

Early influenza virus characterisation and vaccine effectiveness in England in autumn 2025, a period dominated by influenza A(H3N2) subclade K

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Keywords

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Abstract

Influenza A(H3N2) subclade K (J.2.4.1) has dominated the start of the 2025 to 2026 influenza season in England. We found reduced reactivity of subclade K with post-infection ferret antisera raised against the Northern Hemisphere 2025 to 2026 vaccine strains, aligning with World Health Organization reports. Nevertheless, vaccine effectiveness against hospital attendance and admission in the early season currently remains within a typical range at 70 to 75% in children and 30 to 40% in adults. Our data indicates that vaccination remains an effective preventative tool against circulating influenza A(H3N2).

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The end of the Southern Hemisphere 2025 influenza season and the start of the Northern Hemisphere (NH) 2025 to 2026 season has seen rapid growth in activity of influenza A(H3N2) subclade K (formerly referred to as subclade J.2.4.1) which is projected to dominate among H3N2 viruses during the 2025 to 2026 season (1 to 3). The K subclade marks a notable evolution in influenza A(H3N2) viruses since the NH 2025 to 2026 candidate vaccine strains were selected (based on the J.2 subclade) and are characterised by T135K, K189R with 7 additional mutations (HA1: K2N, S144N, N158D, I160K, Q173R,) (2 to 4). Early analysis from the World Health Organization (WHO) influenza vaccine composition meeting (VCM) in September 2025 suggest low reactivity of these viruses with post-infection ferret antisera raised against the NH vaccine strains (5). It is not yet clear how 2025 to 2026 vaccine effectiveness (VE) against clinical disease may be affected by these observations. Here, we report genetic and antigenic characterisation of H3N2 viruses and real-world VE against emergency department (ED) attendance and hospital admission with influenza A in England.

Epidemiological context

Influenza activity in England began unusually early in the 2025 to 2026 season, with a rise in influenza like illness emergency department attendances and influenza test positivity among teenagers and young adults followed by increases in younger children (6). Most all-age influenza indicators, including influenza hospitalisations and intensive care unit admissions went above baseline levels from week 43 2025, the earliest inter-pandemic start to the season in England since 2003 to 2004 (6). Almost all cases (98%) since week 40 have been influenza A and, where subtyping was available for these, 84% were A(H3N2) (Supplementary Figure 1). Early starts to the 2025 to 2026 season have also been observed elsewhere in the NH (7, 8).

England's vaccination programme

The programme in England uses predominantly enhanced vaccines (9): the live attenuated influenza vaccine (LAIV) is the first-line option for most children, followed by the cell-based inactivated vaccine (IIVc). For at-risk adults aged 18 to 64 years, IIVc or recombinant (IIVr) inactivated influenza vaccines are recommended, from 50 to 64 years adjuvanted vaccine (aIIV) and from 60 to 64 years high-dose vaccine (IIV-HD) are also included among recommended vaccines. From 65 years and above aIIV, IIV-HD or IIVr are recommended. Standard dose egg-based vaccines are only recommended where other vaccines are not available. Up to 2 November 2025, the provisional influenza vaccine uptake was 34% in 2 to 3 year olds, 29% in those aged under 65 years in a clinical risk group and 62% in adults aged 65+ (uptake data not available for school-aged children) (6).

Influenza A(H3N2) genetic characterisation

Genetic characterisation by whole genome sequencing of viruses collected from primary and secondary care in England has shown predominance of antigenically drifted A(H3N2) viruses belonging to subclade K since week 35 2025; 156 of 179 (87%) belong to this novel subclade (Table 1 and Supplementary Figure 2). Some J.2 and J.2.4 viruses continue to be detected. The distribution of all genetically characterised influenza A detections since week 20 2025 is described in Supplementary Figure 2a.

Table 1. Influenza A(H3N2) viruses in England that were genetically characterised by whole genome sequencing, between week 10 2025 to week 43 2025

Type	Subtype	Clade	Subclade	Week 10 to week 20	Week 21 to week 34	Week 35 to week 43	Number of detections
				(03/03/2025-18/05/2025)	(19/05/2025-24/08/2025)	(25/08/2025-20/10/2025)	
A	H3N2	2a.3a.1	J	1	0	0	1
A	H3N2	2a.3a.1	J.1.1	2	0	0	2
A	H3N2	2a.3a.1	J.2	63	6	11	80
A	H3N2	2a.3a.1	J.2.2	25	1	0	26
A	H3N2	2a.3a.1	J.2.3	0	1	0	1
A	H3N2	2a.3a.1	J.2.4	0	1	11	12
A	H3N2	2a.3a.1	K (J.2.4.1)	0	2	156	158
A	H3N2	2a.3a.1	J.2.5	0	0	1	1
				91	11	179	281

Influenza A(H3N2) antigenic characterisation

Antigenic characterisation by haemagglutination inhibition (HAI) assay of 41 A(H3N2) influenza viruses isolated from clinical samples collected in England between March and October 2025 with antisera raised against current vaccine strains found a trend towards reduced reactivity over time, consistent with the observed genetic diversification (Figure 1). Most viruses from the J.2 and J.2.2 subclades reacted well (titres within 4-fold of the homologous titre) with post-infection ferret antisera raised against the NH 2025 to 2026 vaccine strains: egg-propagated A/Croatia/10136RV/2023 (14/25; 56%) and cell-propagated A/District of Columbia/27/2023 (25/25 100%).

Viruses in subclade J.2.3, J.2.4 and J.2.4 (135N) were low reactors with ferret antisera raised against NH 2025 to 2026 vaccine strains.

Ten subclade K viruses isolated between August and October 2025 were antigenically characterized and all (100%) showed a >32-fold reduction in reactivity with ferret antisera raised against egg-propagated A/Croatia/10136RV/2023 and an at least 8-fold reduction with antisera raised against cell-propagated A/District of Columbia/27/2023. Ferret antisera raised against A/England/189/2025 (a SH 2026 A/Sydney/1359/2024-like virus) recognized viruses from K subclade moderately well with 4/8 viruses (50%) reacting within 4-fold of the homologous titre.

Figure 1. Influenza A(H3N2) viruses from England that were antigenically characterised by haemagglutination inhibition (HAI) assay, March to October 2025. Individual clinical virus isolates from England defined by month of sample collection, genetic subclade and reactivity with post-infection ferret antisera. Key indicates fold change in HAI titre achieved by clinical virus isolates compared to the homologous titre for the post-infection ferret antisera for the vaccine and reference virus strains.

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Individual clinical virus isolates from England defined by month of sample collection, genetic subclade and reactivity with post-infection ferret antisera. Key indicates fold change in HAI titre achieved by clinical virus isolates compared to the homologous titre for the post-infection ferret antisera for the vaccine and reference virus strains.



Vaccine effectiveness against influenza A and influenza A(H3N2)

VE against influenza was estimated using a test-negative case-control (TNCC) study design (10 to 13). Cases were influenza positive PCR tests from individuals attending ED or admitted to hospital, and controls were negative influenza PCR tests from comparable individuals. Individuals were considered vaccinated 14 days after vaccination.

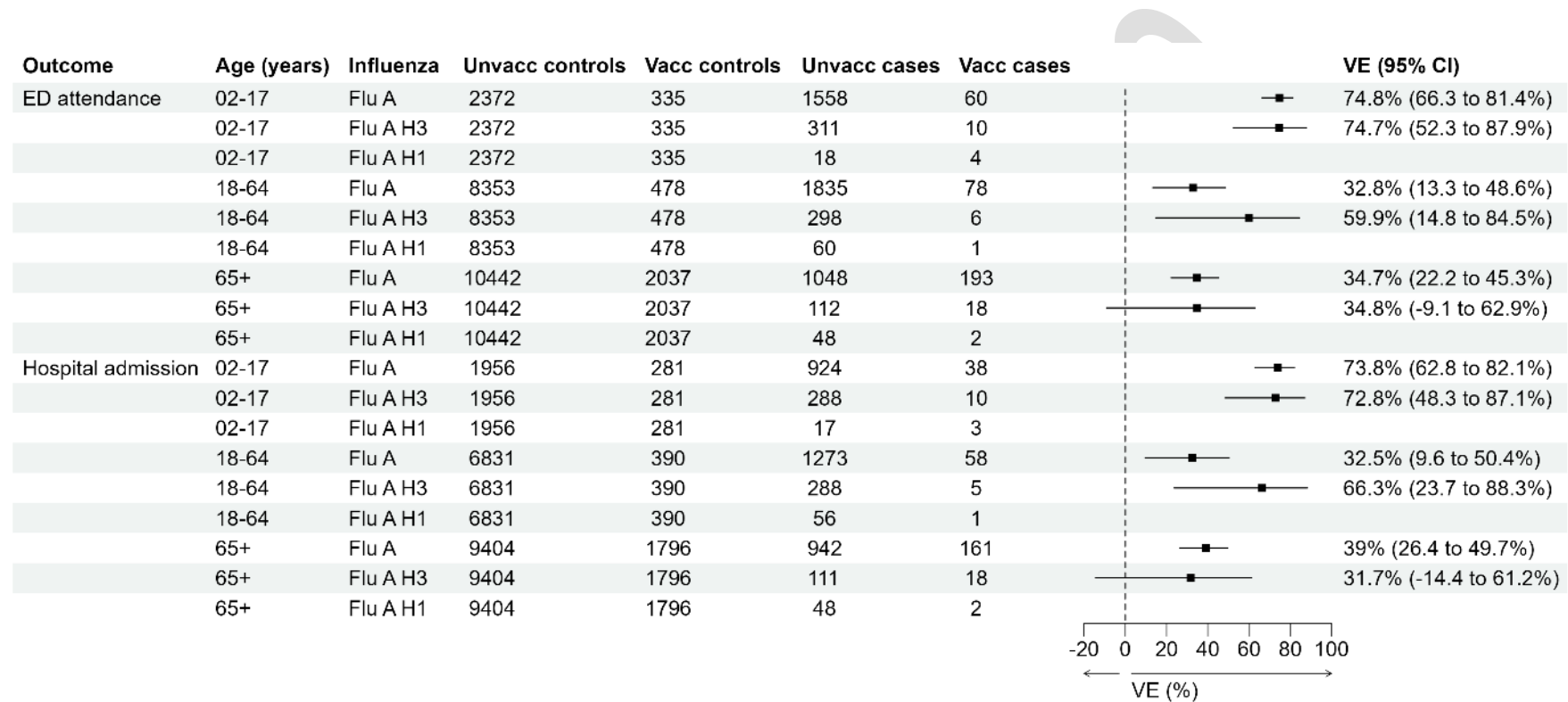
Multivariable logistic regression was used with the test result as the outcome, vaccination status as the primary exposure variable of interest and with confounder adjustment for test week, age group, region and clinical risk status. VE was estimated for any vaccine type against ED attendance and hospital admission stratified by age group and by influenza type and sub-type, where possible. Sensitivity analyses were undertaken restricting to ED attendances and hospital admissions with a respiratory code. See Supplementary Appendix for details on the data sources, exclusion criteria and methods.

The main analysis included tests from 29 September 2025 to 2 November 2025. The temporal distribution of cases and controls is shown in Supplementary Figure 3, and descriptive characteristics are presented in Supplementary Tables 1 to 6.

Amongst children aged 2 to 17 years, overall, VE against ED attendance and hospital admission with influenza A was high at 74.8% (95% CI 66.3 to 81.4%) and 73.8% (95% CI 62.8 to 82.1%), respectively (Figure 2). VE against ED attendance and hospital admission with influenza A(H3N2) was also high; 74.7% (95% CI 52.3 to 87.9%) and 72.8% (95% CI 48.3 to 87.1%), respectively. Moderate VE against influenza A and influenza A(H3N2) was observed in all adults (Figure 2). In adults aged 18 to 64 years, VE against ED attendance and hospital admission with influenza A was 32.8% (95% CI 13.3 to 48.6%) and 32.5% (95% CI 9.6 to 50.4%) respectively. VE against ED attendance and hospital admission with A(H3N2) was 59.9% (95% CI 14.8 to 84.5%) and 66.3% (95% CI 23.7 to 88.3%) (Figure 2). In adults aged 65+, VE against ED attendance and hospital admission with influenza A was 34.7% (95% CI 22.2 to 45.3%) and 39.0% (95% CI 26.4 to 49.7%) respectively. VE against ED attendance and hospital admission with A(H3N2) was 34.8% (95% CI 9.1 to 62.9%) and 31.7% (95% CI 14.4 to 61.2%), respectively, (Figure 2).

Sensitivity analyses restricting to respiratory-coded ED attendances and hospital admissions showed similar VE estimates (Supplementary Figure 4) and sensitivity analyses using a different source of hospitalisation data also found similar results (Supplementary Figure 5).

Figure 2. Vaccine effectiveness against emergency department (ED) attendance and hospital admission for children aged 2 to 17 years, adults aged 18 to 64 years and adults aged 65+



Discussion

In line with WHO reports (5), we also found reduced reactivity of viruses in England belonging to influenza A(H3N2) subclade K with post-infection ferret antisera raised against the NH 2025 to 2026 vaccine strains. Nevertheless, we find reassuring early evidence that a programme using NH-strain enhanced vaccines continues to offer protection against clinical disease with influenza A. Protection was highest amongst children, where vaccine effectiveness was 70 to 75%. In adults, VE was lower with most estimates around 30 to 40%. Given the high proportion of characterised viruses belonging to the influenza A(H3N2) K subclade in England over the study period, these results are likely to be reflective of VE against this subclade. The observed early VE is similar to end of season VE estimates typically seen in adults in recent years in the UK, Europe and Canada (10, 11, 14 to 18).

Our high VE results in children are consistent with some previous LAIV vaccine investigations – a small number of efficacy and effectiveness studies undertaken in earlier seasons with circulating antigenically drifted H3N2 viruses (19 to 21). Several of these studies show that LAIV can provide significant protection against laboratory confirmed infection in children, even with less well matched strains (57 to 86%) – most notably Belshe *et al.* who reported excellent protection against a drifted circulating H3 strain in younger children in 1997 to 1998 (20). However, these findings were not seen in 2014 to 2015 in the UK, another H3 drift season, where LAIV (and IIV) effectiveness in children was more limited (22). The apparent cross protection against antigenically drifted viruses that we see in children may be a result of the breadth of the immune response provided by LAIV. Our own antigenic analysis indicates that the reduction in reactivity is greater with antisera raised against the NH 2025 to 2026 egg strain compared to the cell strain. The wide use of enhanced vaccines, including a preference for non-egg based vaccines in adults in the UK, may have contributed to the maintained VE seen in adults.

Overall, our results are encouraging, though it is important to note that these observations are from a period very soon after vaccination when there has been no waning in effectiveness. Recent end of season analyses highlighted waning in effectiveness in adults over the course of an influenza season (Whitaker *et al.*, 2025, *In press*, DOI: 10.1111/irv.70194) and it will be important to continue to monitor duration of protection this year. To date, the burden of influenza has been greatest in children and young adults in England. The lower VE results seen in adults, when compared to children, is similar to previous seasons but does not exclude a larger reduction in protection in older adults as the season progresses. Alternatively, the reason for the lower VE results in adults than children may be explained by higher pre-existing background immunity against the circulating strains, in which cases the vaccine would offer less additional benefit. Seroprevalence analyses will be needed to confirm this.

Since influenza testing in most ED departments is targeted at those with acute respiratory infection symptoms, to maximise statistical power in the main analyses, all ED attendances and hospitalisations temporally associated with an influenza test were included (12). Sensitivity analyses restricting to those with a respiratory code showed very similar estimates. We used ED and hospital data from the Emergency Care Dataset (ECDS) in the primary analysis as ECDS data is less lagged than admitted patient data from the Secondary Users Survey (SUS) used in England's previous hospitalisation studies(11), but sensitivity analyses also found similar estimates against influenza A overall when using SUS hospitalisation as the outcome. Due to the relatively small proportion of viruses that were subtyped, estimates of VE against Influenza A(H3N2) had relatively wide confidence intervals. Results in children and adults aged 65+ were

very similar to the overall influenza A results, whereas in 18 to 64 year olds point estimates were higher for A(H3N2). It is also noted that secondary care samples referred to the national reference laboratory for viral characterisation are dependent on voluntary referral practices. Data in early season may therefore not be geographically representative, for example one hospital site contributed a large proportion of the secondary care samples characterised during this period. Furthermore, case numbers are currently too low to estimate effectiveness by vaccine type, but this will also be important to assess.

Conclusion

Despite the emergence of a drifted influenza A(H3N2) strain driving an unusually early 2025 influenza season in England and some other countries in the NH, our early estimates provide reassurance that the 2025 to 2026 NH enhanced vaccines provide important protection in children and adults in the early period post-vaccination. The high VE in children, strengthens the case for optimising vaccine uptake in this group, where we may also see indirect protection of other age cohorts (23).

Ethical statement

The study protocol was subject to an internal review by the UK Health Security Agency Research Ethics and Governance Group and was found to be fully compliant with all regulatory requirements. As no regulatory issues were identified, and ethical review is not a requirement for this type of work, it was decided that a full ethical review would not be necessary.

UKHSA has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases and as such, individual patient consent is not required to access records.

Funding statement

This work was funded by UK Health Security Agency. No external funding was received.

Data availability

All sequence data is publicly available on GISAID.

Since the vaccine effectiveness work is carried out under Regulation 3 of The Health Service (Control of Patient Information; Secretary of State for Health, 2002) using patient identification information without individual patient consent as part of the UKHSA legal requirement for public health surveillance and monitoring of vaccines, authors cannot make the underlying dataset publicly available for ethical and legal reasons. However, all the data used for this analysis is included as aggregated data in the manuscript tables and appendix. Applications for relevant anonymised data should be submitted to the [UKHSA Office for Data Release](#).

Conflicts of interest

The Immunisations and Vaccine Preventable Diseases division at UKHSA has undertaken post-marketing surveillance and regulatory analyses requested by influenza vaccine manufacturers for which cost-recovery charges have been made. No other conflicts of interest have been declared.

Authors' contributions

FCMK, HW and JLB designed the vaccine effectiveness study. FCMK undertook the data management, linkage and processing for vaccine effectiveness analyses. FCMK and HW undertook statistical analyses. TT, BK, CT, KH, MZ and AS undertook the virological and antigenic characterisation. NAA, CR, REG, CQ, NG, EW, AA, CW undertook epidemiological surveillance of influenza since week 40. SM undertook vaccine uptake analysis. FCMK, AS, JLB wrote the first draft of the manuscript. RP and MR provided feedback and review of the manuscript. All authors provided final approval of the submitted version.

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