Transition from Quadrivalent to Trivalent Influenza Vaccination Compared with Continued Quadrivalent Vaccination for Preventing Severe Influenza Outcomes in Populations in Indonesia: Implications from the 2025–2026 Epidemiological Landscape

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ABSTRACT

Seasonal influenza remains a global public health challenge, with an estimated 1 billion infections and 290,000-650,000 respiratory deaths each year. The 2024-2025 season recorded a high disease burden in the United States, with tens of millions of symptomatic cases and hundreds of thousands of hospitalizations, as well as the highest hospitalization rates in the FluSurv-NET surveillance era. Entering the 2025-2026 season, a shift in dominance toward influenza A(H3N2) has been observed in various regions, including the emergence of subclade K (J.2.4.1), which has spread globally and become the dominant variant in several regions. In Indonesia, surveillance data indicate an increase in influenza activity in late 2025, followed by a decline in early 2026, with the positivity rate peaking during this period before returning to low activity levels. Subclade K has been detected across multiple provinces with wide geographic distribution, and most cases present with mild to moderate clinical manifestations. Serological studies have shown reduced antigenic reactivity between the vaccine and circulating viruses; however, real-world vaccine effectiveness data indicate that protection against severe disease remains preserved, with higher effectiveness observed in children compared to adults. The World Health Organization has recommended transitioning from quadrivalent to trivalent vaccines since 2023, following the absence of the B/Yamagata lineage in global circulation since 2020. This study presents an updated overview of global and national influenza epidemiology and its implications for vaccination policy, providing a scientific basis to support consideration of transitioning to trivalent vaccines in Indonesia.

Keywords*: *influenza, subclade K, A(H3N2), trivalent vaccine, quadrivalent vaccine, B/Yamagata, Indonesia, epidemiology

INTRODUCTION

Seasonal influenza is an acute respiratory infection caused by influenza viruses and imposes a significant global disease burden. The World Health Organization (WHO) estimates that approximately 1 billion influenza cases occur each year, with 3-5 million severe cases and 290,000 to 650,000 deaths associated with respiratory disease.[1,2] In developing countries, this burden is exacerbated by limited healthcare infrastructure and low vaccination coverage, resulting in 99% of deaths among children under 5 years old due to influenza-related lower respiratory tract infections occurring in these regions.[3,4]

The year 2025 marks a significant shift in the global influenza epidemiological landscape. The 2024-2025 influenza season in the United States was recorded as one of the highest-burden seasons in the past decade, with preliminary estimates of at least 43 million symptomatic cases, 19 million medical visits, 560,000 hospitalizations, and 38,000 deaths.[5,6] The cumulative hospitalization rate reached 128.3 per 100,000 population, the highest since the initiation of FluSurv-NET surveillance in the 2010-2011 season.[5]

Entering the 2025-2026 season, there has been an increase in the circulation of influenza A(H3N2) across various regions, driven by the emergence of subclade K (J.2.4.1), which has rapidly spread globally and become the dominant strain within the H3N2 group.[7-11] At the same time, the World Health Organization has recommended a transition from quadrivalent vaccines (QIV) to trivalent vaccines (TIV) since September 2023, based on the absence of B/Yamagata detection in global circulation since March 2020.[12,13] This paper aims to present the current epidemiological landscape of influenza from the global, regional, and national levels in Indonesia, as well as its implications for vaccine transition policy.

GLOBAL INFLUENZA SITUATION

Global Disease Burden

Influenza continues to be one of the leading causes of morbidity and mortality due to respiratory infections worldwide. WHO estimates indicate 290,000-650,000 respiratory deaths annually on a global scale, with the elderly population (over 65 years old) and young children bearing the greatest burden.[1,2] The latest estimates from Lafond et al. (2021) report that among adult populations, influenza accounts for 11.5% of hospitalizations due to lower respiratory tract infections worldwide.[14]

Shift in Dominant Subtypes and the Emergence of Subclade K

Entering the 2025-2026 season, there has been a shift in influenza virus circulation patterns, with an increasing proportion of influenza A(H3N2) across various regions. Subclade K (J.2.4.1) emerged as a rapidly expanding variant since mid-2025, with a significant increase in detection since August 2025 in Australia and New Zealand.[15,16] By November 2025, subclade K accounted for 89% of all A(H3N2) sequences submitted to GISAID from the WHO Western Pacific Region, and had been detected in more than 34 countries globally.[15]

Genetically, subclade K is characterized by T135K and K189R mutations in the hemagglutinin gene along with seven additional mutations that result in significant antigenic changes.[10] Serological studies using post-infection ferret antisera have shown reduced reactivity to the Northern Hemisphere 2025-2026 vaccine strain, indicating clinically relevant antigenic drift.[10] Nevertheless, early data from the United Kingdom show that vaccine effectiveness against emergency department visits and hospital admissions remains within the typical range: 72-75% in children and adolescents (<18 years) and 32-39% in adults.[10] Similar data from Canada estimate vaccine effectiveness at around 40% against A(H3N2), including subclade K, at the primary care level.[17]

Epidemiologically, there is no evidence of a significant increase in clinical severity in subclade K infections compared to previous A(H3N2) variants.[15] However, seasons dominated by A(H3N2) have historically often been associated with higher hospitalization and mortality burdens, particularly among the elderly population.[18-22]

REGIONAL SITUATION IN ASIA

WHO South-East Asia Region (SEAR)

The World Health Organization South-East Asia Region comprises 11 member countries with a population of approximately 2 billion people, representing more than 25% of the world's population. Eight out of the 11 countries are classified as Low-Income or Lower-Middle Income Countries according to the World Bank classification.[23] Throughout 2025, there was an increase in influenza activity in the Asian region, with A(H3N2) dominance in several countries. WHO surveillance data indicate that influenza positivity rates exceeded 30% during the late 2025 period in a number of countries in this region.[15,24]

Most SEAR countries do not yet have comprehensive seasonal influenza vaccination policies, and influenza vaccine coverage remains low regionally. WHO recognizes this region as a critical reservoir for the emergence of new influenza strains, given the combination of large populations, high density, intense human-animal interaction, and still-limited surveillance capacity.[23]

WHO Western Pacific Region

WHO Western Pacific surveillance data show a significant increase in influenza activity in several countries during the last quarter of 2025. Japan experienced the onset of the influenza season approximately 5 weeks earlier than usual, with a national epidemic declared on 3 October 2025. At its peak (17-23 November 2025), Japan reported 196,895 cases per week from 3,000 sentinel medical institutions, with 94% of cases being A(H3N2) subclade K, accompanied by partial or full closure of 8,817 schools and kindergartens.[25-27]

Malaysia reported a sharp increase in influenza clusters in October 2025, from 14 clusters in EW39 to 97 clusters in EW40 (a sevenfold increase), then peaking at 202 clusters in EW41, with the majority (66%) occurring in school settings. Approximately 6,000 students were reported infected across various states, forcing the closure of several schools. Two children were reported to have died in Sarawak and Terengganu.[25,28,29] Thailand recorded more than 940,000 cumulative cases throughout 2025, with 100 deaths, of which 94% had never received an influenza vaccination. The median age of death was 61 years, and 57% had comorbidities.[25,30,31]

In Australia and New Zealand, the 2025 influenza season lasted longer than usual due to the emergence of subclade K, which has dominated circulation since August 2025.[15,16] This pattern is consistent with global observations showing the rapid spread and dominance of subclade K across multiple regions.[15,16]

NATIONAL SITUATION IN INDONESIA

Surveillance Infrastructure

Indonesia has an integrated influenza surveillance system through the Ministry of Health of the Republic of Indonesia, which includes 39 Influenza-Like Illness (ILI) sentinel primary health centers, 35 Severe Acute Respiratory Infection (SARI) sentinel hospitals, and 14 Health Quarantine Offices at points of entry.[32] This system enables continuous monitoring of influenza activity and viral characteristics.

Influenza Dynamics in Indonesia: October 2025 - January 2026

Surveillance data indicate that influenza activity in Indonesia increased in late 2025, followed by a decline in early 2026. In the first week of 2026, the influenza positivity rate reached 43%, then decreased to 16% in the following week, with overall activity levels categorized as low.[32] During this period, there was a shift in the dominant subtype from A(H3N2) in the previous phase to A (H1N1) pdm09 in early 2026.

This pattern reflects the typical dynamics of influenza waves in tropical countries: a sharp increase over 3-5 weeks, followed by a gradual decline. Unlike in temperate countries, the timing of influenza waves in Indonesia cannot be predicted based on classical seasonal patterns, emphasizing the need for year-round preparedness.[33-36]

Subclade K in Indonesia

Analysis of subclade K distribution shows that this variant has been detected in at least 13 provinces in Indonesia, with the highest

proportions in East Java and South Kalimantan (each 24%), followed by West Java (15%).[17] Most cases occur among children and young adults, and are clinically dominated by mild to moderate manifestations, with severe cases primarily occurring in high-risk groups.

INFLUENZA VACCINE COMPOSITION 2025-2026: TRANSITION TO TRIVALENT

WHO Recommendations

The World Health Organization recommends the following trivalent vaccine composition for the Northern Hemisphere 2025-2026: (a) A/Victoria/4897/2022 (H1N1)pdm09-like (egg-based) or A/Wisconsin/67/2022-like (cell/recombinant); (b) A/Croatia/10136RV/2023 (H3N2)-like (egg-based) or A/District of Columbia/27/2023-like (cell/recombinant); and (c) B/Austria/1359417/2021 (B/Victoria lineage)-like.[37]

For the Southern Hemisphere 2026, the components are updated to: (a) A/Missouri/11/2025-like (H1N1)pdm09; (b) A/Singapore/GP20238/2024-like (H3N2) becoming a better-matched strain to circulating viruses, which epidemiologically coincides with the increasing circulation of subclade K in various regions; and (c) B/Austria/1359417/2021-like (B/Victoria).[38]

Exclusion of B/Yamagata

The WHO's decision to recommend the exclusion of the B/Yamagata component from influenza vaccines is based on the fact that this lineage has not been detected in global circulation since March 2020. Although it is considered too early to declare extinction, since September 2023, the World Health Organization has consistently no longer recommended the inclusion of the B/Yamagata component in seasonal influenza vaccine composition, and this position has been maintained in subsequent recommendations.[37,38]

The transition to trivalent vaccines applies to all production platforms: egg-based, cell culture, recombinant, and nucleic acid-based. For quadrivalent vaccines still in production or distribution, the B/Yamagata component continues to use the B/Phuket/3073/2013-like strain; however, WHO will no longer issue updated recommendations for this component.[38]

Vaccine Effectiveness against Subclade K

Although serological studies show reduced antigenic reactivity between vaccines and subclade K, real-world data from several countries provide sufficiently convincing evidence that vaccination remains clinically effective. Kirsebom et al. (2025) reported vaccine effectiveness against emergency department visits at 74.8% (95% CI: 66.3-81.4%) in children aged 2-17 years and effectiveness against hospital admissions at 32-39% in adults in the United Kingdom.[10] Separovic et al. (2026) from Canada estimated vaccine effectiveness at around 40% against A(H3N2), including subclade K, in primary care settings, with the interpretation that meaningful protection persists despite substantial vaccine mismatch.[17]

Interim data from eight European countries during the 2024/25 season also show consistent vaccine effectiveness against influenza A, supporting the recommendation that vaccination remains the most effective public health intervention.[39]

IMPLICATIONS FOR VACCINATION POLICY IN INDONESIA

The epidemiological data presented in this paper have several strategic implications for influenza vaccination policy in Indonesia. First, the absence of the B/Yamagata lineage in global circulation since 2020, along with the recommendation from the World Health Organization to no longer include this component in seasonal influenza vaccines, provides a scientific basis for considering a transition to trivalent vaccines.[37,38]

Second, the transition to TIV has the potential to improve production efficiency and reduce cost per dose, which in turn could expand access to vaccination, an especially relevant factor for lower-middle-income countries such as Indonesia. With adult influenza vaccination coverage still very low, reduced vaccine prices could act as a catalyst for increasing coverage.[40]

Third, data from countries in the region show that the majority of influenza-related

deaths occur in unvaccinated individuals. Data from Thailand, indicating that 94% of influenza-related deaths occurred among unvaccinated individuals, provide strong empirical evidence to prioritize increasing vaccination coverage in high-risk groups, regardless of the vaccine formulation used.[25,30,31]

Fourth, the dynamics of influenza in Indonesia, which do not follow classical seasonal patterns and may involve year-round circulation, highlight the need for a flexible and continuous vaccination approach, in contrast to seasonal strategies used in temperate countries.[32,40]

Fifth, the successful implementation of vaccination policies, including the potential transition from quadrivalent to trivalent vaccines, requires effective risk communication to healthcare workers and the public. It is important to emphasize that changes in vaccine composition are based on scientific considerations related to virus circulation dynamics, and do not represent a reduction in the quality of the intervention.[37,38]

CONCLUSION

The global and national influenza epidemiological landscape during the 2025-2026 period shows the dominance of A(H3N2), including subclade K, across various regions, with rapid spread but no evidence of a significant increase in clinical severity to date. In Indonesia, the increase in influenza activity observed in late 2025 declined in early 2026, with the positivity rate returning to low activity levels. Influenza vaccination remains one of the most effective public health interventions to prevent severe disease and mortality, despite reduced antigenic match between the vaccine and circulating viruses.

The transition from quadrivalent to trivalent vaccines, as recommended by the World Health Organization since 2023, is supported by the absence of the B/Yamagata lineage in global circulation since 2020. In addition to virological considerations, this transition also has strategic implications, including the potential for increased production efficiency and expanded access to vaccination.

For Indonesia, this momentum can be leveraged to strengthen influenza surveillance systems, increase vaccination coverage, especially among high-risk groups, and develop preparedness strategies that are adaptive to influenza dynamics in tropical regions, which do not follow classical seasonal patterns.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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None.

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