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STATEMENT ON THE TRANSITION FROM QUADRIVALENT TO TRIVALENT SEASONAL INFLUENZA VACCINES IN AUSTRALIA

It is important to read this statement in conjunction with the Australian Immunisation Handbook, available at immunisationhandbook.health.gov.au

Overview of key points and updates

- Australia is transitioning from using quadrivalent influenza vaccine (QIV) to trivalent influenza vaccine (TIV) formulations for influenza immunisation in our population. During the transition period, ATAGI supports the use of either QIV or TIV.
- In Australia, the TIV was used for many years until 2016, when the QIV became available on the National Immunisation Program (NIP). However, in late 2023, the World Health Organization (WHO) and the Australian Influenza Vaccine Committee (AIVC) recommended that the B/Yamagata lineage component is no longer warranted in seasonal influenza vaccines. This is because the Yamagata lineage of the influenza B virus has not circulated for several years.
- WHO recommends trivalent vaccines for use in the 2024–25 influenza season in the Northern Hemisphere and with select strains depending on whether using egg-, cell-, or recombinant-based technology. However, the B/Yamagata lineage component remains unchanged in any available QIV.[1]
- The TIV includes the haemagglutinin antigen of an A/H1 subtype, an A/H3 subtype and a B lineage, which are selected to match the circulating strains for each influenza season as well as possible. The QIV comprises both B lineages of the influenza virus.
- During the transition from QIV to TIV, Australia will ensure that the supply of vaccine is adequate and secure. Some TIV formulations may become available in 2025 to be used alongside QIV, which will continue to be available. It is anticipated that TIV may be used exclusively by the 2026 influenza season.
- Studies comparing egg-based QIV with TIV have shown no significant differences in safety and reactogenicity outcomes. This indicates that a return to the TIV formulation for all influenza vaccines is not expected to adversely impact influenza vaccine safety.
- Studies have also demonstrated that, for each of the shared strains contained in the egg-based QIV compared with the corresponding TIV formulation, any differences in antibody response were minimal. This is true for both the standard-dose and the enhanced (high-dose and adjuvanted) influenza vaccines. Immunogenicity was consistent across age groups and in pregnant people.
- While there are no data comparing cell-based influenza vaccines, it is not anticipated that there will be any immunogenicity or safety differences between cell-based TIV and cell-based QIV.
- Annual vaccination remains the most important strategy to prevent influenza and its complications, and is recommended for all people aged ≥6 months. Even though the B/Yamagata lineage is no longer circulating, high disease burden associated with influenza A (H1N1 and H3N2) subtypes and the influenza B/Victoria lineage continues.

Summary of key considerations

Epidemiology

- Currently, QIVs are designed to protect against 4 different strains of influenza virus each season — 2 A strains and 2 B strains. However, circulation of the B/Yamagata lineage has not been detected globally since March 2020, leaving only one B lineage in circulation, B/Victoria.
- COVID-19 mitigation strategies may have contributed to elimination of B/Yamagata. However, influenza disease burden on the population overall has returned to similar levels as pre-pandemic years.
- In the year to date, up to 11 August 2024, there were 285,965 influenza notifications reported to the National Notifiable Diseases Surveillance System (NNDSS), which is higher than the number of notifications in the same period for the previous five-year mean (excluding 2020 and 2021). In the year to date, up to 28 July 2024, there were 238 influenza-associated deaths notified to the NNDSS.[2]

- Since influenza surveillance commenced on 1 April 2024, there were 2,511 patients admitted with influenza to Influenza Complications Alert Network (FluCAN) sentinel hospitals, of whom 6.5% (162/2,511) were admitted directly to intensive care.[2]
- In the year to date, up to 11 August 2024, the WHO Collaboration Centre (WHOCC) characterised 2,316 influenza viruses, of which 47.9% (1,109/2,316) were influenza A(H1N1), 47.8% (1,107/2,316) were influenza A(H3N2) and 4.3% (100/2,316) were influenza B/Victoria. In the year to date, up to 11 August 2024, the WHOCC has not characterised any influenza B/Yamagata viruses.[2]

Vaccine reactogenicity and safety

- The proportion of solicited local and systemic adverse events reported from randomised controlled trials (RCTs) were similar between groups who had received either QIV or TIV that include the B/Victoria lineage (TIV-Vic) as the standard dose.
- The relative risk (RR) of a local adverse event occurring after receiving a standard-dose QIV compared to standard-dose TIV is 0.91–1.16.[3-5] Reviews of systemic adverse events also suggest no, or only small, differences (RR = 1.05–1.10).[3-5]
- Regarding standard-dose influenza vaccines, rates of serious adverse events (SAEs) reported were low and similar between groups (0–4.5% for QIV and 0–6.3% for TIV). None of the SAEs were considered related to the study vaccine.[6-10] A systematic review of RCTs showed similar safety profiles between QIV and TIV in rates of SAEs (RR = 0.91 [95% CI: 0.67–1.23]).[5]
- In an RCT comparing high-dose QIV to high-dose TIV pooled, the proportions of any unsolicited adverse events were similar between groups (16.4% and 16.5%, respectively).[11] Reports of SAEs were generally similar between groups. Among these, a single case of neuropathy was reported 42 days after QIV administration; however other factors were noted to be potentially contributory. No other events were considered related to the vaccine.[11]
- In an RCT comparing adjuvanted QIV with adjuvanted TIV-Vic, the proportions of any unsolicited adverse events were similar between groups (15.3% and 11.3%, respectively).[6] Reports of SAEs were also generally similar between groups and none were considered related to the study vaccine.
- Although data on SAEs are reported in RCTs, these studies are not statistically powered to detect rare SAEs. As TIVs were widely used before the introduction of QIVs, no new SAEs are anticipated with transitioning back to TIVs.

Vaccine efficacy/effectiveness

- An observational study in the United States compared TIV to QIV across 6 influenza seasons. The study included more than 25,000 participants across different age groups (6 months to ≥65 years). In seasons where the main circulating B strain was the one included in the TIV in that season, the vaccine effectiveness of QIV and TIV against influenza B cases was largely comparable across all age groups when compared to unvaccinated people (Table 1).[12]

Table 1. Vaccine effectiveness of QIV and TIV against influenza B cases when compared to unvaccinated people

Age group	Vaccine	Adjusted vaccine effectiveness (95% CI)
≥6 months	TIV	56% (43–67)
	QIV	53% (40–63)
6 months to 17 years	TIV	73% (50–86)
	QIV	51% (27–67)
18-49 years	TIV	61% (35–77)
	QIV	69% (49–81)
≥50 years	TIV	46% (20–63)
	QIV	41% (13–60)

International observational studies also examined the original transition from TIV to QIV. The incremental protective benefit of QIV compared to TIV has been modest (relative vaccine effectiveness 8–12% against hospitalisation) in seasons dominated by the influenza B lineage not contained in TIV.[13]

Vaccine immunogenicity

- Systematic reviews and RCTs have evaluated the immunogenicity of QIV compared to TIV. The shared strains of QIV and TIV had no statistically significant differences in immunogenicity for the **standard dose influenza vaccine across various age groups**, in **pregnant people**, and for the **enhanced influenza (adjuvanted and high-dose influenza) vaccines** used in older adults.[3,6,9-11,14]

Changing landscape of influenza vaccines and program in Australia

- Since WHO and the AIVC recommended that the B/Yamagata lineage component is no longer warranted in seasonal influenza vaccines, TIV formulations will replace QIV formulations during manufacturing.
- The pace of the transition to using TIV formulations will be subject to Therapeutic Goods Administration (TGA) approval requirements and timelines, manufacturers' abilities to produce secure supplies of the various TIV formulations and current QIV contractual arrangements.
- During the transition period, QIV may continue to be supplied for the NIP while TIV is being gradually re-introduced for use in Australia, both for private prescription and for the NIP. It is anticipated that TIV formulations may become available for private prescription from 2025, and transition to exclusive TIV use may be completed for the 2026 influenza season.
- This transition will involve vaccine platforms that have previously been used for producing TIV (that is, those that were registered before the switch to QIV), as well as influenza vaccine platforms that have only been registered as QIV in Australia. This includes cell-based (cIV) and recombinant influenza vaccines (RIV) and, potentially, other newer platforms such as mRNA vaccines. The registration of TIV formulations using these newer platforms will be subject to TGA approval requirements and timelines.
- The Australian Government Department of Health and Aged Care, in collaboration with all states and territories, will continue to systematically plan for the rollout of using TIV on the NIP. Further information and guidance for immunisation providers will be provided when it becomes available.

Impact and evaluation

- As there are no changes to the delivery of the vaccine program, seasonal influenza vaccine will remain available for all who are recommended to receive it, including at-risk population groups. No disadvantage to any recommended or funded group is anticipated.
- Australian and international surveillance systems continue to monitor the vaccine effectiveness of QIV and TIV.

Key information for discussion with patients

- No specific issues of concern regarding vaccine safety or effectiveness are anticipated regarding the change from using QIV to TIV formulations.
- During the transition period, it is acceptable to offer a QIV formulation if TIV is not yet available.
- The TIV formulation contains the same antigens as the QIV formulation, except for the B/Yamagata lineage, which is no longer circulating. WHO has recommended using a TIV formulation, and is an appropriate seasonal influenza vaccine.
- Immunisation providers can reassure people about these points. Availability or accessibility of influenza vaccines will not change, and people eligible for NIP-funded influenza vaccines will stay eligible.[15,16]

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