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Emerging Influenza A(H3N2) Subclade K: A Narrative Review

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ABSTRACT: Viruses spread rapidly by antigenic drift, with the impetus to mismatch vaccines and early season epidemics. One new variant of Subclade K in multiple regions in late 2024 and early 2025 appeared at a rapid rate, becoming the dominant contributor to influenza activity in multiple regions. This narrative review summarizes existing evidence regarding the subclade's viral characteristics, epidemiological behavior, clinical relevance and public health implications, from a peer-reviewed literature, genomic surveillance data, antigenic assays, and initial vaccine effectiveness estimates from ECDC and UKHSA. In addition, subclade K contains multiple hemagglutinin substitutions that reduce antigenic similarity to the 2025–2026 vaccine strain, with serological tests showing minimal cross-reactivity and suggesting immune escape. Within the EU/EEA, the subclade has risen rapidly over the last year, although there is no evidence of increased intrinsic virulence. The burden of health care could increase if early season transmission is further delayed. Early estimates of vaccine effectiveness provide strong protection in children of 72–75 per cent, with protection reduced by adults to 32–39 per cent. Subclade K is a major evolutionary event which presents the need for increased genomic surveillance, timely vaccination and coordinated public health preparedness to mitigate its present and future consequences.

1. INTRODUCTION

The acute incidence of seasonal influenza A viruses remains the largest and consistent global health problem, with A(H3N2) a significant predictor of high mortality rates, mortality and year-to-year variation in vaccine performance. H3N2 is the primary cause of antigenic drift, particularly because its amino-acid substitutions in immunodeficient portions of the hemagglutinin gene have been associated with highest rates of antigenic drift among circulating influenza subtypes [1]. These substitutions alter viral antigenicity by altering epitopes located on the receptor-binding site, thereby reducing binding and helping to escape immune immunity [2] [3]. While it is a theory that even a small change in sequence can have the effect of counterbalancing circulating viruses, they have been found to be based on evidence of basic antigenic shifting that even tiny changes in sequence can result in major antigenic shifts that can significantly alter the balance between vaccine strain and [4] [5]. H3N2 has long been associated with lower vaccine efficacy & vulnerability, increased epidemic variability and recurrent mismatches during seasonal influenza vaccination [6] [7].

In this larger evolutionary context, European and the U.S. genomic surveillance systems detected a new A(H3N2) variant subclade K (J.2.4.1) during late 2024 and early 2025 in Europe and the US Early reports from European Centre for Disease Prevention and Control 2025 and UK Health Security Agency 2025 suggested that it rapidly increased in prevalence, exceptionally early seasonal circulation patterns, and antigenic characteristics differing from the Northern Hemisphere 2025-2026 vaccine strain. Like previous drift events, Subclade K has multiple HA substitutions in functional epitopes, many of which have been previously linked in prior studies to antigenic novelty, altered receptor affinity, and enhanced viral fitness [8] [9]. These mutations are consistent with viral strategies that enable immune escape, especially in populations with narrower antibody repertoires mediated by imprinting or relatively low emergence from influenza infection [10] [11].

ECDC and UKHSA's antigenic and serological samples indicate less cross-reactivity between Subclade K and the ferret antisera raised against the 2025–2026 vaccine strain, confirming their suspicion that there might be a mismatch between Subclade K and the vaccine strain. This is consistent with earlier results that egg-adapted vaccine components and antigenic drift can thus simultaneously limit VE, especially in adult and older [12] [13]. Early UKHSA estimates of children's protection from 72–75 percent, but significantly smaller VE in adults, are consistent with the historical trend. Several studies with evidence for age-stable differences indicate children exhibit greater, more diverse antibody responses, and adults have smaller memory repertoires that are based on prior exposures [14] [15].

In epidemiological terms, phylogenetic analyses show that Subclade K accounts for most of A(H3N2) detections across EU/EEA countries with early-season circulation as early as May 2025. This may partly reflect population evasion after some of the most frequently observed atypical seasons characterized by suppression of influenza circulation that could also be associated with reduced population immune status among relatively rare populations in countries with immunity gaps and post-pandemic transmission dynamics While this was not a coincidence among drift-dominated H3N2 seasons, underlying the risk of higher seasonal burden, early-season transmission and antigenic divergence are correlated with increased seasonal burden even if virulence was suppressed without increased intrinsic virulence [16].

Subclade K, while currently in circulation, points to the difficulties and uneven balancing of the influenza surveillance systems in the world. With genomic monitoring capacity growing in recent years, yet coverage remains somewhat limited, particularly in low- and middle-income regions. As they consistently point out, there is a common misconception that these differences may delay detection of antigenically drifted variants and inhibit coordinated global response efforts [17] [18] [19]. A tighter integration of genomic, antigenic and epidemioligical data to real time influenza forecasting and vaccine strain selection is argued necessary in order to successfully tackle new variants of subclade K, Lee et al. [20] and Boni [21]. By way of setting these conditions, A(H3N2) Subclade K maybe arrives as an opportune moment to reexamine vaccination policy, global genomic surveillance and improve modelling influenza predictions. In summary, in this narrative review we bring together information on the virology, antigenicity, epidemiology, clinical implications and public health implications of Subclade K, and seeks to place it in the general evolutionary background of H3N2 and incongruent with relevant uncertainties requiring urgent attention in science and policy.

2. LITERATURE REVIEW

A persistent pattern of rapid antigenic transformation, recurrent mismatches, and high epidemic variability persists in seasonal influenza A (H3N2). For example, Boni [21]; Koel et al. [1] found that the HA protein of H3N2 viruses is frequently swapped for a specific amino acid in immunodominant regions to drive antigenic drift and to evade population immunity [1] [21]. Fundamental research indicates that strategic substitutions at the receptor binding site are the primary contributor to major antigenic shifts, and their loss of significantly reduced antibody recognition in vaccine-induced antigen selection [1] [2]. That rapid antigenic development contributes to H3N2's relatively low vaccine efficacy and more frequent outbreak surges over the season than other influenza subtypes [6] [7].

Recent research on global circulation patterns shows that regional advancing of emergence H3N2 subclades carries implications for the regional dominance of new subclades and can easily displace old lines [22] [23]. This information provides a crucial background to understanding the evolution of A(H3N2). The K Subclade (J.2.4.1). Subclade K shows a set of HA mutations that appear to reflect antigenic drift, low antigenic relatedness to the 2025–2026 vaccine strain and can provide evidence for immune escape. Early antigenic and serological tests using ferret antisera show a reduction in the ability to react negatively to vaccine-strain antisera and reinforces the risk of an antigenic mismatch [24].

The results of the evidence from the literature on influenza antigenic evolution support that drifted strains are likely to have selective advantages by being better receptor bound, better replication fitness, or superior immune escape [1] [2]. These mechanisms can explain the rapid increase in Subclade K in genomic surveillance databases and phylogenetic analyses of ECDC 2025. Its rapid regional expansion reflects the pattern of previous seasons where antigenically distinct H3N2 variants became dominant, particularly when populations were low in influenza circulation [11] [25].

As research on vaccine effectiveness (VE) also implies, there is a consequence. In a prioritized literature, there has been limited VE through antigenic drift, egg-adaptive mutations that occur during vaccine production, and immune imprinting effects in adults and juveniles [12] [14]. Early UKHSA VE estimates for Subclade K showed the normal or high protection levels among

children, but substantial reductions of VE among adults. The pattern is consistent with prior findings suggesting that adult immune history tends to spork the antibody repertoire that performs poorly on drifted H3N2 lines. The new literature on antibody landscape variation is further evidence that individual-level immune histories exert significant influence on the susceptibility and cross-reactivity of drifted H3N2 variants [26].

While subclade K clinical data is limited, monitoring evidence suggests no evidence of increased intrinsic severity yet. This is consistent with other observations of drifted H3N2 viruses where antigenic novelty affects transferibility and VE rather than pathogenicity. However, the literature identifies that the presence of early-season circulation and decreased immune response, together with reduced immunity, can substantially expand healthcare costs regardless of the intrinsic virulence [16].

Given the fast growth of Subclade K, international health concerns are growing over geographic inequities in influenza surveillance. In low and middle-income countries, genomic sequencing has been documented to be limited, obscuring the early detection of antigenically drifted variants and slow coordinated responses, as demonstrated in Carter et al. [18]. Current ECDC and UKHSA recommendations for increased genomic surveillance and early vaccination align with existing public health policy, with a focus on rapid detection, cross-border data sharing, and timely vaccination campaigns during seasons with early activity or antigenic mismatch [24].

2. MATERIALS AND METHODS

3.1 Scope and Purpose of the Review

This narrative study was intended to synthesize and critically analyze evidence of a recently identified variant of influenza A (H3N2) Subclade K, J.2.4.1, that has been rapidly growing in several regions during the 2023–2024 influenza season. The review seeks to strengthen existing knowledge on the subclade's virological characteristics, antigenic properties, epidemiological forms, clinical implications and public health relevance. This research focus was on understanding the relationship between observed antigenic drift and seasonal vaccine performance and finding gaps in global surveillance and research.

3.2 Search Strategy

The searches for influenza A (H3N2), SPCK mutations, antigenic drift, vaccine efficacy and hemagglutinin mutations were conducted from PubMed, Scopus, and Web of Science through multiple terms associated with influenza A(H3N2), the new Subclade K, the emerging Subclade K, antigenic drift, vaccine effectiveness, and hemagglutinin mutations. These surveys were limited to publications between 2013 and 2024, as the primary research on H3N2 evolution and recent evidence of Subclade K-based SKUs. As is typically used for narrative reviews on viral evolution and strain monitoring, information from GISAID was accessed indirectly through public health agency reports, adapted to the existing guidelines for narrative reviews on viral evolution and strain monitoring.

3.3 Inclusion and Exclusion Considerations

For example, if sources provided empirical or surveillance data on H3N2, antigenic drift mechanisms, subclade K genomic change, vaccine performance, or epidemiological change, they were included. It was favored to use peer-reviewed papers, certified surveillance papers by government agencies, and genomic analyses that could be described clearly. The publications were not excluded if they had lack methodological clarity; were speculatively quoted without supporting data; did not relate to influenza A(H3N2) or did not fall within the defined date frame.

3.4 Analytical Approach

All the recovered sources were assessed using the thematic analysis of consistency, methodological integrity and conceptual relevance. Data from genomic and antigenic, epidemiological and immunological research was presented in a systematic manner and contextualized over multiple themes, including mutation patterns, antigenic evolution, vaccine mismatch, early-season circulation, age-specific susceptibility. ECDC 2025 and UK Health Security Agency 2025 published reports, due to their timely genomic surveillance, detailed antigenic assessments and early vaccine efficiency assessments that included the ECDC 2025 and UK Health Security Agency 2025.

3.5 Rationale for Employing a Narrative Review

The best methodological approach for a narrative review was to examine first-stage data from surveillance systems rather than controlled clinical studies, as it was most appropriate given Subclade K's emerging nature and large presence of early-stage data extracted from surveillance systems rather than controlled clinical research. Narrative synthesis has an advantage in combining genomic analysis, epidemiology reports and laboratory-based antigenic assays to formulate an effective interpretation over incomplete or rapidly changing data set, with the ability to integrate multiple data types in narrative synthesis to the full. The method does identify conceptual links, contextual patterns, and policy implications that may not be found through systematic methods.

3.6 Methodological Limitations

In addition, the assessment acknowledges many built-in constraints associated with the present state of evidence. First, a significant amount of the data included herein was produced from European-based surveillance efforts; therefore, it may not accurately reflect complete global distribution patterns. Second, while vaccine effectiveness has been established in controlled settings (i.e., laboratory trials), no one can provide a comprehensive estimate as to how vaccines will function in "real world" environments. Third, because there are few or no clinical studies related to Subclade K, we cannot make definitive determinations regarding disease severity. Finally, differences in the frequency and geographic scope of Subclade K's dissemination may have affected the appearance of its spread and/or intensity. These constraints indicate the preliminary nature of scientific inquiry into the origins of this family and highlight the need for continued genomic surveillance and international collaboration to maintain momentum.

4. RESULTS

4.1 Virological and Antigenic Characteristics of Subclade K

The genome and antigenic comparisons have demonstrated that A (H3N2) has been identified as a clonal group. Specifically, sub-clade K of J.2.4.1, shows many amino acid changes in the HA protein, which are located in the immunodominant sites on the human immunogenic map associated with the major antigenic shift events. Such substitutions reduce the antigenic similarity of the 2025-2026 northern hemisphere vaccine strain to the 2025-2026 northern hemisphere vaccine. Such an antigenic distance was supported by serologic tests showing decreased reactivity in ferrets using sera made from viruses of the vaccine-strain.

These results reflect the literature on H3N2, and indicate that the substitutions near receptor-binding or antigenic sites can be instrumental in how immune escape, viral fitness, and lineage turnover are mediated [1] [2] [21]. If immune-mediated selection is occurring, then, Subclade K has rapid expansion in sequence databases and thus is probably immunologically mediated selection rather than stochastic emergence.

Table 1 summarizes the key genetic and antigenic characteristics of Subclade K compared with the current vaccine strain.

Table 1: Key Genetic and Antigenic Features of A(H3N2) Subclade K Compared with 2025–2026 Vaccine Strain

Feature	Subclade K (J.2.4.1) Findings	Implications	Sources
HA Amino-Acid Substitutions	Multiple Mutations in Antigenic sites A and B	Suggests Antigenic Drift and Altered Antibody Binding	[1] [24]
Ferret Antisera Cross-Reactivity	Reduced Reactivity to Vaccine-Strain Antisera	Indicates Potential Vaccine Mismatch	[24]
Antigenic Distance	Increased Relative to 2025/26 Vaccine Component	Suggests Reduced Vaccine-Induced Neutralization	[2] [21]
Evolutionary Pattern	Rapid Phylogenetic Expansion	Likely Immune Escape and Fitness Advantage	[6] [23]

4.2 Epidemiological Emergence and Spread

Subclade K has rapidly spread to EU/EEA countries during the 2025 season, with ECDC noting a dramatically increased number of detections beginning in early May and lasting through late autumn. By November 2025, almost half of all the

A(H3N2) sequences that were used in GISAID from the region belong to this subclade [24]. Similarly, an expanded expansion is consistent with previous H3N2 drift cases when the gap in antigen novelty and population immunity gaps resulted in rapid lineage dominance [22] [23] [25].

As influenza generally occurs early in the season, it is particularly significant that circulation begins early. This suggests Subclade K has been exploiting a reduced population defense after several atypical influenza seasons with limited viral transmission. These conditions are associated with increased susceptibility, especially in adult and older populations with narrow antibody profiles formed by imprinting and prior exposures [11].

Table 2 presents the primary epidemiological indicators associated with Subclade K during the 2024–2025 season.

Table 2: Epidemiological and Clinical Indicators of Subclade K Circulation (2024–2025 Season)

Indicator	Observed Patterns	Interpretation	Sources
Early-Season Circulation	Significant Detections from May–November 2025	Suggests Early Transmission Relative to Typical Seasonal Curves	[24]
Proportion of A(H3N2) Detections	Up to ~50 Percent of Sequences in EU/EEA	Indicates Rapid Displacement of Prior H3N2 Subclades	[24]
Severity Signals	No Evidence of Increased Intrinsic Virulence	Impact Driven Mainly by Higher Caseload, Not Severity	[24]
Age-Specific Susceptibility	Adults Appear More Affected Than Children	Consistent With Immune Imprinting and Drift	[14] [11]

4.3 Clinical Presentation and Severity Patterns

There is no evidence of increased intrinsic severity in previous H3N2 variants but existing surveillance results do not indicate any additional intrinsic severity increase in the frequency of large-scale clinical trials associated with Subclade K. For cases in which there has been increased case volume or unusual symptoms the incidence of clinically adverse effects is less likely to be caused by greater virulence than increased virulence. In this view, these analyses support the historical evidence for drifted H3N2 viruses, which commonly exhibit improved transmission and immune escape in spite of significant changes in pathogenicity.

However, the early season surge and increases in the number of patients entering hospitals and demand for diagnostic services, as part of the early season increase in the Subclade K influx may strain healthcare systems and hamper healthcare, particularly in communities at the border with other respiratory pathogens. In recent seasons, the mismatched H3N2 variants are particularly prevalent among older and comorbid individuals, resulting in greater awareness of the importance of proactive health system preparedness [16].

4.4 Vaccine Effectiveness and Immune Response

Subclade K remains a highly effective agent for influenza in the 2025–2026 season, as has been shown in UK Health Security Agency VE results. Children's VE is high at 72–75 per cent and indicates that children are vulnerable to large cross-reactive immunity, which can protect them against drifted variants. In contrast, VE in adults is significantly smaller (32–39 per cent) due to the strong vulnerability to low antibody repertoires, immune imprinting, and repeated exposure to an H3N2 variant in closely observed mutated populations. [12] [14].

This difference in VE underscores the heterogeneity of immunological interaction between vaccine-induced responses and antigenic drift. While the historical data in Subclade K suggest that even small antigenic drift is less harmful to adult immunity than it is, infant protection remains relatively intact, at least based on early evidence from Subclade K. Table 3 provides a summary of early VE estimates across population groups.

Table 3: Early Real-World Vaccine Effectiveness (VE) Against Subclade K

Population Group	VE Estimate (%)	Interpretation	Sources
Children and Adolescents (<18 years)	72–75	High Protection Despite Antigenic Drift	[24]

Adults	32–39	Reduced Protection Likely Due to Antigenic Mismatch and Immune History	[12]
Elderly	No Estimate Yet Available	Likely to Show Lower VE Based on Historical H3N2 Patterns	Historical inference

4.5 Overall Interpretation of Emerging Evidence

The results, when combined, suggests that A (H3N2) is a cause of A(H3N2). Subclade K was a significant evolutionary change across seasonal influenza landscape. With no overlap in genetic variability, antigenic drift, rapid epidemiological expansion, age-specific VE characteristics this strongly resembles earlier H3N2 drift events with seasonal impact. While this doesn't identify an increase in intrinsic severity and early transmission and lower adult immunity suggests, Subclade K could still pose a considerable public health burden in the 2024-2025 and surrounding seasons.

5. DISCUSSION

During the 2024-2025 season, Influenza A(H3N2) Subclade K (J.2.4.1) became identified, and was viewed as important and predictable, during the larger evolutionary patterns that define H3N2 dynamics. The genomic, antigenic, epidemiological, and vaccine efficacy analyses posit Subclade K as part of an emerging family of drift-driven shifts uncovered in the influenza literature in Koel et al. [1]; Petrova & Russell [6]; and Boni [21]. The presentation merges these data together to understand the evolutionary mechanisms that underlie Subclade K's rise, its epidemiological and clinical significance and implications for influenza vaccination and public health preparedness.

5.1 Subclade K in the Context of H3N2 Antigenic Drift

Under this description, the subclade K mutation profile serves to show the centrality of antigenic drift as the dominant driver of H3N2. Multiple substitutions in HA antigenic sites A and B reflect the past drift events that led to significant antigenic transitions and vaccine mismatches, such as the 3C.2a and 3C.2a1b lineages [1] [4] [5]. Analysis of structural findings in Wu et al. [2] showed that even single-point mutations near the receptor binding site could substantially alter epitope presentation and antibody binding if they were in proximity to the receptor binding site [2] [3]. Under these conditions, antigenic test results for Subclade K suggest that the virus has lost cross-reactivity with vaccine-strain ferret antisera, which strongly suggests an emerging antigenic mismatch [24].

These findings support the hypothesis that Subclade K rises is mostly caused by immune escape. The same patterns of rapid lineage expansion and antigenic drift have been observed in the world, with antigenically new H3N2 variants emerging efficiently within populations with accumulated immunity gaps [22] [23]. These historic patterns suggest that Subclade K in EU/EEA genome sequences accelerated dramatically.

5.2 Epidemiological Acceleration and Immunity Landscape Dynamics

The early-season surge associated with Subclade K may be due to broader shifts in the landscape of immunity during multiple years of predominately atypical influenza transmission. Several studies indicate that decreased exposure during the COVID-19 pandemic altered population-level immunity, enabling drifted variants to spread more rapidly, in a time period which was interrupted by the resumption of transmission [27] [28]. This is probably attributed to the unusually early occurrence of A (H3N2) detections across Europe in 2025 with Subclade K accounting for over half of A (H3N2) detections in Europe in 2025.

Other age specific susceptibility patterns can be traced to modern immunological theory. Adults exhibit narrower imprinting-driven antibody repertoires that respond poorly to drifted H3N2 variants; while infants remain broad-span antibody cross-reactivity in addition to older exposure and vaccinations [8] [15]. These immune landscape dynamics reflect the increased vaccine efficacy of the Subclade K season for children and adults for children and adults. As a result, age-dependent VE gradients are consistent with previous seasonal seasons in which drifted H3N2 viruses dominate [7] [12].

5.3 Towards clinical impact and Absence of enhanced virulence

This is not supported by evidence that Subclade K displays higher intrinsic virulence. The influence of antigenic novelty on transmission and vaccine match may be much greater than pathogenicity in most drift cases, as explained by Fleming et al. [16].

No surveillance data indicate atypical severity, unusual symptom profiles or elevated hospitalization severity compared with other recent H3N2 clusters in UKHSA, 2025.

It can be assumed that Subclade K is a clinical burden and not to be underestimated. In spite of higher virulence, early transmission increases cumulative case number, further stressing healthcare infrastructures even with greater virulence. For older persons and comorbidities, particularly when seasonal conditions are dominated by drifted H3N2 lineage, older adults and people with comorbidity often come to the hospital due to lower immune and lower [16] [29]. If Subclade K continues to dominate the season, similar patterns can be seen.

5.4 Impacts of Vaccination Strategy and Immunization Policy

It appears several elements of how flu vaccine are developed and implemented will be impacted by the antigenic divergence in subclade k. Although current vaccines may offer some degree of protection against severe disease, it is clear from this data that the 20-64 year old age group has experienced lower rates of vaccine effectiveness (VE) than expected, suggesting continued issues associated with "immune imprinting" resulting from the repeated exposure to H3N2 and "egg adaptive mutations" resulting from changes made to the vaccine manufacturing process [7] [12].

The observed lower VE among 20-64 year olds, therefore, emphasizes the ongoing need to continue to slowly update our vaccines, use more modern technology such as cell culture or recombinant based technologies, and consider using either higher doses or adjuvant containing formulations for older adults. Literature also demonstrates that early vaccination is particularly important during times of antigenic mismatch and/or early circulating viruses. The ECDC and UKHSA both emphasize the importance of providing vaccines to high risk individuals as soon as possible after an outbreak is identified so that early transmission can be prevented and these at risk individuals can receive the most benefit from the vaccine [24]. Therefore, the emergence of subclade k supports the concept that early vaccination should occur regardless of whether there is evidence of antigenic drift and that moderate levels of VE can lead to substantial reductions in hospitalization and severe illness.

5.5 The Priorities of Surveillance and the Need for Global Coordination

Rapid detection of sub-clade K by the UK's and Europe's public health surveillance networks show that their methods are robust, however there is a significant gap between sequencing capacity in high income countries and those in low- and middle-income countries. Carter et al. [18] and Polansky et al. [19], both reported that this data gap complicates the tracking of drifted strains and overall risks associated with them globally. Understanding the world-wide distribution of sub-clade K will provide the most accurate information available regarding how we can plan which vaccine strain should be used to protect against future outbreaks of sub-clade K.
Genome based antigen specific characterization of new sub-types, along with serologic mapping and mobility informed epidemiologic models are being utilized to integrate surveillance to predict changes in the influenza virus over time [20]. It is the evolutionary process and spread of sub-clade K that increases the necessity to have these types of multi-level approaches to understand the evolutionary process of the influenza virus.

5.6 Remaining Knowledge Gaps

While new information has provided some insights into Subclade K, at least the following critical things remain to be discovered:

1. Mechanistic virology: how do substitutions to HA relate to receptor affinity, immune escape, and fitness, what are the functional studies hinting at?

2. Serological mapping: the populations of these antibody landscapes are only dimly mapped across children, adults, and older adults.

3. The global epidemiology; most current sequencing is from Europe and the UK; curious about the rest of the world and also how Subclade K fits into the rest of the world.

4. Clinical outcomes, bolster those cohort studies which have not yet reported increases in severity across age and risk groups.

5. Long-term VE; as we start to learn about stratified VE from this season we start also to form judgments about the durability of this protection.

This lack of depth constrains future predictions of Subclade K's evolution and points to the need for continued scientific care.

A(H3) N2 was introduced in the 2024-2025 period and the 2024–2025 outbreak of A(H3) N2. Subclade K shows a role of antigenic drift, immune landscape, and post-pandemic vaccine change in seasonal influenza severity. Although this subclade does not represent high prevalence of high virulence, differences in antigenic characteristics and high rates of emergent age-specific vaccine efficacy to this subclade are adaptive vaccine strategies, surveillance and coordinated public health planning. Finally, Subclade K shows how H3N2's volatility and global coordination and collaboration is necessary to control influenza worldwide.

6. Conclusion

When Influenza A (H3N2) Subclade K emerged, it was a major evolutionary change in the seasonal influenza landscape, rapidly expanding geographic space and early-season transmission. The results in this study imply that the subclade K has a mutation profile as consistent with an established immune escape pathway and a reduction in antigenic similarity between the 2025–2026 Northern Hemisphere vaccine strain. ECDC and UKHSA surveillance data are consistent with widespread regional dominance and early circulation in large numbers, likely contributed by populations immunity gaps during the last few atypical influenza seasons.

There are no current reports that there is an increased intrinsic virulence in the subclade, yet these antigenic divergence and early season increases pose major public health challenges. Early studies have suggested that vaccines will provide protection against serious disease in the initial years; however, younger individuals (children) may be protected from clinical illness much better than older populations (adults). The lower level of protection among adult populations could be attributed to the presence of both an individual's history of exposure to antigenic strains and an individual's previous experience (imprinting), which would result in a greater risk for the development of long term resistance to vaccination. Therefore, it is essential that timely public health initiatives be developed and implemented to address these issues, as well as to increase the level of genomic surveillance and improve communication within the general population about the risks associated with antigenic mismatch and increased vigilance of vaccine.

As an example, the findings from this study demonstrate that there are numerous knowledge gaps. To understand if there exists a direct correlation between viral transmission and immunologic escape through mechanisms of mutation and/or substitution at HA sites, further experimental research is required. Additionally, we require detailed data on serology for all ages to determine their susceptibility and immunity. Finally, in order to evaluate the geographical distribution and evolutionary dynamics of Subclade K across the globe, adequate global surveillance must occur along with improved access to genetic sequences in high-risk regions.

Subclade K represents unprecedented volatility in H3N2 virus strain, thus necessitating continued international cooperation on global influenza surveillance, vaccine development, and preparedness of public health systems. Due to the fact that Subclade K, as well as subsequent drifted influenza viruses will most likely negatively impact public health, it is crucial to monitor the continued changes occurring in Subclade K and take coordinated public health measures to minimize potential adverse outcomes due to Subclade K or other drifted influenza virus variants.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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