublished thesis). University of Valladolid, 2023.
39. Graham BS: Advances in antiviral vaccine development. Immunol Rev 255: 230-242, 2013.
40. Altman MO, Angeletti D and Yewdell JW: Antibody immunodominance: The key to understanding influenza virus antigenic drift. Viral Immunol 31: 142-149, 2018.
41. Tjärnhage E: Exploring the field of respiratory virus preventions: How to deal with future pandemics (unpublished thesis). University of Oslo, 2024.
42. Dunning J, Thwaites RS and Openshaw PJM: Seasonal and pandemic influenza: 100 years of progress, still much to learn. Mucosal Immunol 13: 566-573, 2020.
43. Volz EM, Koelle K and Bedford T: Viral phylodynamics. PLoS Comput Biol 9: e1002947, 2013.
44. White MC and Lowen AC: Implications of segment mismatch for influenza A virus evolution. J Gen Virol 99: 3-16, 2018.
45. Yong OX: Epidemiological and evolutionary dynamics of influenza B viruses in Kuala Lumpur, Malaysia between 2012 and 2014. MSc thesis, University of Malaya, 2016.
46. Holmes EC, Ghedin E, Miller N, Taylor J, Bao Y, St George K, Grenfell BT, Salzberg SL, Fraser CM, Lipman DJ and Taubenberger JK: Whole-genome analysis of human influenza A virus reveals multiple persistent lineages and reassortment among recent H3N2 viruses. PLoS Biol 3: e300, 2005.
47. Nelson MI, Viboud C, Simonsen L, Bennett RT, Griesemer SB, St George K, Taylor J, Spiro DJ, Sengamalay NA, Ghedin E, *et al*: Multiple reassortment events in the evolutionary history of H1N1 influenza A virus since 1918. PLoS Pathog 4: e1000012, 2008.
48. Ellis JS, Alvarez-Aguero A, Gregory V, Lin YP, Hay A and Zambon MC: Influenza A H1N2 viruses, United Kingdom, 2001-02 influenza season. Emerg Infect Dis 9: 304-310, 2003.
49. Hsieh YH, Huang HM and Lan YC: On temporal patterns and circulation of influenza virus strains in Taiwan, 2008-2014: Implications of 2009 pH1N1 pandemic. PLoS One 11: e0154695, 2016.
50. Xu X, Smith CB, Mungall BA, Lindstrom SE, Hall HE, Subbarao K, Cox NJ and Klimov A: Intercontinental circulation of human influenza A (H1N2) reassortant viruses during the 2001-2002 influenza season. J Infect Dis 186: 1490-1493, 2002.
51. Wong SS and Webby RJ: Traditional and new influenza vaccines. Clin Microbiol Rev 26: 476-492, 2013.
52. Eichelberger MC and Monto AS: Neuraminidase, the forgotten surface antigen, emerges as an influenza vaccine target for broadened protection. J Infect Dis 219 (Suppl 1): S75-S80, 2019.
53. Shoham D: The modes of evolutionary emergence of primal and late pandemic influenza virus strains from viral reservoir in animals: An interdisciplinary analysis. Influenza Res Treat 2011: 861792, 2011.
54. Van Reeth K and Vincent AL: Influenza viruses. In: Diseases of Swine. 10th edition. Wiley-Blackwell, Hoboken, NJ, pp576-593, 2019.
55. Webster RG: Antigenic variation in influenza viruses. In: Origin and Evolution of Viruses. Elsevier, pp377-401, 1999.
56. Gatherer D: The 2009 H1N1 influenza outbreak in its historical context. J Clin Virol 45: 174-178, 2009.
57. Bush RM and Cox NJ: Influenza evolution. In: Infectious Disease and Host-Pathogen Evolution. Dronamraju KR (ed). Cambridge University Press, pp175-197, 2004.
58. Patriarca PA and Cox NJ: Influenza pandemic preparedness plan for the United States. J Infect Dis 176 (Suppl 1): S4-S7, 1997.
59. Chen L, Shao C, Li J and Zhu F: Impact of immunosenescence on vaccine immune responses and countermeasures. Vaccines (Basel) 12: 1289, 2024.
60. Frasca D, Blomberg BB, Garcia D, Keilich SR and Haynes L: Age-related factors that affect B cell responses to vaccination in mice and humans. Immunol Rev 296: 142-154, 2020.
61. Gustafson CE, Kim C, Weyand CM and Goronzy JJ: Influence of immune aging on vaccine responses. J Allergy Clin Immunol 145: 1309-1321, 2020.
62. Dugan HL, Henry C and Wilson PC: Aging and influenza vaccine-induced immunity. Cell Immunol 348: 103998, 2020.
63. Aiello A, Farzaneh F, Candore G, Caruso C, Davinelli S, Gambino CM, Ligotti ME, Zareian N and Accardi G: Immunosenescence and its hallmarks: How to oppose aging strategically? A review of potential options for therapeutic intervention. Front Immunol 10: 2247, 2019.
64. Müller L, Andrée M, Moskorsz W, Drexler I, Walotka L, Grothmann R, Ptok J, Hillebrandt J, Ritchie A, Rabl D, *et al*: Age-dependent immune response to the Biontech/Pfizer BNT162b2 coronavirus disease 2019 vaccination. Clin Infect Dis 73: 2065-2072, 2021.
65. Mosterín Höpping A, McElhaney J, Fonville JM, Powers DC, Beyer WEP and Smith DJ: The confounded effects of age and exposure history in response to influenza vaccination. Vaccine 34: 540-546, 2016.
66. Saurwein-Teissl M, Lung TL, Marx F, Gschoesser C, Asch E, Blasko I, Parson W, Böck G, Schönitzer D, Trannoy E and Grubeck-Loebenstein B: Lack of antibody production following immunization in old age: Association with CD8(+)CD28(–) T cell clonal expansions and imbalance in Th1/Th2 cytokine production. J Immunol 168: 5893-5899, 2002.
67. Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C and Medaglini D: Vaccination in the elderly: The challenge of immune changes with aging. Semin Immunol 40: 83-94, 2018.
68. Nikolich-Žugich J: Aging of the T cell compartment in mice and humans: From no naive expectations to foggy memories. J Immunol 193: 2622-2629, 2014.
69. Barbouti A, Vasileiou PVS, Evangelou K, Vlasis KG, Papoudou-Bai A, Gorgoulis VG and Kanavaros P: Implications of oxidative stress and cellular senescence in age-related thymus involution. Oxid Med Cell Longev 2020: 7986071, 2020.
70. Fink PJ: The biology of recent thymic emigrants. Annu Rev Immunol 31: 31-50, 2013.

71. Ruf BR and Knuf M: The burden of seasonal and pandemic influenza in infants and children. Eur J Pediatr 173: 265-276, 2014.
72. Sakala IG, Eichinger KM and Petrovsky N: Neonatal vaccine effectiveness and the role of adjuvants. Expert Rev Clin Immunol 15: 869-878, 2019.
73. Rudd BD: Neonatal T cells: A reinterpretation. Annu Rev Immunol 38: 229-247, 2020.
74. Zhang X, Zhivaki D and Lo-Man R: Unique aspects of the perinatal immune system. Nat Rev Immunol 17: 495-507, 2017.
75. Andrew MK, Pott H, Staadegaard L, Paget J, Chaves SS, Ortiz JR, McCauley J, Bresee J, Nunes MC, Baumeister E, *et al*: Age differences in comorbidities, presenting symptoms, and outcomes of influenza illness requiring hospitalization: A worldwide perspective from the global influenza hospital surveillance network. Open Forum Infect Dis 10: ofad244, 2023.
76. Magyari M and Sorensen PS: Comorbidity in multiple sclerosis. Front Neurol 11: 851, 2020.
77. Xu Q, Wei H, Wen S, Chen J, Lei Y, Cheng Y, Huang W, Wang D and Shu Y: Factors affecting the immunogenicity of influenza vaccines in humans. BMC Infect Dis 23: 211, 2023.
78. Prendecki M, Clarke C, Brown J, Cox A, Gleeson S, Guckian M, Randell P, Pria AD, Lightstone L, Xu XN, *et al*: Effect of previous SARS-CoV-2 infection on humoral and T-cell responses to single-dose BNT162b2 vaccine. Lancet 397: 1178-1181, 2021.
79. Kwetkat A and Heppner HJ: Comorbidities in the elderly and their possible influence on vaccine response. Interdiscip Top Gerontol Geriatr 43: 73-85, 2020.
80. Li Y, Cao GY, Jing WZ, Liu J and Liu M: Global trends and regional differences in incidence and mortality of cardiovascular disease, 1990-2019: Findings from the 2019 global burden of disease study. Eur J Prev Cardiol 30: 276-286, 2023.
81. Frasca D and Blomberg BB: B cell function and influenza vaccine responses in healthy aging and disease. Curr Opin Immunol 29: 112-118, 2014.
82. Werba JP, Veglia F, Amato M, Baldassarre D, Massironi P, Meroni PL, Riboldi P, Tremoli E and Camera M: Patients with a history of stable or unstable coronary heart disease have different acute phase responses to an inflammatory stimulus. Atherosclerosis 196: 835-840, 2008.
83. Callahan ST, Wolff M, Hill HR and Edwards KM; NIAID Vaccine and Treatment Evaluation Unit (VTEU) Pandemic H1N1 Vaccine Study Group: Impact of body mass index on immunogenicity of pandemic H1N1 vaccine in children and adults. J Infect Dis 210: 1270-1274, 2014.
84. Honce R and Schultz-Cherry S: Impact of obesity on influenza A virus pathogenesis, immune response, and evolution. Front Immunol 10: 1071, 2019.
85. Harris JA, Moniz MH, Iott B, Power R and Griggs JJ: Obesity and the receipt of influenza and pneumococcal vaccination: A systematic review and meta-analysis. BMC Obes 3: 24, 2016.
86. Sherman AC, Lai L, Bower M, Natrajan MS, Huerta C, Karmali V, Kleinhens J, Xu Y, Rouphael N and Mulligan MJ: The effects of imprinting and repeated seasonal influenza vaccination on adaptive immunity after influenza vaccination. Vaccines (Basel) 8: 663, 2020.
87. Cobey S and Hensley SE: Immune history and influenza virus susceptibility. Curr Opin Virol 22: 105-111, 2017.
88. Jang H and Ross TM: Preexisting influenza-specific immunity and vaccine effectiveness. Expert Rev Vaccines 18: 1043-1051, 2019.
89. McLean HQ, Thompson MG, Sundaram ME, Meece JK, McClure DL, Friedrich TC and Belongia EA: Impact of repeated vaccination on vaccine effectiveness against influenza A (H3N2) and B during 8 seasons. Clin Infect Dis 59: 1375-1385, 2014.
90. Bartoszko JJ, McNamara IF, Aras OAZ, Hylton DA, Zhang YB, Malhotra D, Hyett SL, Morassut RE, Rudziak P and Loeb M: Does consecutive influenza vaccination reduce protection against influenza: A systematic review and meta-analysis. Vaccine 36: 3434-3444, 2018.
91. Zelner J, Petrie JG, Trangucci R, Martin ET and Monto AS: Effects of sequential influenza A (H1N1)pdm09 vaccination on antibody waning. J Infect Dis 220: 12-19, 2019.
92. Chen JR, Liu YM, Tseng YC and Ma C: Better influenza vaccines: An industry perspective. J Biomed Sci 27: 33, 2020.
93. Grohskopf LA, Alyanak E, Broder KR, Blanton LH, Fry AM, Jernigan DB and Atmar RL: 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 69: 1-24, 2020.
94. Rolfes MA, Flannery B, Chung JR, O'Halloran A, Garg S, Belongia EA, Gaglani M, Zimmerman RK, Jackson ML, Monto AS, *et al*: Effects of influenza vaccination in the United States during the 2017-2018 influenza season. Clin Infect Dis 69: 1845-1853, 2019.
95. McElhaney JE, Kuchel GA, Zhou X, Swain SL and Haynes L: T-cell immunity to influenza in older adults: A pathophysiological framework for development of more effective vaccines. Front Immunol 7: 41, 2016.
96. Janssens Y, Joye J, Waerlop G, Clement F, Leroux-Roels G and Leroux-Roels I: The role of cell-mediated immunity against influenza and its implications for vaccine evaluation. Front Immunol 13: 959379, 2022.
97. Tsang TK, Lam KT, Liu Y, Fang VJ, Mu X, Leung NHL, Peiris JM, Leung GM, Cowling BJ and Tu W: Investigation of CD4 and CD8 T cell-mediated protection against influenza A virus in a cohort study. BMC Med 20: 230, 2022.
98. L'Huillier AG, Ferreira VH, Hirzel C, Nellimarla S, Ku T, Natori Y, Humar A and Kumar D: T-cell responses following natural influenza infection or vaccination in solid organ transplant recipients. Sci Rep 10: 10104, 2020.
99. Velasco-Medina AA, García-León ML, Velázquez-Sámano G and Wong-Chew RM: The cellular and humoral immune response to influenza vaccination is comparable in asthmatic and healthy subjects. Hum Vaccin Immunother 17: 98-105, 2021.
100. Rosendahl Huber SK, Hendriks M, Jacobi RHJ, van de Kassteele J, Mandersloot-Oskam JC, van Boxtel RAJ, Wensing AMJ, Rots NY, Luytjes W and van Beek J: Immunogenicity of influenza vaccines: Evidence for differential effect of secondary vaccination on humoral and cellular immunity. Front Immunol 9: 3103, 2019.
101. Quiñones-Parra S, Loh L, Brown LE, Kedzierska K and Valkenburg SA: Universal immunity to influenza must outwit immune evasion. Front Microbiol 5: 285, 2014.
102. Schmolke M and García-Sastre A: Evasion of innate and adaptive immune responses by influenza A virus. Cell Microbiol 12: 873-880, 2010.
103. Rashid F, Xie Z, Li M, Xie Z, Luo S and Xie L: Roles and functions of IAV proteins in host immune evasion. Front Immunol 14: 1323560, 2023.
104. Hale BG, Albrecht RA and García-Sastre A: Innate immune evasion strategies of influenza viruses. Future Microbiol 5: 23-41, 2010.
105. Van de Sandt CE, Kreijtz JH and Rimmelzwaan GF: Evasion of influenza A viruses from innate and adaptive immune responses. Viruses 4: 1438-1476, 2012.
106. Hsu ACY: Influenza virus: A master tactician in innate immune evasion and novel therapeutic interventions. Front Immunol 9: 743, 2018.
107. Kim P, Jang YH, Kwon SB, Lee CM, Han G and Seong BL: Glycosylation of hemagglutinin and neuraminidase of influenza A virus as signature for ecological spillover and adaptation among influenza reservoirs. Viruses 10: 183, 2018.
108. Su G, Chen Y, Li X and Shao JW: Virus versus host: Influenza A virus circumvents the immune responses. Front Microbiol 15: 1394510, 2024.
109. Zhao T, Cai Y, Jiang Y, He X, Wei Y, Yu Y and Tian X: Vaccine adjuvants: mechanisms and platforms. Signal Transduct Target Ther 8: 283, 2023.
110. Shichinohe S and Watanabe T: Advances in adjuvanted influenza vaccines. Vaccines (Basel) 11: 1391, 2023.
111. Facciolà A, Visalli G, Laganà A and Di Pietro A: An overview of vaccine adjuvants: Current evidence and future perspectives. Vaccines (Basel) 10: 819, 2022.
112. Li Z, Zhao Y, Li Y and Chen X: Adjuvantation of influenza vaccines to induce cross-protective immunity. Vaccines (Basel) 9: 75, 2021.
113. Chan L, Alizadeh K, Alizadeh K, Fazel F, Kakish JE, Karimi N, Knapp JP, Mehrani Y, Minott JA, Morovati S, *et al*: Review of influenza virus vaccines: the qualitative nature of immune responses to infection and vaccination is a critical consideration. Vaccines (Basel) 9: 979, 2021.
114. Zanobini P, Bonaccorsi G, Lorini C, Haag M, McGovern I, Paget J and Caini S: Global patterns of seasonal influenza activity, duration of activity and virus (sub)type circulation from 2010 to 2020. Influenza Other Respir Viruses 16: 696-706, 2022.
115. Yadegari I, Omidi M and Smith SR: The herd-immunity threshold must be updated for multi-vaccine strategies and multiple variants. Sci Rep 11: 22970, 2021.

116. Plans-Rubió P: The vaccination coverage required to establish herd immunity against influenza viruses. Prev Med 55: 72-77, 2012.
117. Jung H and Albarracín D: Concerns for others increase the likelihood of vaccination against influenza and COVID-19 more in sparsely rather than densely populated areas. Proc Natl Acad Sci USA 118: e2007538118, 2021.
118. Böhm R and Betsch C: Prosocial vaccination. Curr Opin Psychol 43: 307-311, 2022.
119. Al-Hasan A, Khuntia J and Yim D: Does seeing what others do through social media influence vaccine uptake and help in the herd immunity through vaccination? A cross-sectional analysis. Front Public Health 9: 715931, 2021.
120. Froes F, Timóteo A, Almeida B, Raposo JF, Oliveira J, Carrageta M, Duque S and Morais A: Influenza vaccination in older adults and patients with chronic disorders: A position paper from the Portuguese Society of Pulmonology, the Portuguese Society of Cardiology, the Portuguese Society of Diabetology, the Portuguese Society of Infectious Diseases and Clinical Microbiology, the Portuguese Society of Geriatrics and Gerontology, and the Study Group of Geriatrics of the Portuguese Society of Internal Medicine. Pulmonology 30: 422-436, 2024.
121. Lutz CS, Biggerstaff M, Rolfes MA, Lafond KE, Azziz-Baumgartner E, Porter RM, Reed C and Bresee JS: Estimating the number of averted illnesses and deaths as a result of vaccination against an influenza pandemic in nine low-and middle-income countries. Vaccine 39: 4219-4230, 2021.
122. Stuurman AL, Rizzo C and Haag M: Investigating the procurement system for understanding seasonal influenza vaccine brand availability in Europe. PLoS One 16: e0248943, 2021.
123. Dhar R, Ghoshal AG, Guleria R, Sharma S, Kulkarni T, Swarnakar R, Samaria JK, Chaudhary S, Gaur SN, Christopher DJ, *et al*: Clinical practice guidelines 2019: Indian consensus-based recommendations on influenza vaccination in adults. Lung India 37 (Supplement): S4-S18, 2020.
124. Igboh LS, Roguski K, Marcenac P, Emukule GO, Charles MD, Tempia S, Herring B, Vandemaele K, Moen A, Olsen SJ, *et al*: Timing of seasonal influenza epidemics for 25 countries in Africa during 2010-19: A retrospective analysis. Lancet Glob Health 11: e729-e739, 2023.
125. Yoon D, Kim JH, Lee H and Shin JY: Updates on vaccine safety and post-licensure surveillance for adverse events following immunization in South Korea, 2005-2017. Yonsei Med J 61: 623-630, 2020.
126. Cuschieri S and Grech V: A comparative assessment of attitudes and hesitancy for influenza vis-à-vis COVID-19 vaccination among healthcare students and professionals in Malta. Z Gesundh Wiss 30: 2441-2448, 2022.
127. Wang SY, Pan XJ, Deng X, Zhang HJ and Chen ZP: An exploratory framework of vaccine hesitancy monitoring and early warning system in China. Zhonghua Yu Fang Yi Xue Za Zhi 55: 925-930, 2021 (In Chinese).
128. Lim CML, Komarasamy TV, Adnan NAAB, Radhakrishnan AK and Balasubramaniam VR: Recent advances, approaches and challenges in the development of universal influenza vaccines. Influenza Other Respir Viruses 18: e13276, 2024.
129. World Health Organization (WHO): SAGE working group on vaccine hesitancy: Report. WHO, Geneva, 2024. https://www.who.int/docs/default-source/immunization/sage/2014/october/sage-working-group-revised-report-vaccine-hesitancy.pdf.
130. Osterholm MT, Kelley NS, Sommer A and Belongia EA: Efficacy and effectiveness of influenza vaccines: A systematic review and meta-analysis. Lancet Infect Dis 12: 36-44, 2012.
131. Bullard BL and Weaver EA: Strategies targeting hemagglutinin as a universal influenza vaccine. Vaccines (Basel) 9: 257, 2021.
132. Mader K and Dustin LB: Beyond bNAbs: Uses, risks, and opportunities for therapeutic application of non-neutralising antibodies in viral infection. Antibodies (Basel) 13: 28, 2024.
133. Fu Y, Zhang Z, Sheehan J, Avnir Y, Ridenour C, Sachnik T, Sun J, Hossain MJ, Chen LM, Zhu Q, *et al*: A broadly neutralizing anti-influenza antibody reveals ongoing capacity of haemagglutinin-specific memory B cells to evolve. Nat Commun 7: 12780, 2016.
134. Krammer F, Palese P and Steel J: Advances in universal influenza virus vaccine design and antibody mediated therapies based on conserved regions of the hemagglutinin. Curr Top Microbiol Immunol 386: 301-321, 2015.
135. Aartse A, Mortier D, Mooij P, Hofman S, van Haaren MM, Corcoran M, Karlsson Hedestam GB, Eggink D, Claireaux M, Bogers WMJM, *et al*: Primary antibody response after influenza virus infection is first dominated by low-mutated HA-stem antibodies followed by higher-mutated HA-head antibodies. Front Immunol 13: 1026951, 2022.
136. Qiu X, Duvvuri VR and Bahl J: Computational approaches and challenges to developing universal influenza vaccines. Vaccines (Basel) 7: 45, 2019.
137. Jackson NAC, Kester KE, Casimiro D, Gurunathan S and DeRosa F: The promise of mRNA vaccines: A biotech and industrial perspective. NPJ Vaccines 5: 11, 2020.
138. Petsch B, Schnee M, Vogel AB, Lange E, Hoffmann B, Voss D, Schlake T, Thess A, Kallen KJ, Stitz L, *et al*: Protective efficacy of in vitro synthesized, specific mRNA vaccines against influenza A virus infection. Nat Biotechnol 30: 1210-1216, 2012.
139. Park HJ, Bang YJ, Kwon SP, Kwak W, Park SI, Roh G, Bae SH, Kim JY, Kwak HW, Kim Y, *et al*: Analyzing immune responses to varied mRNA and protein vaccine sequences. NPJ Vaccines 8: 84, 2023.
140. Huang J, Yuen D, Mintern JD and Johnston AP: Opportunities for innovation: Building on the success of lipid nanoparticle vaccines. Curr Opin Colloid Interface Sci 55: 101468, 2021.
141. Teng M, Yao Y, Nair V and Luo J: Latest advances of virology research using CRISPR/Cas9-based gene-editing technology and its application to vaccine development. Viruses 13: 779, 2021.
142. Al Fayez N, Nassar MS, Alshehri AA, Alnefaie MK, Almughem FA, Alshehri BY, Alawad AO and Tawfik EA: Recent advancement in mRNA vaccine development and applications. Pharmaceutics 15: 1972, 2023.
143. Chauhan RP and Gordon ML: Review of genome sequencing technologies in molecular characterization of influenza A viruses in swine. J Vet Diagn Invest 34: 177-189, 2022.
144. Gong X, Hu M, Chen W, Yang H, Wang B, Yue J, Jin Y, Liang L and Ren H: Reassortment network of influenza A virus. Front Microbiol 12: 793500, 2021.
145. Zhao AP, Li S, Cao Z, Hu PJH, Wang J, Xiang Y, Xie D and Lu X: AI for science: predicting infectious diseases. J Saf Sci Resil 5: 130-146, 2024.
146. Danchin A: Artificial intelligence-based prediction of pathogen emergence and evolution in the world of synthetic biology. Microb Biotechnol 17: e70014, 2024.
147. Mohamed T, Sayed S, Salah A and Houssein EH: Deep neural network for virus mutation prediction: A comprehensive review. In: Integrating Meta-Heuristics and Machine Learning for Real-World Optimization Problems. Studies in Computational Intelligence. Houssein EH, Abd Elaziz M, Oliva D and Abualigah L (eds). Vol 1038. Springer, Cham, 2022.
148. Gong M, Liu L, Sun X, Yang Y, Wang S and Zhu H: Cloud-based system for effective surveillance and control of COVID-19: useful experiences from Hubei, China. J Med Internet Res 22: e18948, 2020.
149. Mustafa MI and Makhawi AM: SHERLOCK and DETECTR: CRISPR-Cas systems as potential rapid diagnostic tools for emerging infectious diseases. J Clin Microbiol 59: e00745-20, 2021.
150. Kulkarni A, Tanga S, Karmakar A, Hota A and Maji B: CRISPR-based precision molecular diagnostics for disease detection and surveillance. ACS Appl Bio Mater 6: 3927-3945, 2023.
151. Umar Ibrahim A, Pwavodi PC, Ozsoz M, Al-Turjman F, Galaya T and Agbo JJ: CRISPR biosensing and AI-driven tools for detection and prediction of COVID-19. J Exp Theor Artif Intell 35: 489-505, 2023.
152. Rutherford N: The transductive flu: Disruptive virality and biosocial immunity (unpublished thesis). Université d'Ottawa, 2024.
153. Hannings AN, Darley A, Kearney JC, Upchurch BL and Groft K: Marketing mobile influenza vaccine clinics on a college campus. J Am Pharm Assoc 62: 551-554.e1, 2022.
154. Tuckerman J, Kaufman J and Danchin M: Effective approaches to combat vaccine hesitancy. Pediatr Infect Dis J 41: e243-e245, 2022.
155. Steffens MS, Dunn AG, Leask J and Wiley KE: Using social media for vaccination promotion: practices and challenges. Digital Health 6: 2055207620970785, 2020.
156. Benjamin-Chung J, Arnold BF, Kennedy CJ, Mishra K, Pokpongkiat N, Nguyen A, Jilek W, Holbrook K, Pan E and Kirley PD: Evaluation of a city-wide school-located influenza vaccination program in Oakland, California, with respect to vaccination coverage, school absences, and laboratory-confirmed influenza: a matched cohort study. PLoS Med 17: e1003238, 2020.

157. Gualano MR, Santoro PE, Borrelli I, Rossi MF, Amantea C, Tumminello A, Daniele A, Beccia F and Moscato U: Employee participation in workplace vaccination campaigns: A systematic review and meta-analysis. Vaccines 10: 1898, 2022.
158. Hill I, Porter Z, Mayer J, Verdeflor A, Brown K and Lawrence D: Building the evidence base for advancing vaccine equity. 2023.
159. Friede M, Palkonyay L, Alfonso C, Pervikov Y, Torelli G, Wood D and Kieny MP: WHO initiative to increase global and equitable access to influenza vaccine in the event of a pandemic: supporting developing country production capacity through technology transfer. Vaccine 29: A2-A7, 2011.
160. World Health Organization (WHO): Influenza (avian and other zoonotic). WHO, Geneva, 2026. https://www.who.int/news-room/fact-sheets/detail/influenza-%28avian-and-other-zoonotic%29. Accessed March 5, 2026.
161. Centers for Disease Control and Prevention (CDC): 1957-1958 pandemic (H2N2 virus). CDC, Atlanta, GA, 2019. https://archive.cdc.gov/www_cdc_gov/flu/pandemic-resources/1957-1958-pandemic.html. Accessed March 5, 2026.
162. Centers for Disease Control and Prevention (CDC): 1968 pandemic (H3N2 virus). CDC, Atlanta, GA, 2019. https://archive.cdc.gov/www_cdc_gov/flu/pandemic-resources/1968-pandemic.html. Accessed March 5, 2026.
163. Komadina N, McVernon J, Hall R and Leder K: A historical perspective of influenza A(H1N2) virus. Emerg Infect Dis 20: 6-12, 2014.
164. Jester BJ, Uyeki TM and Jernigan DB: Fifty years of influenza A(H3N2) following the pandemic of 1968. Am J Public Health 110: 669-676, 2020.
165. Centers for Disease Control and Prevention (CDC): Types of influenza viruses. CDC, Atlanta, GA, 2025. https://www.cdc.gov/flu/about/viruses-types.html. Accessed March 5, 2026.
166. Centers for Disease Control and Prevention (CDC): How flu viruses can change: 'Drift' and 'Shift'. CDC, Atlanta, GA, 2024. https://www.cdc.gov/flu/php/viruses/change.html. Accessed March 5, 2026.
167. Centers for Disease Control and Prevention (CDC): Understanding influenza viruses. CDC, Atlanta, GA, 2024. https://www.cdc.gov/flu/php/viruses/index.html. Accessed March 5, 2026.
168. World Health Organization: Global influenza surveillance and response system (GISRS). https://www.who.int/initiatives/global-influenza-surveillance-and-response-system. Accessed March 5, 2026.
169. World Health Organization (WHO): Recommendations for influenza vaccine composition for the 2026-2027 northern hemisphere season. WHO, Geneva, 2026. https://www.who.int/news/item/27-02-2026-recommendations-for-influenza-vaccine-composition-for-the-2026-2027-northern-hemisphere-season. Accessed March 5, 2026.
170. World Health Organization (WHO): Recommended composition of influenza virus vaccines for use in the 2026-2027 northern hemisphere influenza season. WHO, Geneva, 2026. https://www.who.int/publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2026-2027-northern-hemisphere-influenza-season. Accessed March 5, 2026.
171. World Health Organization (WHO): Questions and answers: Recommended composition of influenza virus vaccines for use in the 2026-2027 northern hemisphere influenza season. WHO, Geneva, 2026. https://cdn.who.int/media/docs/default-source/vcm-northern-hemisphere-recommendation-2026-2027/b.-27-feb-2026-frequently-asked-questions.pdf. Accessed March 5, 2026.
172. World Health Organization: Global influenza virological surveillance (FluNet/GISRS overview). https://www.who.int/data/gho/data/themes/global-influenza-virological-surveillance. Accessed March 5, 2026.
173. Hay AJ and McCauley JW: The WHO global influenza surveillance and response system (GISRS)-A future perspective. Influenza Other Respir Viruses 12: 551-557, 2018.