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REVIEW

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Seasonal influenza vaccine performance and the potential benefits of mRNA vaccines

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ABSTRACT

Influenza remains a public health threat, partly due to suboptimal effectiveness of vaccines. One factor impacting vaccine effectiveness is strain mismatch, occurring when vaccines no longer match circulating strains due to antigenic drift or the incorporation of inadvertent (eg, egg-adaptive) mutations during vaccine manufacturing. In this review, we summarize the evidence for antigenic drift of circulating viruses and/or egg-adaptive mutations occurring in vaccine strains during the 2011–2020 influenza seasons. Evidence suggests that antigenic drift led to vaccine mismatch during four seasons and that egg-adaptive mutations caused vaccine mismatch during six seasons. These findings highlight the need for alternative vaccine development platforms. Recently, vaccines based on mRNA technology have demonstrated efficacy against SARS-CoV-2 and respiratory syncytial virus and are under clinical evaluation for seasonal influenza. We discuss the potential for mRNA vaccines to address strain mismatch, as well as new multi-component strategies using the mRNA platform to improve vaccine effectiveness.

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Influenza; vaccination; vaccine effectiveness; vaccine manufacturing; antigenic drift; egg-adaptive mutations; mRNA vaccines

Introduction

Influenza, a vaccine-preventable disease,[1] remains a considerable public health threat, with approximately 1 billion cases and 3.2 million hospitalizations occurring globally each year.[2,3] Between 1999 and 2015, an estimated 291,000 to 646,000 (median 409,000) annual respiratory deaths among people of all ages were associated with influenza virus infection globally.[4] In the United States alone during the 2019–2020 season, there were an estimated 35 million individuals with symptomatic illness, 389,000 hospitalizations, and 25,000 deaths related to influenza virus infection.[5] Although influenza is a concern for all age groups, influenza-associated respiratory deaths occur disproportionately among individuals aged ≥75 years, accounting for 41% of all influenza-associated respiratory deaths globally.[4]

There are four influenza virus types, but only types A and B cause seasonal epidemics in humans, experienced mainly during the winter season in temperate geographic regions.[2] Between 2009 and 2020, the predominant circulating influenza viruses in humans were two subtypes of the influenza A virus, A/H1N1 (derived from the 2009 pandemic virus [pdm09]) and A/H3N2, and two lineages of the influenza B virus, Victoria and Yamagata.[6] Notably, B/Yamagata has not been isolated or sequenced since March 2020 (from the onset of the COVID-19 pandemic).[7,8] In the United States, influenza A/H3N2 has accounted for the most influenza-attributable respiratory deaths (between 1999 and 2018) and hospitalizations (between 1997 and 2009) among people of all ages, followed by influenza B, with A/H1N1 attributed to the least number of these medical events.[9,10]

Influenza vaccines are available and updated annually based on circulating influenza virus activity, which is monitored by the World Health Organization (WHO) Global Influenza Surveillance and Response System (GISRS) to recommend trivalent (A/H1N1 and A/H3N2 along with one lineage of influenza B) or quadrivalent (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata) seasonal influenza vaccine compositions for Northern Hemisphere and Southern Hemisphere seasons each year.[2] While most influenza vaccines are manufactured using an egg-based platform, vaccines using cell culture- and recombinant protein-based platforms are also available.[11] Vaccination remains a valuable means of mitigating the public health threat of influenza, but vaccine effectiveness (VE) between 2004 and 2015 was low to moderate against seasonal influenza globally, particularly for A/H3N2 (pooled VE 33%) relative to A/H1N1 (pooled VE 61% for pdm09; pooled VE 67% for pre-2009) and type B viruses (pooled VE 54%).[12]

Several factors may contribute to the low VE of currently available influenza vaccines,[13] including virus- and host-specific factors. Among virus-specific factors, antigenic drift is a key characteristic of influenza viruses that enables circulating viruses to evade immune detection via accumulation of amino acid substitutions in hemagglutinin (HA) and neuraminidase (NA), the major surface glycoproteins of influenza viruses.[6] A/H3N2 HA antigenic drift is particularly prevalent, with approximately 5-fold higher rates relative to B/Victoria, 7-fold higher than B/Yamagata, and 18-fold higher than A/H1N1 (since 2009).[13,14] A key challenge specific to current egg- and cell culture-based vaccine platforms is the approximate 6-month production time after initial vaccine composition recommendations, allowing time for an antigenically divergent clade to predominate and potentially cause mismatch to vaccine strain compositions.[1] Moreover, influenza viruses have acquired

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additional characteristics that aid immune evasion such as glycan modifications at specific amino acid motifs. Glycosylation patterns in the HA globular head may shield the antigenic-binding sites preventing antibody recognition and binding.[13] Increased glycosylation is suggested to be a key contributor to low VE, particularly against A/H3N2 strains that have over time acquired multiple glycosylation sites in the HA head.[13] Egg-based vaccines have the potential for inadvertent incorporation of egg-adapted mutations during vaccine production that can possibly impact antigenic properties by causing a mismatch of the vaccine strain to circulating virus strains.[1,15] Notably, egg-adapted vaccine strains lacking the glycosylation sites found in circulating viruses due to site mutations during egg-propagation have also been suggested to contribute to lower VE.[13,16]

Vaccine effectiveness is also affected by host-related factors, such as within-season waning of vaccine-mediated protection,[13,17] previous vaccinations affecting subsequent vaccine responses,[13,18] and suboptimal immune responses to current vaccine platforms in immunocompromised individuals and older adults (immunosenescence).[19,20] For example, a systematic review and meta-analysis of influenza VE data from test-negative design studies published between 2004 and 2015 showed that VE against A/H3N2 decreased with older age.[12] For A/H3N2, VE ranged from 43% in those aged <20 years, 35% in adults aged 20–64 years, and 24% in adults aged ≥60 years.[12] Adjuvanted and higher antigenic-dose influenza vaccines are preferable to conventional standard-dose vaccines to boost VE in older adults.[21–23]

Understanding the factors that impact influenza VE is important for determining current challenges and optimizing vaccination strategies. In this review, we summarize the published literature (PubMed) reporting on Northern Hemisphere seasons with documented instances of antigenic drift and egg-adapted mutations leading to strain mismatch, potentially impacting VE between 2011 and 2020. Based on these findings, we highlight the challenges current vaccine platforms face against strain mismatch and discuss the potential for alternative vaccine platforms to address these limitations. In particular, we focus on messenger RNA (mRNA) technology, which has demonstrated its potential against respiratory disease as exemplified by vaccines against SARS-CoV-2 (the virus causing COVID-19) and respiratory syncytial virus, the latter of which received breakthrough therapy designation by the United States Food and Drug Administration (FDA) in January 2023. We discuss how an mRNA-based vaccine platform can address the specific limitations of current seasonal influenza vaccines associated with strain mismatch due to antigenic drift and egg-adapted mutations. For further details on the mRNA platform, we refer the reader to comprehensive reviews on such matters.[24–26]

Antigenic drift or egg-adapted mutations and potential impact on influenza VE during the 2011–2020 seasons

Antigenic drift

Our literature search identified five studies that reported evidence of antigenic drift potentially impacting influenza VE for four seasons: 2011–2012, 2014–2015, 2018–2019, and 2019–2020.[27–31] Table 1 summarizes the key findings of the literature search, and Table S1 provides a summary on the designs of each identified study.

2011–2012 influenza season

In Canada, the 2011–2012 influenza season was characterized by co-circulating influenza A subtypes and B lineages (Figure 1), for which VE was found to be favorable against well-matched A/H1N1 (80%) and B lineages (71%) but suboptimal against A/H3N2 (51%).[27] Circulating A/H3N2 isolates for this season were similar to the 2011–2012 vaccine component (A/Perth/16/2009), although hemagglutination inhibition (HAI) titers were reduced ≥4-fold in 27% of tested isolates.[27] A subset of A/H3N2 viruses were sequenced for phylogenetic analysis, which determined that none of the sentinel viruses belonged to the A/Perth/16/2009 vaccine clade, with the majority (72%) belonging to clade 3B, followed by clade 3C, clade 6, and clade 5 – all of these clades are substantially diverged from A/Perth/16/2009.[27] This substantial genetic variation was identified as a potential contributor to the low VE observed in Canada for the 2011–2012 season (Table 1).[27] In the United States and Europe, strain-specific VE against A/H3N2 (the most prevalent strain that season)[59,75] was estimated to be 39% for the 2011–2012 season in the United States[84] and 38% in Europe during the start of the influenza season (from week 46 of 2011 to week 6 of 2012) that was reduced to -1% later in the season (weeks 7 to 17 of 2012).[50]

2014–2015 influenza season

Antigenic drift of A/H3N2 was also detected early in the 2014–2015 influenza season.[28,29] In the United States, A/H3N2 predominated the 2014–2015 season[60] and overall VE against A/H3N2 for the season was estimated to be 6%.[85] While the vaccine-included strain for this season belonged to clade 3C.1 HA genetic clade (A/Texas/50/2012), predominant circulating viruses in the United States instead belonged to an emergent, substantially drifted clade 3C.2a.[28,29] Based on Flu VE Network sites in the United States, low VE against the 3C.2a clade (1%) during this season was consistent with antigenic drift.[29] Further, a study using reverse genetics determined that mutations in HA antigenic site B were the primary antigenic contributor to the low VE for this season (Table 1).

2018–2019 influenza season

The 2018–2019 influenza season was also marked by antigenic drift early in the season, with HA in circulating A/H3N2 viruses in the United States quickly and increasingly representing clade 3C.3a rather than clade 3C.2a1 of the vaccine component (A/Singapore/INFIMH-16–0019/2016 [Table 1]).[30] However, the newly circulating 3C.3a viruses were antigenically distinct from previously circulating 3C.3a viruses, such as those targeted by the 2015–2016 vaccine component A/Switzerland/9715293/2013.[32] Of note, while A/H1N1 was the predominant strain in the United States (~54%) for this season, A/H3N2 accounted for a large proportion (~42%) of influenza virus infections.[61] VE against A/H3N2 was estimated at 9% for this season in the United States,[86] while VE by genetic subgroup was 46% for 3C.2a1 (vaccine matched clade) and 5% for 3C.3a (predominant, mismatched circulating clade).[30]

Table 1. Northern Hemisphere vaccine composition and reports of antigenic drift or egg-adapted mutations in the literature analysis of Northern Hemisphere 2011–2020 influenza seasons.

Season (Northern Hemisphere)		WHO-recommended vaccine composition for the Northern Hemisphere[32–41]	Articles reporting evidence of antigenic drift and the potential impact on VE in the Northern Hemisphere	Articles reporting evidence of egg-adapted mutations and the potential impact on VE in the Northern Hemisphere
2011–2012	A/H1N1 A/H3N2 B/Victoria B/Yamagata	A/California/7/2009 A/Perth/16/2009 B/Brisbane/60/2008 Not applicable	Antigenic drift of A/H3N2 as the season progressed. WHO recommended that the 2012–2013 Northern Hemisphere vaccine composition be updated to include the A/Victoria/361/2011 (H3N2)-like virus[38]	Six antigenic-site mutations (S45N, G186V, S214I, S228T, I260M, R261Q) from the reference strain were identified in the egg-passaged vaccine strain for A/H3N2, but whether this affected HAI titers against circulating strains was not assessed[27]
2012–2013	A/H1N1 A/H3N2 B/Victoria B/Yamagata	A/California/7/2009 A/Victoria/361/2011 B/Brisbane/60/2008 *(if quadrivalent)* B/Wisconsin/1/2010		Egg-adapted mutations were identified in the A/H3N2 vaccine strain (H156Q and G186V substitutions at antigenic site B, and S219Y mutation at antigenic site D), which reduced HAI titers to the WHO-recommended strain[42] Recommendation that A/Texas/50/2012 be used in the 2013–2014 Northern Hemisphere vaccine composition due to egg-adapted mutations (H156Q, G186V, S219Y) in earlier A/Victoria/361/2011-like vaccine viruses[33]
2013–2014	A/H1N1 A/H3N2 B/Victoria B/Yamagata	A/California/7/2009 A/Texas/50/2012 B/Brisbane/60/2008 *(if quadrivalent)* B/Massachusetts/2/2012		
2014–2015	A/H1N1 A/H3N2 B/Victoria B/Yamagata	A/California/7/2009 A/Texas/50/2012 B/Brisbane/60/2008 *(if quadrivalent)* B/Massachusetts/2/2012	Reduced VE caused by antigenic drift of A/H3N2 virus: 3C.2a, 3C.3, and 3C.3a HA clades predominated, leading to mismatch with the H3N2 component of the vaccine (A/Texas/50/2012; 3C.1 HA clade); due to multiple mutations in the HA antigenic site B including F159S[28,29] WHO recommended that the 2015–2016 vaccine be updated to include A/Switzerland/9715293/2013[40]	
2015–2016	A/H1N1 A/H3N2 B/Victoria B/Yamagata	A/California/7/2009 A/Switzerland/9715293/2013 B/Brisbane/60/2008 *(if quadrivalent)* B/Phuket/3073/2013		Single egg-adapted HA receptor binding site mutation (Q226R) in A/H1N1 viral strain (A/California/7/2009-X-179A), which in ~ 5% of vaccine recipients reduced antibody titers against wild-type HA[43] Single egg-adapted substitution on HA (L194P) in A/H3N2 viral strain affecting the structural conformation of antigenic site B and leading to decreased neutralizing antibody binding[44]
2016–2017	A/H1N1 A/H3N2 B/Victoria B/Yamagata	A/California/7/2009 A/Hong Kong/4801/2014 B/Brisbane/60/2008 B/Phuket/3073/2013 *(if quadrivalent)*		Egg-adapted substitution (T160K) in HA antigenic site B of A/H3N2 virus causing loss of putative N-glycosylation site, which resulted in reduced antibody titers against circulating viruses[16,45]
2017–2018	A/H1N1 A/H3N2 B/Victoria B/Yamagata	A/Michigan/45/2015 A/Hong Kong/4801/2014 B/Brisbane/60/2008 B/Phuket/3073/2013 *(if quadrivalent)*		Egg-adapted substitution (T160K) in antigenic site B of A/H3N2 virus may have contributed to low VE observed, which is attributed to loss of putative N-glycosylation site[45] A study of hospitalized adults with infections from this season suggests that antibody responses among vaccinated individuals were specific to egg adaptations in the A/H3N2 vaccine strain that were not conserved in circulating strains including T160K and L194P (antigenic site B) and N96S (antigenic site D)[46]
2018–2019	A/H1N1 A/H3N2 B/Victoria B/Yamagata	A/Michigan/45/2015 A/Singapore/INFIMH-16-0019/2016 B/Colorado/06/2017 (B/Victoria/2/87 lineage) B/Phuket/3073/2013 (B/Yamagata/16/88 lineage) *(if quadrivalent)*	Antigenic drift of the A/H3N2 virus: 3C.3a HA clades predominated, leading to mismatch with the H3N2 component of the vaccine (A/Singapore/INFIMH-16–0019/2016; 3C.2a1 HA clade)[30] WHO recommended that the 2019–2020 vaccine be updated to include A/Kansas/14/2017 (clade 3C.3a)[30,36]	Egg-adapted mutations (T160K, L194P, and D225G) identified in the HA head of the A/H3N2 viral strain[47] Antibodies collected from vaccinated individuals showed reduced neutralizing responses against the wild-type A/H3N2 virus versus the egg-propagated vaccine virus, which was likely attributed to the combination of 3 egg-adapted mutations in the HA head (T160K, L194P, and D225G)[47]

(*Continued*)

Table 1. (Continued).

Season (Northern Hemisphere)		WHO-recommended vaccine composition for the Northern Hemisphere[32–41]	Articles reporting evidence of antigenic drift and the potential impact on VE in the Northern Hemisphere	Articles reporting evidence of egg-adapted mutations and the potential impact on VE in the Northern Hemisphere
2019–2020	A/H1N1 A/H3N2 B/Victoria B/Yamagata	A/Brisbane/02/2018 A/Kansas/14/2017 B/Colorado/06/2017 (B/Victoria/2/87 lineage) B/Phuket/3073/2013 (B/Yamagata/16/88 lineage) *(if quadrivalent)*	Antigenically drifted A/H1N1 emerged over the course of the season; early in the season, clade 6B.1.A (which includes the vaccine strain) subclade 5A viruses genetically diversified and exhibited substitutions at D187A and Q189E in HA[31]; further amino acid changes (K130N, N156K, L161I, V250A, and E506D; termed 5A + 156K viruses) occurred and predominated by mid-season[31] Genetic diversification in circulating A/H1N1 may have contributed to reduced VE, particularly for 6B.1A 5A + 156K viruses[31] Antigenically drifted B/Victoria circulated throughout the season (V1A.3, containing a 3-amino acid deletion [162–164] in the HA protein, as opposed to a 2 amino-acid deletion [162–163] for V1A.1 in the vaccine), but this was not linked to a reduction in VE, possibly due to some cross-reactivity[31]	

HA hemagglutinin; *HAI* hemagglutination inhibition; *VE* vaccine effectiveness; *WHO* World Health Organization.
For context, the findings of the targeted literature review are presented alongside the recommended vaccine compositions for each influenza season provided by the World Health Organization.[32-41]

2019–2020 influenza season

During the 2019–2020 season in the United States, B/Victoria viruses predominated earlier in the season, but ultimately A/H1N1 became the most predominant strain for that season.[62] Antigenic drift of A/H1N1 was documented to occur over the course of the influenza season in the United States, with the majority of circulating strains belonging to the phylogenetic subclade 6B.1A 183P-5A +156K that mismatched with clade 6B.1A of the vaccine component (A/Brisbane/02/2018 [Table 1]).[31] VE against A/H1N1 for this season was reported to be 30% in the United States,[87] which was lower than typical seasons.[31] Furthermore, VE was only 7% against the group of A/H1N1 viruses that were predominantly circulating later in the season (183P-5A +156K).[31] Antigenically drifted B/Victoria also circulated throughout the 2019–2020 season in the United States, with circulating viruses belonging to clade V1A.3 rather than clade V1A.1 of the vaccine component (B/Colorado/06/2017); however, these antigenic differences were not linked to a reduction in VE, with the authors concluding that this was possibly due to vaccination-mediated cross-reactivity to V1A.3 that provided protection against disease.[31] VE against B/Victoria for this season was 45%.[31]

Egg-adapted mutations

Evidence of egg-adapted mutations in a seasonal influenza vaccine component was reported by eight studies (study designs are summarized in Table S1) for six seasons: in the A/H3N2 vaccine component for the 2011–2012, 2012–2013, 2015–2016, 2016–2017, 2017–2018, and 2018–2019 seasons,[16,27,42,44-47] and for the A/H1N1 vaccine component in the 2015–2016 season (evidence is summarized in Table 1).[43]

2011–2012 influenza season

For the 2011–2012 influenza season, when A/H3N2 was predominant in the United States (Figure 1),[59] A/Perth/16/2009 was the recommended vaccine component, and manufacturers used the egg-passaged strain A/Victoria/210/2009-NYMC X-187 for the vaccine.[27] Although X-187 was initially considered antigenically equivalent to A/Perth/16/2009, a phylogenetic analysis showed it to have six antigenic-site mutations (Table 1).[88] As stated previously, this season was also notable for detectable antigenic drift of A/H3N2 occurring during this season that impacted VE in Canada.

2012–2013 influenza season

An egg-adapted mutation of the A/H3N2 vaccine component was also detected for the 2012–2013 season.[42] An in-depth sequencing analysis identified three mutations in antigenic sites B and D in the egg-passaged component that reduced HAI titers by 16-fold relative to a cell-passaged comparator and by 32-fold relative to the WHO-recommended strain.[42] VE against A/H3N2 in Canada for this season was estimated to be 41%, and low VE was concluded to be related to mutations in the egg-adapted A/H3N2 strain used in vaccine production rather than antigenic drift in circulating viruses (Table 1).[42] In the United States, A/H3N2 also predominated during the 2012–2013 season and VE against A/H3N2 was 39%.[63,89] In Europe, the 2012–2013 influenza season was characterized by co-circulating influenza A subtypes and B lineages, with VE against A/H3N2 of 42%.[51,76] The WHO recommended that A/Texas/50/2012 be used for the following Northern Hemisphere season (2013–2014) due to egg-adapted mutations in the A/Victoria/361/2011-like vaccine viruses.[33] However, it remains notable that a later study in 2018 found that low VE might not be solely attributable to this egg-adapted mutation, but also potentially due to varied immunological responses to the influenza vaccine due to prior exposure.[90]

2015–2016 influenza season

Two studies also reported on egg-adapted mutations in either the A/H1N1 or A/H3N2 strains during the 2015–2016

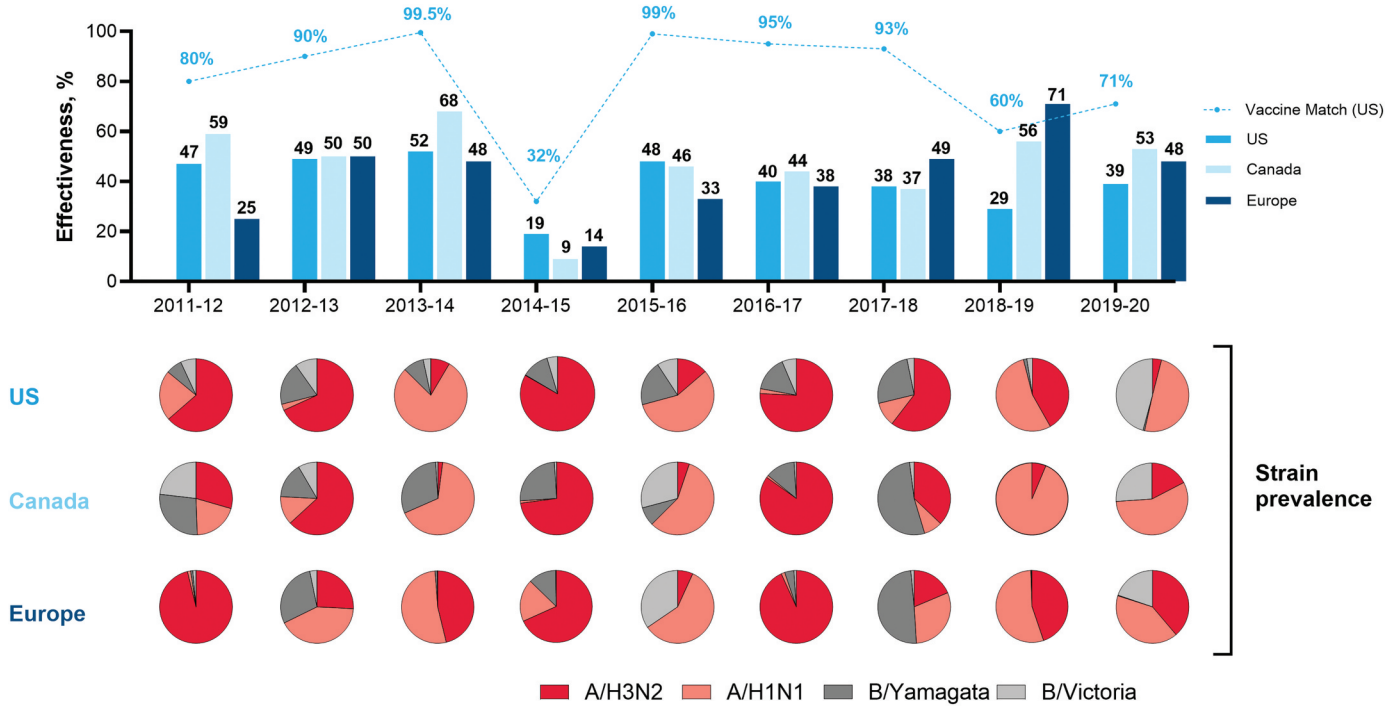

Figure 1. Influenza vaccine effectiveness, vaccine match, and strain prevalence by Northern Hemisphere influenza season and geographic region. Vaccine effectiveness estimates were based on information from the United States Centers for Disease Control and Prevention (CDC),[48] the Canadian Sentinel Practitioner Surveillance Network,[49] and I-MOVE (Influenza – Monitoring Vaccine Effectiveness in Europe; European Union primary care-based, multi-country cohort).[50–58] Overall vaccine effectiveness (across strains) is presented for the United States and Canada. Vaccine effectiveness for the predominant strain each season is presented for Europe. Dotted line represents the overall percentage of antigenic match of the vaccine to circulating viruses in the United States, calculated as a sum of the antigenic match values for each of the four strains weighted by their relative prevalence during the season. Antigenic match values were published in the CDC's Morbidity and Mortality Weekly Reports and were based on titers with ferret antisera,[59–68] Strain prevalence estimates were based on CDC's *Morbidity and Mortality Weekly Report*,[59–67] the Canadian Sentinel Practitioner Surveillance Network,[27,42,69–74] and the European Centre for Disease Prevention and Control.[75–83] The proportion of unknown influenza A or influenza B lineages is not shown.

season.[43,44] Among US-based vaccine recipients for the 2015–2016 season (during which influenza was largely caused by A/H1N1[64] and VE against A/H1N1 for that season was 45%),[91] approximately 5% of recipients possessed HAI titers that were ≥4-fold higher to the egg-adapted A/H1N1 strain (A/California/7/2009-X-179A; candidate vaccine virus component of the 2015–2016 influenza vaccine) than the circulating strain (Table 1).[43] In a separate study, a commonly found egg-adapted mutation (L194P) in the A/H3N2 viral strain was found to affect the antigenic properties of the A/H3N2 vaccine component for the 2015–2016 season (A/Switzerland/9715293/2013).[44] This mutation affected the conformation of antigenic site B to disrupt a large portion of the RBS, leading to decreased neutralizing antibody binding (Table 1).[44] As antigenic site B was immunodominant in A/H3N2 viruses, the authors concluded this mutation was likely to have profound implications for VE.[44] However, infections with A/H3N2 in the United States were uncommon for this season.[91]

2016–2017 and 2017–2018 influenza seasons

A/HongKong/4801/2014 was the WHO-recommended A/H3N2 vaccine strain for both the 2016–2017 and 2017–2018 influenza seasons.[34,35] During these two seasons, the circulating A/H3N2 viruses were antigenically equivalent to the WHO-recommended prototype.[16] However, an egg-adapted mutation in antigenic site B of the vaccine strain used for both seasons may have lowered VE (Table 1).[16,45] A/H3N2 was predominant in the United States for both these seasons,[65,66] and VE against A/H3N2 was estimated to be 33% in 2016–2017 and 22% in 2017–2018 seasons.[92] For the 2016–2017 season, the egg-propagated vaccine was found to elicit antibody responses that poorly neutralized the circulating H3N2 virus strains, which contained an antigenic site B glycosylation site that was lacking in the egg-adapted vaccine strain.[16] An analysis of hospitalized adults with A/H3N2 virus infections during the 2017–2018 season demonstrated that antibody responses were specific to egg adaptations in the A/H3N2 vaccine strain that were not found in circulating strains (Table 1).[46] Titers against wild-type A/H3N2 strains (3C.2a1 and 3C2a2) were significantly correlated with protection against infection during the 2017–2018 season.[46]

2018–2019 influenza season

For the 2018–2019 season, three egg-adapted mutations were identified in the HA head of the A/H3N2 vaccine component (A/Singapore/INFIMH-16–0019/2016).[47] Antibodies collected from vaccinated individuals showed reduced neutralizing responses against the cell-propagated wild-type A/H3N2 virus versus the egg-propagated vaccine virus, likely due to the antibodies targeting egg-adapted epitopes.[47] As stated previously, antigenic drift of A/H3N2 was also detected during this season, and an update to the following Northern Hemisphere season's vaccine composition for A/H3N2 was recommended by the WHO to address antigenic drift.[30,36]

Potential for mRNA technology to address strain mismatch challenges for influenza vaccines

During the 2011–2020 influenza seasons, antigenic drift causing vaccine mismatch to circulating strains was identified in four seasons, and evidence of egg-adapted mutations in vaccine strains was identified in six seasons. Overall, these findings emphasize the specific challenges of influenza vaccine development and the need for alternative vaccine approaches to increase protection against disease. One such alternative platform is mRNA technology. There are already multiple mRNA vaccines against seasonal influenza currently under clinical development by various manufacturers, with two vaccines having progressed to phase 3 evaluations. Of these, Moderna, Inc.'s investigational quadrivalent seasonal influenza vaccine, mRNA-1010, has shown an acceptable safety profile and was immunogenic in both younger and older adults across phase 1/2 and phase 3 studies (Clinicaltrials.gov, NCT04956575, NCT05415462, NCT05566639, NCT05827978).[93,94] Phase 3 evaluations of Pfizer, Inc.'s mRNA seasonal influenza vaccine candidate are also underway (Clinicaltrials.gov, NCT05540522).[95] As previously mentioned, future iterations of mRNA seasonal influenza vaccines are also in clinical development, including vaccine candidates with additional HA antigens for broader coverage, as well as candidates that incorporate mRNA encoding for both HA and NA. Moreover, mRNA vaccines have recently demonstrated an acceptable safety profile and efficacy against other respiratory diseases, notably SARS-CoV-2[96] and respiratory syncytial virus.[97] Below, we discuss the specific potential of mRNA technology for seasonal influenza and mRNA vaccines currently in clinical development.

Rapid, scalable manufacturing process

A major advantage of mRNA technology for seasonal influenza is that the platform does not rely on a continuous egg supply for vaccine manufacturing.[15] Currently, egg- and cell-based technologies require approximately 6 months for vaccine manufacturing,[98] beginning after WHO releases the recommended vaccine composition in February and September ahead of the forthcoming Northern Hemisphere and Southern Hemisphere influenza seasons, respectively (Figure 2).[32] By comparison, mRNA vaccines follow a simplified and highly reproducible manufacturing process that utilizes the same raw materials regardless of the encoded antigens.[96] For SARS-CoV-2, updated recommendations for variant-containing COVID-19 vaccines were made by the FDA in June 2022, with the updated mRNA vaccines made available in September 2022, suggesting an mRNA vaccine manufacturing timeline of 2–3 months,[99,100] which could be applicable to seasonal influenza as well. This could possibly allow for strain selection closer to the start of the influenza season to decrease the risk of a mismatch due to before-season antigenic drift[99] if recommended by WHO and other public health recommending bodies based on their assessment of risks/benefits. Further, the flexibility and speed of the mRNA platform would likely be advantageous in the event of an emergent pandemic influenza strain, whereby a coordinated effort across multiple stakeholders would be warranted to develop and deploy mRNA vaccines targeting this strain, as observed during the COVID-19 pandemic.

The manufacturing process for mRNA vaccines is also scalable, which was integral in the context of the rapidly emerging SARS-CoV-2 behind the COVID-19 pandemic.[101] In addition, mRNA technology is flexible and can adapt to an evolving pathogen over time,[101] as underscored by the development and authorization of new variant-updated mRNA vaccines formulated to address emergent SARS-CoV-2 variants.[102,103]

Multi-component vaccine compositions

Another advantage of mRNA technology over current designs is that it allows for generation of difficult-to-manufacture protein complexes and flexibility in antigenic composition.[96] These elements may enable an mRNA-based vaccine to broaden protection against influenza viruses. So far, HA from each of the four seasonal influenza viruses has been the main antigenic component of quadrivalent seasonal influenza vaccines.[1] mRNA technology can allow for inclusion of more than four HA antigens in a single vaccine, which may allow public health agencies to expand their recommendations for current quadrivalent vaccine compositions, which could allow for regionalization beyond broad Northern and Southern Hemisphere compositions. Possibilities also include targeting multiple clades/sub-clades of each seasonal influenza virus and targeting antigens beyond HA. Two mRNA vaccine candidates undergoing clinical evaluation (mRNA-1011 and mRNA-1012) include additional HA antigens for influenza A (Clinicaltrials.gov, NCT05827068). Another mRNA-based formulation incorporates all 20 of the known HA subtypes of influenza A and B viruses that have the potential to enter the human population and has demonstrated strain-specific immune responses against each HA subtype in a preclinical study.[101,104] While this study provides proof of concept of the potential of multivalent mRNA vaccines, further study is required to determine the value of an influenza vaccine targeting non-circulating strains in humans. The mRNA platform also allows for the addition of other antigens besides HA in a single vaccine to potentially broaden protection against seasonal influenza. NA is one such antigen under clinical consideration, as individuals infected with influenza A or B viruses generate inhibitory antibodies against both surface glycoproteins HA and NA, which facilitate viral entry and viral release from host cells, respectively.[1,6] Anti-NA immunity has previously been shown to reduce influenza virus infection-associated illness in an independent manner from HA-based immunity.[105,106] The genetic evolution of NA appears to be discordant from HA,[107,108] and vaccines targeting both proteins may limit the ability of the virus to escape immune responses through antigenic drift. mRNA influenza vaccines targeting both HA and NA are currently in clinical development (mRNA-1020 and mRNA-1030, Clinicaltrials.gov, NCT05333289),[109] along with an mRNA vaccine targeting only NA (Sanofi).

Beyond vaccines targeting only influenza, the flexibility of this platform provides the capability to develop combination vaccines against multiple respiratory pathogens[96]; multi-component mRNA-based seasonal influenza vaccines currently

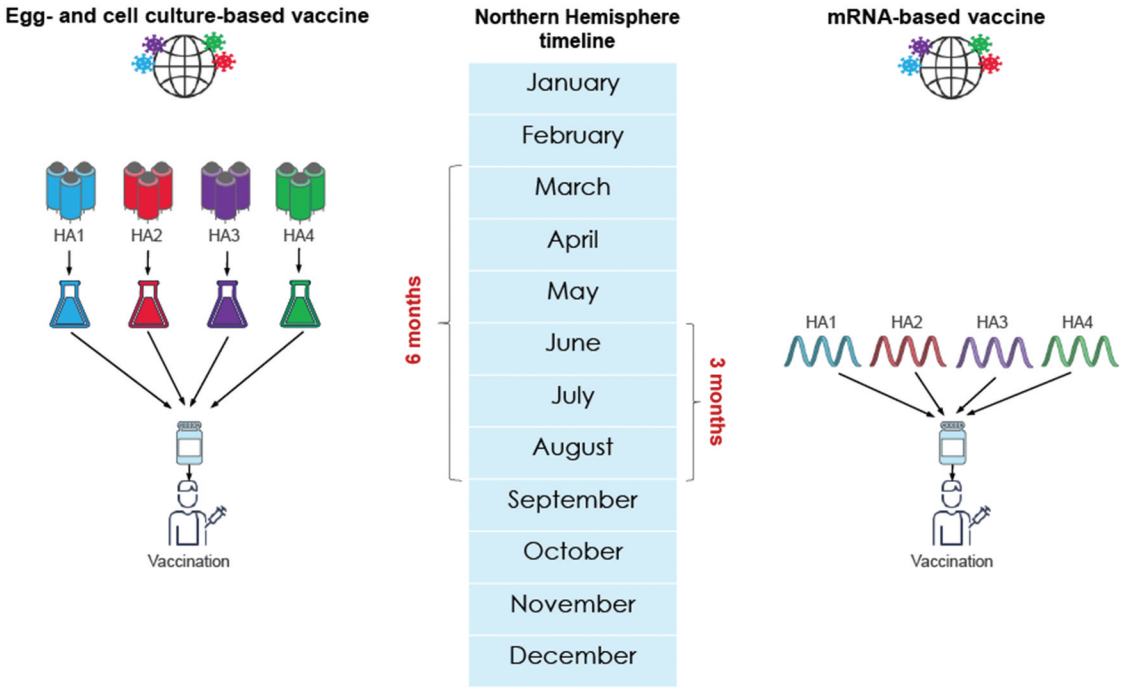

Figure 2. Influenza vaccine manufacturing using egg-based, cell culture-based, and mRNA-based platforms. *HA* hemagglutinin; *mRNA* messenger RNA. Currently, egg- and cell culture-based technologies require approximately 6 months for vaccine manufacturing[98] after the World Health Organization releases the recommended vaccine composition in February/March ahead of the forthcoming Northern Hemisphere influenza season,[32–35,37–41] By comparison, an mRNA-based influenza vaccine platform may only take 2–3 months to manufacture (based on the timeline for SARS-CoV-2 vaccine manufacturing).[99,100]

undergoing clinical investigation are targeting both influenza and SARS-CoV-2 (mRNA-1073, Clinicaltrials.gov, NCT05375838; mRNA-1083, Clinicaltrials.gov NCT05827926; qIRV plus bivalent BNT162b2, Clinicaltrials.gov, NCT05596734), as well as influenza, SARS-CoV-2, and RSV (mRNA-1230, Clinicaltrials.gov, NCT05585632).

Avoidance of egg- and cell-adapted mutations

In bypassing the egg and cell culture propagation process, mRNA vaccines could potentially show improved VE by avoiding mutations in vaccine-produced strains that cause antigenic mismatch to circulating viruses. The scale of potential inefficiencies of traditional egg-based manufacturing technology has been acknowledged in a Delphi-style panel interview of nine influenza experts.[110] Based on the European data from 2014 to 2019, these experts estimated VE could potentially increase by 9% (against all influenza strains) and up to 16% (against A/H3N2 in the 18–64-year age range) if egg adaptations that arise when employing the traditional egg-based manufacturing process are avoided.[110] Beyond the season of vaccine administration, the presence of egg-adapted mutations in vaccines can have long-term implications due to immune imprinting at the time of first exposure to influenza in childhood, which influences antibody responses to subsequent influenza exposures over a lifespan.[47] Subsequent exposures may boost antibody responses to antigens with egg-adapted substitutions that are not found in the wild-type strains.[47]

Currently, aside from egg-based platforms, only cell-based and recombinant protein platforms are available for influenza vaccines, although they are less extensively used.[11] For cell-based vaccines, it remains less well understood if cell culture-propagated vaccine viruses have fewer adaptations than observed with egg-propagated vaccines, as the extent of antigenic match between each vaccine platform (egg- or cell-based) and circulating strains has not been routinely reported for each influenza season. However, it is also possible for mutations in viruses to occur during cell culture propagation, which has been demonstrated for A/H3N2 and B strains.[111,112] A literature analysis of the antigenic similarity of egg-propagated and cell culture-propagated influenza viruses to worldwide circulating viruses for influenza seasons 2008 to 2018 found high antigenic similarity between both cell culture- and egg-propagated viruses with circulating A/H1N1 strains and B/Yamagata strains.[113] However, from 2012 to 2018, a substantially higher proportion of circulating A/H3N2 and B/Victoria strains were antigenically similar to cell culture-propagated viruses than egg-propagated viruses.[113]

Comparisons of VE for egg-derived and cell culture-derived influenza vaccines for the 2017–2020 US seasons among individuals aged ≥65 years have not consistently demonstrated a benefit for cell culture-propagated over egg-propagated vaccines.[114–116] Notably, egg-derived seed viruses were used in cell culture-based vaccine manufacture before the 2017–2018 influenza season for A/H3N2,[11,115,117] before the 2019–2020 season for A/H1N1[115] and at least until the 2017–2018 season for influenza B strains.[115] As such, cell-propagated vaccines derived from egg-derived seed viruses may also carry egg-adapted mutations.[117] From the 2021–2022 season onward, all four influenza strains used in the cell culture – based vaccines were developed in an egg-independent manner, and therefore allow a more definitive comparison of effectiveness relative to egg-derived vaccines.[118] In contrast to egg- and cell culture-based platforms, recombinant protein-based

vaccines have a negligible mutation risk.[11] However, studies reporting their VE versus egg-based vaccines have been limited and provided varied results.[116,119–121] Further studies of VE for the recombinant protein-based and mRNA vaccines for seasonal influenza are warranted.

Conclusions

Overall, vaccine mismatch to circulating strains due to either antigenic drift or egg-adapted mutations was documented to occur in all but one of the 2011–2020 influenza seasons. The presence of antigenic drift and/or egg adaptation likely contributed to reduced influenza VE observed during certain seasons of this time period. However, a limitation of this literature review is that evidence of antigenic drift may not have always been documented, but natural viral evolution likely occurred nonetheless; the true impact of seasonal antigenic drift therefore may not be fully captured in this review. The impact of egg-adapted mutations may also be underestimated because the identified publications focused on reporting larger effects on VE. In addition, this review is primarily based on findings from North America, with few studies identified from Europe or elsewhere. Further understanding of the true impact of egg propagation on VE and patient outcomes is needed.

Development of optimized next-generation vaccines with higher effectiveness against seasonal influenza is important for reducing disease burden worldwide. If other vaccine manufacturing platforms result in vaccines that demonstrate increased VE, then scaling up the manufacture of those vaccines, particularly if they allow vaccine strain selection to occur nearer to the start of the influenza season, may help to address current challenges. The use of alternative vaccine manufacturing platforms, such as mRNA, is currently under evaluation and may help to reduce these challenges. Although still under clinical development, the mRNA platform may be advantageous due to a rapid, scalable manufacturing process and no requirement for egg or cell culture propagation to therefore avoid egg- or cell-adapted mutations. Regulatory challenges of mRNA seasonal influenza vaccines are evident as delayed strain selection to more closely match circulating strains relies on a coordinated effort between the WHO, regulatory bodies, and vaccine manufacturers to convene later strain selection procedures. In addition, mRNA vaccines have the potential for multi-component compositions (eg, against multiple clades/sub-clades of each seasonal influenza virus and against multiple influenza virus proteins) that may broaden protection. However, certain challenges for this platform also need to be considered, including the potential for reactogenicity to limit vaccine uptake. The widespread distribution of COVID-19 mRNA vaccines has allowed for rigorous clinical and post-authorization evaluations of mRNA vaccine safety. Overall, most events after mRNA vaccination are temporary in duration and mild to moderate in severity, occurring at increased frequency compared with other vaccine platforms. Long-term safety assessments of COVID-19 mRNA vaccines are ongoing and continue to be informed by clinical studies and real-world monitoring of safety events. For annually administered seasonal influenza vaccines, understanding consumer preferences for vaccine attributes and the underlying drivers of vaccine choice will thus be important. Notably, a discrete-choice experiment among US adult consumers indicated that the vaccine choice was largely driven by a preference for avoiding the risk of flu-like symptoms and improved vaccine efficacy, with consumers more tolerant of the risk of adverse reactions in exchange for increased vaccine efficacy.[122] Overall, the success of mRNA vaccines for SARS-CoV-2 has indicated the immense potential of mRNA vaccines in mitigating infectious diseases, and validation of mRNA vaccines for seasonal influenza is eagerly awaited.

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Disclosure statement

Parinaz Ghaswalla, Yoonyoung Park, Nevena Vicic, Jintanat Ananworanich, Raffael Nachbagauer, and Deborah Rudin are employees of Moderna, Inc., and may hold stock/stock options in the company.

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Employees of Moderna, Inc. had a role in the concept/design of the work, data analysis/interpretation, as well as the drafting/critical review of the manuscript content and its approval for publication. Concept/design of the work: Parinaz Ghaswalla, Yoonyoung Park, Nevena Vicic, Jintanat Ananworanich, Raffael Nachbagauer, Deborah Rudin.

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Data availability

Data sharing is not applicable to this article as no datasets were generated, and all analyzed data are in the public domain; data sources are cited in this article.

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