Open Forum Infectious Diseases

MAJOR ARTICLE

Effectiveness of the 2023 Southern Hemisphere Influenza Vaccine Against Outpatient Influenza-Like Illness: A Multi-Country Test-Negative Design Study

Annette K. Regan,[1,2,3,a] Radhika Gharpure,[4,a] Monique Chilver,[5] Nigel Stocks,[5] Siobhan St George,[6] Sibongile Walaza,[7,8] Anne von Gottberg,[7,9] Nicole Wolter,[7,9] Cheryl Cohen,[7,8] Aaron M. Samuels,[4,10] Kriengkrai Prasert,[11,12] Prabda Praphasiri,[12,13] William W. Davis,[13] Chakrarat Pittayawonganon,[14] Sheena G. Sullivan,[2,5,15] and Eduardo Azziz-Baumgartner[4]

[1]Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, California, USA, [2]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, California, USA, [3]School of Nursing and Health Professions, University of San Francisco, San Francisco, California, USA, [4]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, [5]The Discipline of General Practice, The University of Adelaide, Adelaide, South Australia, Australia, [6]Public Health and Surveillance Branch, Interim Australian Centre for Disease Control, Australian Government Department of Health, Disability and Ageing, Canberra, Australian Capital Territory, Australia, [7]Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases of the National Health Laboratory Service, Johannesburg, South Africa, [8]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [9]School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [10]Influenza Program, Centers for Disease Control and Prevention, Pretoria, South Africa, [11]Nakhon Phanom Provincial Hospital, Nai Mueang, Mueang Nakhon Phanom District, Nakhon Phanom, Thailand, [12]Faculty of Public Health, Kasetsart University, Chalermprakiat Sakon Nakhon Province Campus, Mueang Sakon Nakhon District, Sakon Nakhon, Thailand, [13]Influenza Program, Thailand Ministry of Public Health-U.S. Centers for Disease Control and Prevention Collaboration, Muang, Nonthaburi, Thailand, [14]Institute of Preventive Medicine, Department of Disease Control, Ministry of Public Health, Muang, Nonthaburi, Thailand, and [15]School of Clinical Sciences, Monash University, Melbourne, Victoria, Australia

Background. Routine monitoring of seasonal influenza vaccine effectiveness (VE) across multiple countries is essential to understand the performance of seasonal vaccine programs.

Methods. Using a test-negative study design, we estimated the effectiveness of the 2023 Southern Hemisphere formulation of the seasonal influenza vaccine in preventing outpatient medically attended influenza-like illness (ILI) in Australia, South Africa, and Thailand. Sentinel surveillance systems identified patients presenting with ILI who were tested by RT-PCR for influenza. VE was estimated as one minus the odds ratio comparing the vaccination status of test-positive cases and test-negative non-cases. Models adjusted for country, patients' age group, sex, underlying medical conditions, and calendar week of symptom onset. We assessed the duration of protection by modeling the effect of the interval between vaccination and symptom onset on influenza status.

Results. About 2469 ILI outpatients were identified, including 966 (39%) test-positive cases and 1503 (61%) test-negative non-cases; 78% ($n = 750/966$) of viruses detected were influenza A; 8% ($n = 72/966$) of test-positive cases and 29% ($n = 439/1503$) of test-negative non-cases had received an influenza vaccine. Pooled VE was 68% (95% CI: 57%, 76%) against ILI with any influenza virus, 62% (95% CI: 39%, 76%) against influenza A(H1N1)pdm09, 60% (95% CI: 38%, 75%) against influenza A(H3N2), and 76% (95% CI: 59%, 86%) against influenza B. VE point estimates declined from 82% to 43% when the time from vaccination increased from 14 days to 150 days.

Conclusions. The 2023 Southern Hemisphere formulation of seasonal influenza vaccines offered protection against ILI in three countries, underscoring the public health benefits of seasonal influenza vaccination programs.

Keywords. influenza vaccine; pooled analysis; surveillance; test-negative design; vaccine effectiveness.

Seasonal influenza vaccination programs can be used to mitigate the impact of the influenza virus and reduce overall disease burden in the community. Assessing the effectiveness of influenza vaccines in real-world settings is crucial for optimizing vaccination strategies and informing evidence-based public health policy decisions. Globally, many countries use data from sentinel surveillance systems, including influenza-like illness (ILI) surveillance for outpatient illnesses [1], to estimate influenza vaccine effectiveness (VE) using the test-negative design [2, 3]. Evaluation of influenza VE in the outpatient setting can provide valuable information to complement inpatient VE estimates [4]. Medically attended outpatient cases can represent a large portion of total influenza illnesses [5, 6], result in substantial economic burden [7, 8], and might represent

Received 15 April 2025; accepted 29 August 2025; published online 17 September 2025

[a]Authors contributed equally.

Correspondence: Annette Regan, PhD, MPH, Department of Research & Evaluation, Kaiser Permanente Southern California, 100 S. Los Robles Ave, Pasadena, CA 91101, USA (annette.k.regan@kp.org); Eduardo Azziz-Baumgartner, MD, MPH, Global Influenza Division, Centers for Disease Control and Prevention, 1600 Clifton Rd N E, Atlanta, GA 30333, USA (eha9@cdc.gov).

Open Forum Infectious Diseases®

© The Author(s) 2025. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

https://doi.org/10.1093/ofid/ofaf560

Downloaded from https://academic.oup.com/ofid/article/12/10/ofaf560/8252015 by guest on 01 December 2025

different patient populations than those captured via inpatient surveillance. Multi-country evaluations offer the opportunity to assess VE with improved power and in a variety of settings with different influenza vaccines, populations, and distribution of influenza viruses.

In this analysis, we estimated VE against outpatient illness for the 2023 Southern Hemisphere formulation of the influenza vaccines (including an A/Sydney/5/2021(H1N1)pdm09-like virus, an A/Darwin/9/2021(H3N2)-like virus, a B/Austria/1359417/2021(B/Victoria lineage)-like virus, and a B/Phuket/3073/2013(B/Yamagata lineage)-like virus) [9] in three countries: Australia; South Africa; and Thailand. We estimated country-specific and pooled VE against medically attended laboratory-confirmed influenza, as well as VE against specific influenza subtypes, among age groups, among children and adults with underlying health conditions, and by the time since influenza vaccination.

METHODS

Data Sources and Study Design

We describe the surveillance systems and networks used in this analysis in Supplementary Table 1. In Australia, surveillance data were obtained from the Australian Sentinel Practices Research Network (ASPREN), a network of 304 general practitioners located nationwide, 93 of whom provided nasopharyngeal swabs for pathogen testing in 2023 [10]. In South Africa, data were obtained from the Viral Watch sentinel influenza surveillance program, including 98 sentinel general practices across eight of the nine provinces [11, 12]. In Thailand, data were obtained from 9 outpatient clinics conducting ILI surveillance across eight provinces [13, 14]. South Africa and Thailand used the standardized case definition for ILI, defined as measured fever of ≥38° C and cough with onset within the last 10 days [1]. Australia used a slightly modified version of this case definition, including ILI patients with onset of symptoms within the last 7 days. For each country, the study period for VE estimation included periods of seasonal influenza virus circulation, as determined by visual examination of weekly influenza virus detections reported for each country in FluNet (Supplementary Table 1) [15].

This multi-country study combined de-identified individual-level data from participating surveillance systems, including: patient demographics (age, sex, and presence of one or more underlying health conditions); influenza vaccination history; dates of illness onset, consultation, and sample collection; reverse transcription polymerase chain reaction (RT-PCR) influenza test results; and influenza type and subtype. Influenza vaccination history was obtained by medical record review, self-report, or review of the national immunization register. In South Africa and Thailand, both trivalent and quadrivalent influenza vaccines were available (Supplementary Table 1). In Australia, only quadrivalent influenza vaccines were available.

Eligibility Criteria

Eligible patients included those who were 12 months of age or older, who presented with an ILI at a participating sentinel site during the influenza season, and were tested by RT-PCR for influenza within 10 days of symptom onset. We deemed ineligible for analysis those patients who had a missing influenza test result, had a date of symptom onset before the 2023 seasonal vaccine campaign or outside the influenza season, were sampled >10 days post-illness onset, or tested positive for SARS-CoV-2. We additionally restricted the final dataset to patients with complete information about the presence of underlying health conditions, sex, and age, since these variables were used as covariables in VE estimation and would be dropped from the model if data were missing. Patients missing their vaccination date or who were vaccinated within 14 days prior to illness onset were excluded. To allow sufficient time for infants to receive both recommended doses of influenza vaccine at first vaccination, the minimum age for inclusion in the study was one year.

Exposure and Outcome Ascertainment

Cases were defined as patients with ILI who tested positive by RT-PCR for influenza virus, while non-cases were patients with ILI who tested negative for both influenza virus and SARS-CoV-2. SARS-CoV-2-positive patients were excluded to avoid selection bias associated with SARS-CoV-2 vaccination [16, 17].

Patients were classified as vaccinated if they had a date of influenza vaccination ≥14 days prior to illness onset or, if missing, consultation, based on medical record review, immunization register data, or self-report. We assumed that all vaccinated patients had received the 2023 Southern Hemisphere formulation offered in their country and were not vaccinated elsewhere. Patients with no history of influenza vaccination during the current season or with a record of vaccination after the date of symptom onset were classified as unvaccinated.

Data Analysis

VE was calculated as one minus the odds ratio (OR) comparing the odds of vaccination among test-positive cases versus test-negative non-cases (VE = [1−OR] × 100%), using logistic regression. Models were adjusted for age group (1–4 years, 5–17 years, 18–44 years, 45–64 years, and ≥65 years), sex, underlying health conditions (≥1 condition or none), and week of symptom onset (fit as a cubic spline).

VE was first estimated separately for each country. To evaluate heterogeneity in VE estimates across countries, we conducted random effects meta-analyses of all countries where there were sufficient data (ie, where there were no zero counts in any cell of the 2 × 2 table, the width of the 95% confidence interval (CI) was restricted to <140%, and where ≥3 country-specific estimates were available). Meta-analyses were conducted overall

Downloaded from https://academic.oup.com/ofid/article/12/10/ofaf560/8252015 by guest on 01 December 2025

and by virus type and subtype. Heterogeneity among country estimates was assessed using I^2 and τ^2 statistics [18]. We deemed I^2 < 40% to be low heterogeneity [18] and the data suitable for pooling.

For pooled VE estimates, a multilevel mixed model was used that included a random intercept for country to account for within-country correlations. Pooled analyses were performed by age group and among those with underlying medical conditions. To evaluate the persistence of protection against influenza, we conducted subgroup analyses to estimate VE by the interval between vaccination and symptom onset. We constructed models treating time since vaccination in days as a continuous variable (fit using natural cubic splines) and as a categorical variable (<45 days, 45–89 days, 90–119 days, 120–149 days, ≥ 150 days). All analyses were performed in Stata SE (17.0) and R (4.2.2).

Ethical Considerations

Surveillance systems and VE networks were reviewed by in-country ethics review committees (Australia: Royal Australian College of General Practitioners; South Africa: University of the Witwatersrand Human Research Ethics Committee [HREC]); Thailand sentinel surveillance did not require ethics review. Additionally, this activity was reviewed by the US Centers for Disease Control and Prevention (CDC), deemed not to constitute human subjects research, and conducted consistent with applicable federal law and CDC policy.

Role of the Funding Source

ASPREN is supported by the Australian Government Department of Health and Aged Care. Surveillance in South Africa was supported by the National Department of Health and the National Institute for Communicable Diseases, South Africa. Sentinel surveillance in Thailand is supported by the US CDC through a cooperative agreement with the Thailand Ministry of Public Health.

Ethics approval. This study was performed in line with the principles of the Declaration of Helsinki. Australian data were collected with approval from the Royal Australian College of General Practitioners National Research and Evaluation Ethics Committee (NREEC 18–003). South African data were collected with approval from the University of the Witwatersrand Human Research Ethics Committee (HREC, M150855). Influenza surveillance in Thailand did not require ethical approval from the Ministry of Public Health. The protocol was reviewed by the US Centers for Disease Control and Prevention (CDC) and deemed to not constitute human subjects research and conducted consistent with applicable federal law and CDC policy.

RESULTS

Between 1 January and 30 November 2023, the three participating countries identified 4218 patients attending outpatient care for ILI (Australia: 1577; South Africa: 600; Thailand: 2041). Among these, 2683 (64%) were eligible for inclusion in the VE analysis (Australia: 987; South Africa: 516; Thailand: 1180; Supplementary Figure 1). We excluded 1068 patients with a date of symptom onset outside of the influenza season, 165 who were <1 year old at symptom onset, 155 who tested positive for SARS-CoV-2, 144 who were sampled >10 days after symptom onset, two with a symptom onset before seasonal vaccine availability, and one with a missing RT-PCR result for influenza.

Among the 2683 eligible patients with ILI, a further 214 (8.0%) were excluded due to missing vaccination status ($n = 21$) or missing covariable information, including those missing information on underlying medical conditions ($n = 168$) or sex ($n = 25$). The final sample for analysis included 2469 patients with ILI: 827 from Australia, 470 from South Africa, and 1172 from Thailand.

Among the 2469 patients with ILI, 966 (39%) tested positive (ie, test-positive cases) for influenza and 1503 (61%) tested negative for influenza (ie, test-negative non-cases) (Table 1). Most viruses detected were influenza A ($n = 750$; 78%), with influenza A(H3N2) making up 49% of viruses detected and influenza A(H1N1)pdm09 making up 27% of viruses detected; 1% of influenza A viruses were not subtyped. The remaining 217 (22%) viruses identified were influenza B. In Australia, 56% of detections were influenza A, with 76% of influenza A detections positive for A(H1N1)pdm09, 21% positive for A(H3N2), and the remainder unsubtyped. In South Africa, 99% of detections were influenza A, of which 97% were A(H3N2) and 1.5% were A(H1N1)pdm09. In Thailand, 75% of detections were influenza A, of which 46% were A(H1N1)pdm09% and 52% were A(H3N2). The peak of influenza detections occurred in late May for South Africa, late June for Australia, and early October for Thailand, though the latter had continued circulation through November (Figure 1).

Among the 966 test-positive cases, 72 (8%) had received a 2023 seasonal influenza vaccine, while 439 (29%) of the test-negative non-cases had received an influenza vaccine. Point estimates for VE against ILI from any influenza virus were 68% (95% CI: 51%, 79%) for Australia, 74% (95% CI: 23%, 91%) for South Africa, and 58% (95% CI: 34%, 73%) for Thailand (Figure 2; Supplementary Table 2). Random effects meta-analysis indicated low heterogeneity in VE estimates by country ($I^2 < 1\%$; $P = .63$), enabling pooling of data across countries.

Pooled estimates, inclusive of data from Australia, Thailand, and South Africa, are shown in Figure 3. Pooled VE was 68% (95%CI: 57%, 76%) against ILI associated with any influenza virus, 63% (95% CI: 49%, 73%) for influenza A, 62% (95%CI: 39%, 76%) against influenza A(H1N1)pdm09, 60% (95% CI: 38%, 75%) against influenza A(H3N2), and 76% (95%CI: 59%, 86%) against influenza B (Figure 2). By age group, point

Downloaded from https://academic.oup.com/ofid/article/12/10/ofaf560/8252015 by guest on 01 December 2025

Table 1. Characteristics of Test-positive Cases and Test-negative Non-cases Among Patients Presenting With Influenza-like Illness—Australia, South Africa, Thailand, 2023

Characteristic	Total ($n = 2469$)		Australia ($n = 827$)		South Africa ($n = 470$)		Thailand ($n = 1172$)	
	Test-Positive Cases ($n = 966$) *n* (%)	Non-cases ($n = 1503$) *n* (%)	Test-Positive Cases ($n = 202$) *n* (%)	Non-cases ($n = 625$) *n* (%)	Test-Positive Cases ($n = 268$) *n* (%)	Non-cases ($n = 202$) *n* (%)	Test-Positive Cases ($n = 496$) *n* (%)	Non-cases ($n = 676$) *n* (%)
Patient sex								
Female	500 (51.8)	811 (54.0)	100 (49.5)	328 (52.5)	148 (55.2)	123 (60.9)	252 (50.8)	360 (53.3)
Male	466 (48.2)	692 (46.0)	102 (50.5)	297 (47.5)	120 (44.8)	79 (39.1)	244 (49.2)	316 (46.7)
Patient age group								
1–18 y	508 (52.6)	607 (40.4)	88 (43.6)	159 (25.4)	83 (31.0)	53 (26.2)	337 (67.9)	395 (58.4)
1–4 y	95 (9.8)	261 (17.4)	13 (6.4)	72 (11.5)	6 (2.2)	5 (2.5)	76 (15.3)	184 (27.2)
5–17 y	413 (42.7)	346 (23.0)	75 (37.1)	87 (13.9)	77 (28.7)	48 (23.8)	261 (52.6)	211 (31.2)
18–64 y	830 (85.9)	1003 (66.7)	178 (88.1)	386 (61.8)	248 (92.5)	179 (88.6)	404 (81.5)	438 (64.8)
18–44 y	184 (19.0)	258 (17.2)	36 (17.8)	102 (16.3)	77 (28.7)	56 (27.7)	71 (14.3)	100 (14.8)
45–64 y	233 (24.1)	399 (26.5)	67 (33.2)	197 (31.5)	94 (35.1)	75 (37.1)	72 (14.5)	127 (18.8)
≥65 y	41 (4.2)	239 (15.9)	11 (5.5)	167 (26.7)	14 (5.2)	18 (8.9)	16 (3.2)	54 (8.0)
Underlying medical condition								
≥1 condition	198 (20.5)	529 (35.2)	75 (37.1)	322 (51.5)	64 (23.9)	204 (76.1)	59 (11.9)	437 (88.1)
No conditions	768 (79.5)	974 (64.8)	127 (62.9)	303 (38.5)	58 (28.7)	144 (71.3)	149 (22.0)	527 (78.0)
Influenza vaccination status								
Vaccinated	72 (7.5)	439 (29.2)	37 (18.3)	323 (51.7)	5 (1.9)	16 (7.9)	30 (6.1)	100 (14.8)
Unvaccinated	894 (92.5)	1064 (70.8)	165 (81.7)	302 (48.3)	263 (98.1)	186 (92.1)	466 (93.9)	576 (85.2)
RT-PCR result								
Influenza positive	966 (100)	–	202 (100)	–	268 (100)	–	496 (100)	–
Influenza A	750 (77.6)	–	113 (55.9)	–	264 (98.5)	–	373 (75.2)	–
A(H1N1)pdm09	263 (27.2)	–	86 (42.6)	–	4 (1.5)	–	173 (34.9)	–
A(H3N2)	474 (49.1)	–	24 (11.9)	–	256 (95.5)	–	194 (39.1)	–
A/unsubtyped	12 (1.2)	–	3 (1.5)	–	4 (1.5)	–	5 (1.0)	–
Influenza B	217 (22.5)	–	89 (44.1)	–	4 (1.5)	–	124 (25.0)	–
Influenza negative	0 (0)	1503 (100)	0 (0)	625 (100)	0 (0)	202 (100)	0 (0)	676 (100)

estimates for pooled VE against ILI from any influenza virus were highest among children 1–4 years old (97% [95% CI: 78%, 100%]) and lowest among adults 35–64 years old (45% [95% CI: 14%, 65%]) and adults 65 years and older (61% [95% CI: −2%, 85%]) (Figure 3; Supplementary Table 3).

Among those with underlying medical conditions, VE against ILI associated with any influenza virus was 59% (95% CI: 36%, 74%). VE was 57% (95% CI: 27%, 74%) against influenza A, 53% (95% CI: 4.1%, 77%) against influenza A(H1N1)pdm09, 50% (95% CI: −7.4%, 77%) against influenza A(H3N2), and 60% (95% CI: 11%, 82%) against influenza B (Figure 4; Supplementary Table 4). Among patients with an underlying medical condition, the point estimate for VE against ILI associated with any influenza virus was highest among children 1–4 years old (95% [95% CI: 17%, 100%]) and lowest among adults 35–64 years old (31% [95% CI: −33%, 64%]) (Figure 4); however, the estimate for children aged 1–4 years with medical conditions was based on a single vaccinated case and should therefore be interpreted with caution.

When we considered the time between vaccination and onset of ILI, we observed a reduction in the point estimates for VE as the interval between vaccination and symptom onset increased, occurring most notably around 120–150 days post-vaccination (Figure 5; Supplementary Table 5). VE against ILI associated with any influenza virus was 82% (95% CI: 63%, 91%) at 14–44 days after vaccination, 69% (95% CI: 52%, 80%) at 45–89 days after vaccination, 74% (95% CI: 52%, 86%) at 90–119 days after vaccination, 42% (95% CI: −8.7%, 69%) at 120–149 days after vaccination, and 43% (95% CI: −22%, 73%) at 150 days or longer after vaccination (Supplementary Table 5 & 6). This pattern was similar for children 1–17 years old and adults 18–64 years old, although estimates for children 1–17 years old included small numbers of vaccinated cases and should therefore be interpreted with caution. Waning was less apparent for adults ≥65 years old (Figure 5); however, confidence intervals were wide and there were insufficient data to assess the time since vaccination among adults ≥65 years old >90 days since vaccination (Supplementary Table 6).

Downloaded from https://academic.oup.com/ofid/article/12/10/ofaf560/8252015 by guest on 01 December 2025

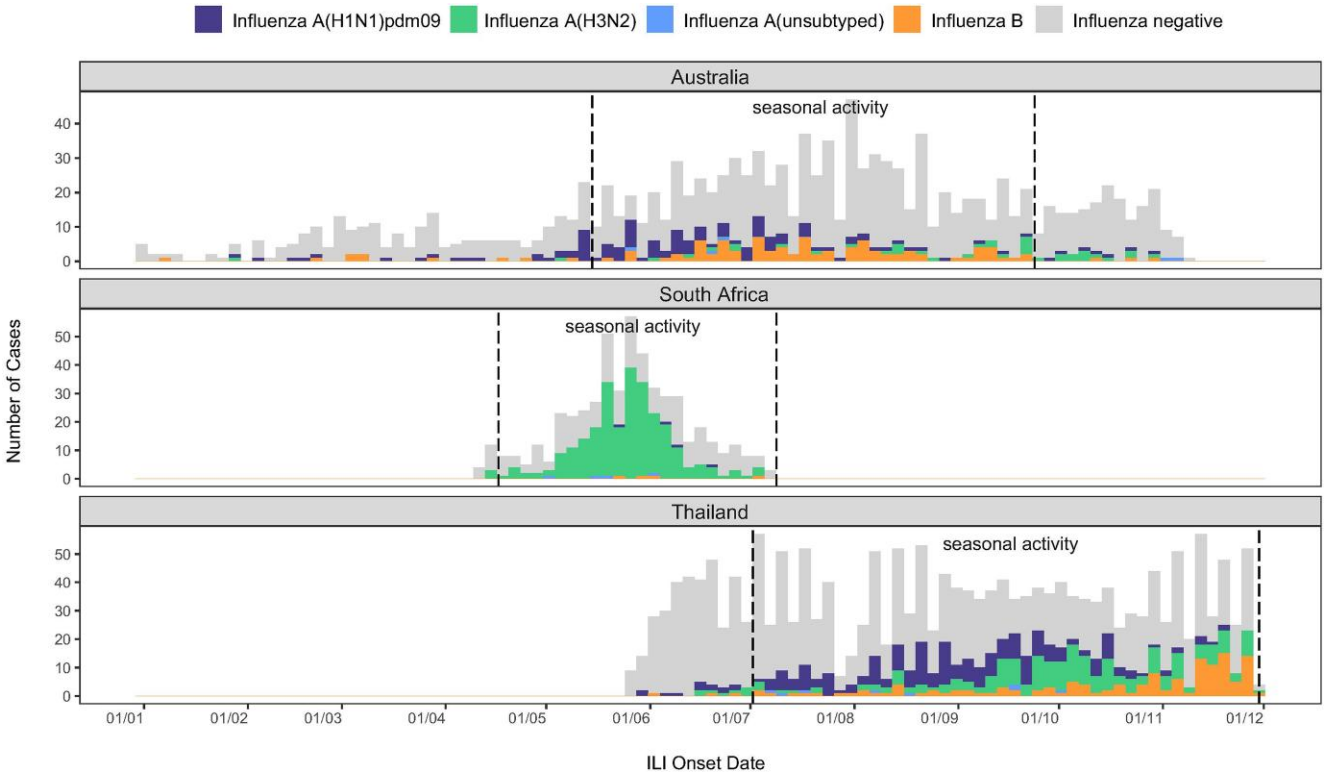

Figure 1. Influenza viruses detected among test-positive cases and test-negative non-cases with influenza-like illness—Australia, South Africa, Thailand, 2023. Abbreviations: ILI, influenza-like illness. NOTE: Dashed lines indicate the study period with seasonal influenza activity. Seasonal influenza activity was determined using Global Influenza Surveillance & Response System (GISRS) FluNet data for the 2023 calendar year (SOURCE: Global Influenza Programme (https://www.who.int/tools/flunet)). For Australia and South Africa, the influenza season was defined as the first week with >5% of specimens testing positive for influenza. For Thailand, the influenza season was defined as the first and last week with >20% of specimens testing positive for influenza.

DISCUSSION

In this study, we estimated the effectiveness of the seasonal influenza vaccine in three countries using the 2023 Southern Hemisphere formulation. Across all participating countries, we identified a pooled VE of 68% against any influenza-associated outpatient illness, and seasonal influenza vaccination was associated with a reduction in influenza-associated outpatient illness in all participating countries. Although the data exhibited differences in seasonal timing and predominant influenza type/subtype across regions, VE estimates were generally homogenous, enabling the pooling of data and more precise subgroup estimation.

For influenza A(H3N2), the Southern Hemisphere vaccine component was A/Darwin/9/2021, which was used in the prior 2022 season [19] and was also the egg candidate vaccine virus (CVV) used for Northern Hemisphere vaccines in 2022–2023 [20] and 2023–2024 [21]. Our pooled estimate was able to include all three countries and was 60% (95% CI: 38%, 75%), which was similar to the interim VE estimates for the following 2023–2024 northern hemisphere season. The US interim 2023–24 estimate for adults aged ≥18 years was similar to our pooled estimate at 54% (95% CI: 11%, 77%) [22], as was the estimate for adults from the UK (VE 49% [95% CI: 26%, 65%]) [23]. However, interim estimates reported from Canada (VE 44% [95% CI: 5%, 67%] among outpatients aged ≥12 years) [24] were somewhat lower, and the VE in Europe was not statistically significant (VE 30% [95% CI: −3%, 54%] among all ages) [25]. VE in those studies may have been lower due to repeated receipt of the same vaccine antigen, which has been observed to potentially attenuate influenza VE [26]. However, we were unfortunately unable to assess VE by the previous season's influenza vaccination status in this study, as this information was not collected by all networks.

For influenza B, the vaccine component used was B/Austria/1359417/2021, which, like A/Darwin/9/2021, has been included in the vaccine since 2022 [19]. Our pooled estimate for all ages was 76% (95% CI: 59%, 86%). Again, these estimates were comparable to preliminary VE estimates from the 2023–24 season in the United States, with point estimates for VE ranging from 64% to 89% across different outpatient networks [27]. There were few estimates reported for the 2022–23 season from North America, but the estimate of VE against influenza B for all ages from Europe was 76% (95% CI: 70%, 81%), which is comparable with our estimate [28]. The European study also

Downloaded from https://academic.oup.com/ofid/article/12/10/ofaf560/8252015 by guest on 01 December 2025

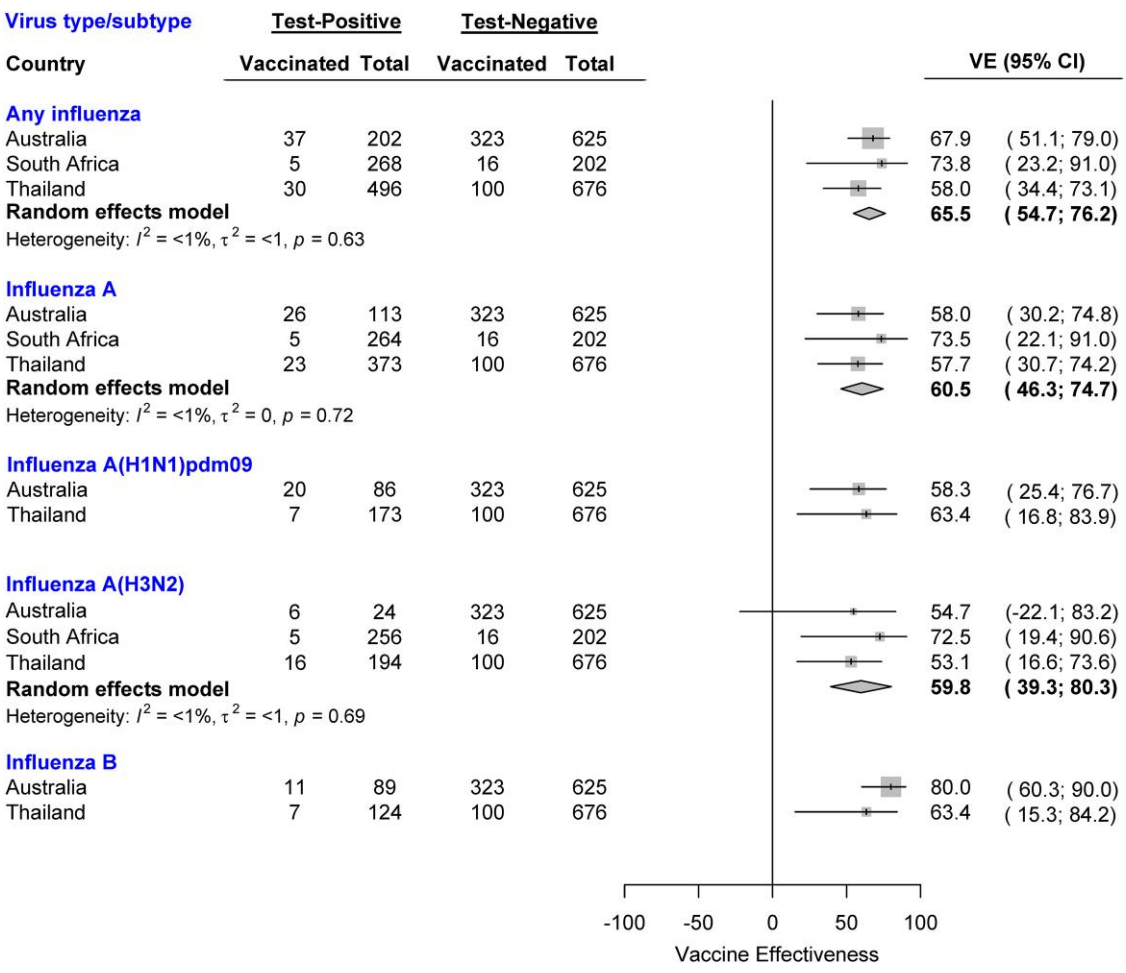

Figure 2. Estimated effectiveness* of the 2023 Southern Hemisphere seasonal influenza vaccine, by country—Australia, South Africa, and Thailand. VE, vaccine effectiveness. *Vaccine effectiveness was estimated using a logistic regression model for each country adjusting for patients' age group, sex, underlying health conditions, and week of symptom onset. A random effects meta-analysis was used to pool estimates across countries.

pooled data across countries, leveraging the variability that can occur across geographic regions during the same season to enhance the precision of VE estimates each season.

For influenza A(H1N1)pdm09, our pooled estimates (VE 62% [95% CI: 39%, 76%] across all age groups) were again comparable with interim estimates reported for the 2023–24 season from the northern hemisphere: Canada (VE 61% [95% CI: 46%, 71%] among outpatients aged ≥12 years) [24], Europe (VE 53% [95% CI: 41%, 63%] among all age groups combined) [25], and the UK (VE 62% [95% CI: 46%, 74%] among adults 18–64 years) [23]. However, our point estimate was higher than the interim estimates for the US (VE 25% [95% CI: 1%, 43%] among outpatients aged ≥18 years) [22] and for working age adults in Europe (VE 40% [95% CI: 17%, 57%] among adults 18–64 years) [25]. Note that these estimates are not directly comparable because of the use of slightly different age groups and because the vaccine component for the Southern Hemisphere vaccine, A/Sydney/5/2021 [29], was antigenically different from the egg-grown CVV used in the Northern Hemisphere, A/Victoria/4897/2022 [21].

Our estimates of VE against outpatient-attended ILI are similar to or higher than estimates of VE against influenza-associated hospitalization from the 2023 southern hemisphere season [4]. Across eight countries during the 2023 season, influenza VE was estimated to be 52%, including 67% in Australia and 39% in Thailand [4]. While outpatient and inpatient estimates were similar for Australia, VE against influenza-associated hospitalization was lower in Thailand. South Africa did not have VE estimates for influenza-associated hospitalization available for comparison. While it is difficult to say for certain why these VE estimates vary, one possible explanation is the differences in vaccines distributed in participating countries. Australia provided free adjuvanted influenza vaccines for older adults, whereas Thailand and several other southern hemisphere countries, where VE was lower, do not. Since adjuvanted and high-dose

Downloaded from https://academic.oup.com/ofid/article/12/10/ofaf560/8252015 by guest on 01 December 2025

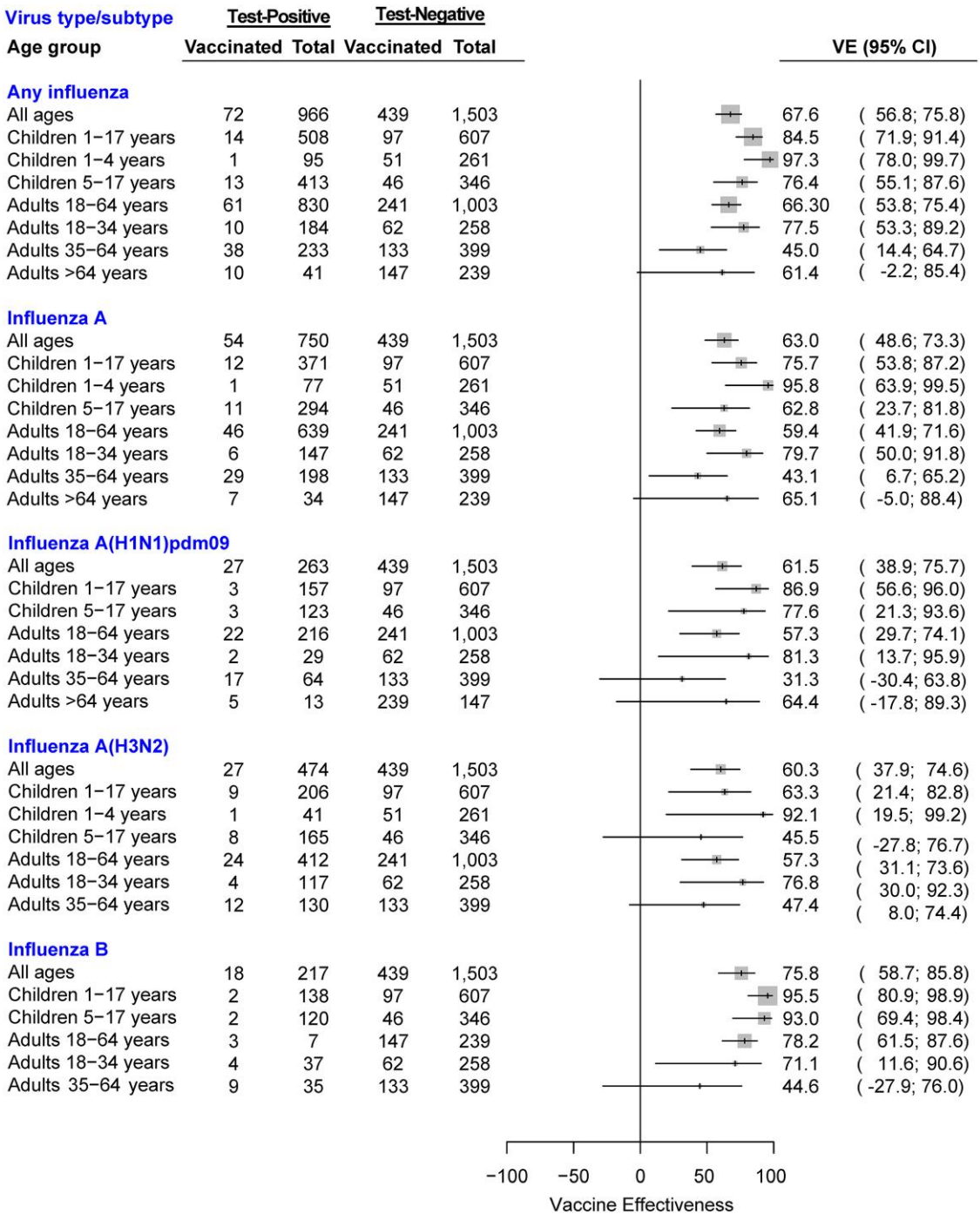

Figure 3. Estimated effectiveness* of the 2023 Southern Hemisphere seasonal influenza vaccine, overall and by age group—pooled data for Australia, South Africa, and Thailand. VE, vaccine effectiveness. *Vaccine effectiveness was estimated using a multilevel mixed logistic regression model with a random intercept for country to account for within-country correlations and adjusted for patients' age group, sex, underlying health conditions, and week of symptom onset. Subgroup analyses by patients' age group did not adjust for age.

influenza vaccines have been shown to be marginally more effective in older adults compared to unadjuvanted, standard-dose influenza vaccines, and older adults are more likely to be captured in hospital-based surveillance, this is one possible explanation for this observation [30].

For all VE estimates, we observed lower point estimates among patients with underlying medical conditions, which included immunocompromising conditions and chronic heart and lung diseases. Certain immunocompromising conditions are known to reduce the effect of vaccination on antibody

Downloaded from https://academic.oup.com/ofid/article/12/10/ofaf560/8252015 by guest on 01 December 2025

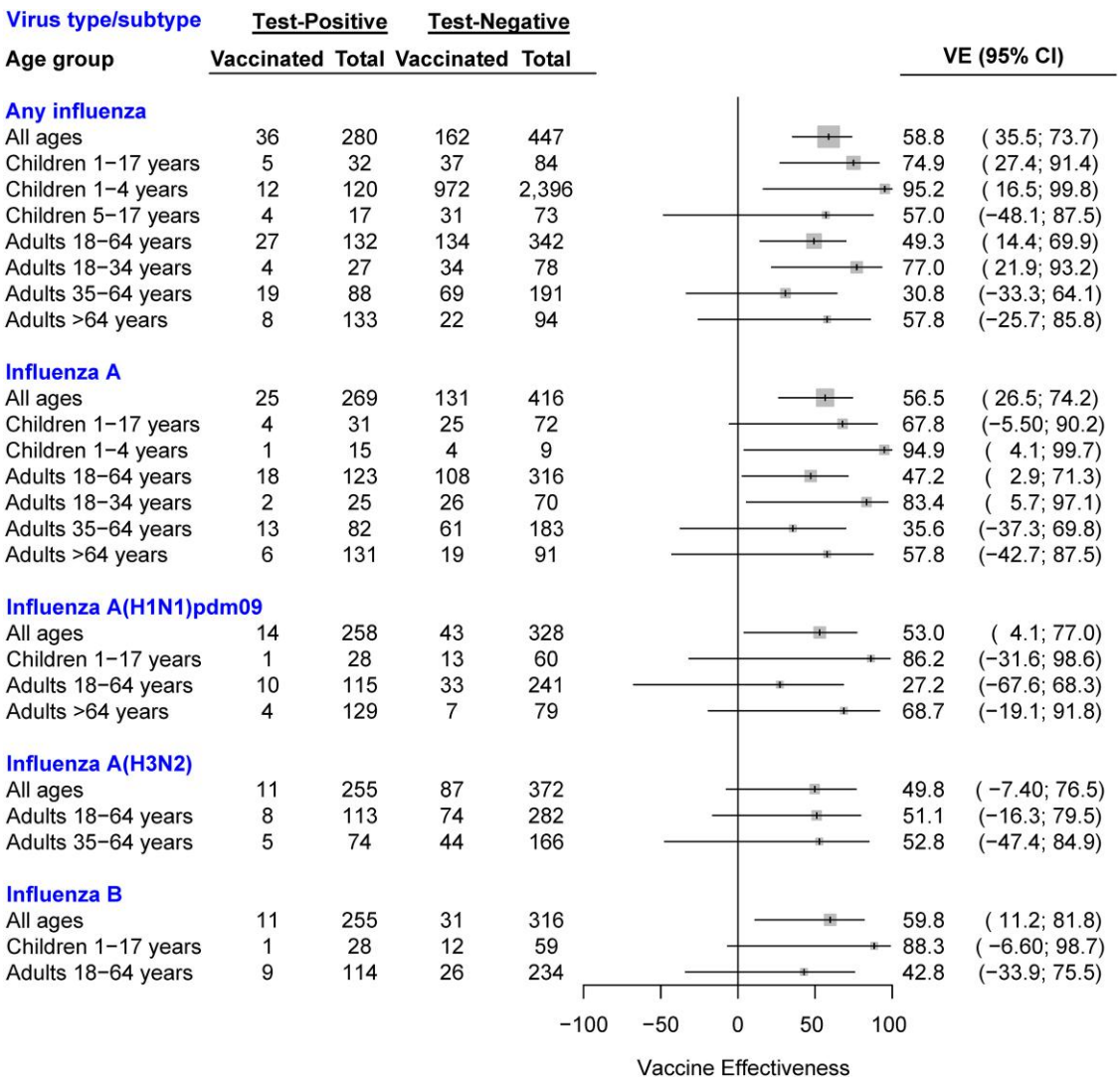

Figure 4. Estimated effectiveness* of the 2023 seasonal influenza vaccine among patients with underlying medical conditions—pooled data for Australia, South Africa, and Thailand. VE, vaccine effectiveness. *Vaccine effectiveness was estimated using a multilevel mixed logistic regression model with a random intercept for country to account for within-country correlations and adjusted for patients' age group, sex, underlying health conditions, and week of symptom onset. Subgroup analyses by patients' age group did not adjust for age.

production [31], which can result in lower vaccine performance. Low VE against influenza-associated hospitalization has been reported in the literature for adults with immunocompromising conditions [32]. Our findings imply that VE of seasonal influenza vaccines may also be lower against outpatient-attended ILI in these individuals. However, we note that VE estimates remained relatively high for children with underlying health conditions, among whom VE was as high as 95%, possibly indicating the influence of age and immunosenescence [33]. Because we were unable to distinguish between specific underlying health conditions in the data, we cannot attribute the observed lower VE to immunosuppressing conditions exclusively, and further research on influenza vaccine performance in these population groups remains needed.

In our analyses of VE by time since vaccination, we observed some evidence suggestive of intra-season waning of vaccine effectiveness. In pooled analyses, we observed a decline in VE among adults 18–64 years old, with VE point estimate decreasing from 74% to 29% as the time between vaccination and illness onset increased from <45 to 120 days post-vaccination. This waning appeared to be less intense for children 1–17 years old, among whom the point estimate for VE decreased from 93% to 56% as the time between vaccination and illness onset increased from <45 days to 120–149 days. There is mounting evidence that VE may wane within seasonal influenza epidemics. A recent pooled analysis of six test-negative case-control studies in Italy showed that for every week since vaccination, the odds of testing positive for any influenza virus increased by 5%, and

Downloaded from https://academic.oup.com/ofid/article/12/10/ofaf560/8252015 by guest on 01 December 2025

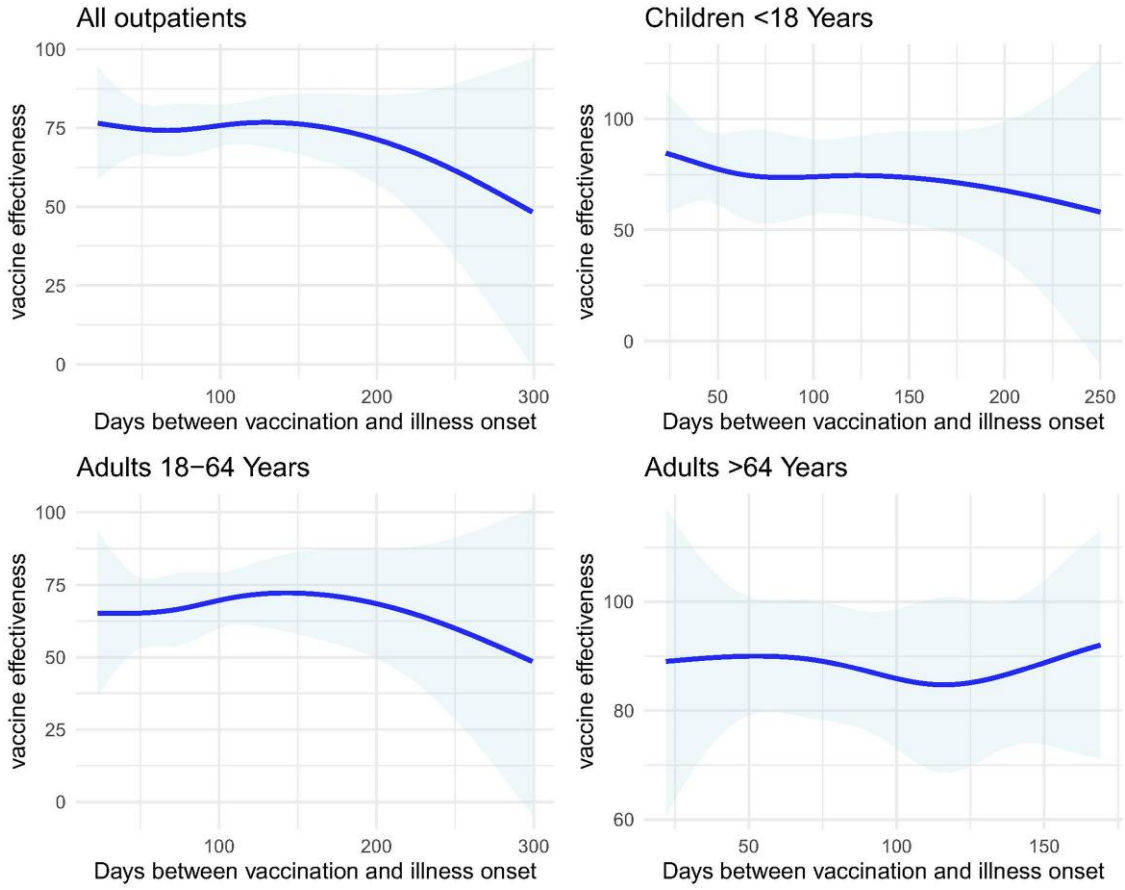

Figure 5. Estimated effectiveness* of the 2023 seasonal influenza vaccine, by interval (in days) between vaccination and onset of influenza-like illness—pooled data for Australia, Thailand, and South Africa. VE, vaccine effectiveness. *Vaccine effectiveness was estimated using a multilevel mixed logistic regression model with time between vaccination and symptom onset as the predictor variable (fit using cubic splines) and a random intercept for country to account for within-country correlations.

this pattern was strongest for young children and older adults [34]. A previous systematic review and meta-analysis of 14 test-negative design studies found evidence supporting a significant decline in VE for influenza A(H3N2) and B antigens, but a more modest decline for influenza A(H1N1)pdm09 [35]. Differences among age groups should be interpreted with caution, however, as the predominant influenza virus type/subtype may differ by age and waning may be expected to be more substantial by type/subtype, with faster waning reported for A(H3N2) compared with A(H1N1)pmd09, for example [36]. Nevertheless, the duration of VE has important implications for interpreting VE estimates, since intra-season waning will result in lower end-of-season VE estimates. As a result, end-of-season VE estimates may under-estimate the true protective effect of influenza vaccines at the start and peak of influenza seasons.

Although our study offers several strengths, including the standardized data collection, laboratory-confirmed outcomes, geographic and demographic representation, and the large sample size of patients with ILI, our study had some limitations. First, several VE estimates for population subgroups were derived from small numbers of vaccinated cases, and for some subgroups, VE estimation was not possible (ie, notably waning in older adults aged ≥65 years). Pooled VE against any influenza was indeed highest for children 1–4 years old at 97% (95% CI: 78%, 100%), but this estimate was based on just one vaccinated case and should be interpreted with caution. The paucity of vaccinated pediatric cases made VE estimation by influenza virus type or subtype infeasible. Second, we were unable to estimate VE by clade, which can provide a better approximation of the effectiveness of the vaccine against antigenically similar and dissimilar circulating influenza viruses. Third, 7% of eligible patients with ILI had missing data, which excluded them from the final analyses. Data were more commonly missing in Australia (16%) and South Africa (9%) compared to Thailand (1%). Despite this, we have no reason to believe that data were missing in a manner that systematically differed by other characteristics. Missing data observed for some sites could have introduced bias in country-specific estimates for Australia and South Africa, as well as pooled estimates. Finally, national vaccination programs varied in terms of influenza vaccine types and

Downloaded from https://academic.oup.com/ofid/article/12/10/ofaf560/8252015 by guest on 01 December 2025

brands used and target groups for immunization, and, notably, the adjuvanted vaccine is used for older adults aged ≥65 years in Australia. Vaccine uptake additionally varied by country, ranging from 4% in South Africa to 43% in Australia. Despite these variations, the consistent VE estimates across countries and low heterogeneity identified in our meta-analyses are reassuring that our pooled approach was appropriate.

CONCLUSIONS

Data from this large, multi-country study indicate that the Southern Hemisphere formulation of the 2023 influenza vaccine was associated with lower odds of influenza-associated ILI, and this protection was consistent across most patient age groups and for those with underlying medical conditions. Timely, pooled estimates using ILI sentinel surveillance data allow for the evaluation of VE within subgroups of patients and can highlight the benefits of influenza vaccination programs. These data support the implementation of seasonal influenza vaccine programs to protect a range of patient groups against influenza-associated ILI.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Author Contributions. E. A. B. conceived the study; N. S., S. W., and K. P. led surveillance in their respective countries; S. G. S., S. W., and K. P. conducted data management cleaning for the pooled analysis; A. K. R. and R. G. conducted data analysis; A. K. R., R. G., and S. G. S drafted the manuscript; all authors reviewed, edited, and approved the manuscript.

Data availability. The datasets generated and/or analyzed during the current study are not publicly available due to the differing national policies on sharing of data. They may be made available upon reasonable request to each national focal point: Australia: Monique Chilver monique.chilver@adelaide.edu.au; South Africa: Sibongile Walaza sibongilew@nicd.ac.za; Thailand: Kriengkrai Prasert gpsiam28@gmail.com. The underlying Stata and R scripts used for this study are not publicly available but may be made available to qualified researchers on reasonable request to the corresponding author.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Financial support. The Australian Sentinel Practices Research Network is supported by the Australian Government Department of Health, Disability, and Ageing (the Department). The opinions expressed in this publication are those of the authors and do not necessarily represent the views of the Department. The South African Viral Watch sentinel surveillance system was supported by the National Department of Health and the National Institute for Communicable Diseases. The Thai sentinel surveillance system is supported by the US Centers for Disease Control and Prevention through a cooperative agreement with the Thailand Ministry of Public Health. Funding for analytical support was provided by the US Centers for Disease Control and Prevention through an Interpersonal Agreement (Recipient: Dr Regan).

Potential conflicts of interest. S. G. S. reports consulting for Pfizer Inc, Moderna Inc, CSL Seqirus, Sanofi, GSK, and Novavax unrelated to the present study. A. K. R. reports membership on a Data Safety Monitoring Board for Moderna Inc unrelated to the present study. R. G. reports employment with Moderna, Inc. post-completion of the present study; during analysis and manuscript preparation, R. G. was employed by the US Centers for Disease Control and Prevention. N. W. received grant funding from the Bill and Melinda Gates Foundation unrelated to this study. C. C., S. W., and A. vG. declare funding from the US Centers for Disease Control and Prevention and the Bill and Melinda Gates Foundation, Sanofi Pasteur and The Task Force for Global Health unrelated to this study. The authors have no other competing interests to declare.

References

1. Fitzner J, Qasmieh S, Mounts AW, et al. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. Bull World Health Organ **2018**; 96:122–8.
2. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine **2013**; 31:2165–8.
3. Sullivan SG, Feng S, Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. Expert Rev Vaccines **2014**; 13:1571–91.
4. Gharpure R, Regan AK, Nogareda F, et al. Effectiveness of 2023 southern hemisphere influenza vaccines against severe influenza-associated illness: pooled estimates from eight countries using the test-negative design. Lancet Glob Health **2025**; 13:e203–11.
5. Tempia S, Walaza S, Moyes J, et al. Quantifying how different clinical presentations, levels of severity, and healthcare attendance shape the burden of influenza-associated illness: a modeling study from South Africa. Clin Infect Dis **2019**; 69:1036–48.
6. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine **2007**; 25:5086–96.
7. Feng S, Cowling BJ, Sullivan SG. Influenza vaccine effectiveness by test-negative design—comparison of inpatient and outpatient settings. Vaccine **2016**; 34: 1672–9.
8. Tenforde MW, Chung J, Smith ER, et al. Influenza vaccine effectiveness in inpatient and outpatient settings in the United States, 2015–2018. Clin Infect Dis **2021**; 73:386–92.
9. WHO. Recommended composition of influenza virus vaccines for use in the 2023 southern hemisphere influenza season. Available at: https://www.who.int/publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2023-southern-hemisphere-influenza-season. Accessed 8 July 2024.
10. Sullivan SG, Chilver MB, Higgins G, Cheng AC, Stocks NP. Influenza vaccine effectiveness in Australia: results from the Australian Sentinel Practices Research Network. Med J Aust **2014**; 201:109–11.
11. NICD. Weekly Respiratory Pathogens Surveillance Report. Available at: https://www.nicd.ac.za/diseases-a-z-index/disease-index-covid-19/surveillance-reports/weekly-respiratory-pathogens-surveillance-report-week/. Accessed 25 March 2025.
12. Budgell E, Cohen AL, McAnerney J, et al. Evaluation of two influenza surveillance systems in South Africa. PLoS One **2015**; 10:e0120226.
13. Chittaganpitch M, Supawat K, Olsen SJ, et al. Influenza viruses in Thailand: 7 years of sentinel surveillance data, 2004–2010. Influenza Other Respir Viruses **2012**; 6: 276–83.
14. Prasert K, Praphasiri P, Nakphook S, et al. Influenza virus circulation and vaccine effectiveness during June 2021–May 2023 in Thailand. Vaccine X **2024**; 19: 100517.
15. WHO. FluNet global influenza programme. Available at: https://www.who.int/tools/flunet. Accessed 11 July 2024.
16. Doll MK, Pettigrew SM, Ma J, Verma A. Effects of confounding bias in coronavirus disease 2019 (COVID-19) and influenza vaccine effectiveness test-negative designs due to correlated influenza and COVID-19 vaccination behaviors. Clin Infect Dis **2022**; 75:e564–71.
17. Payne AB, Ciesla AA, Rowley EAK, et al. Impact of accounting for correlation between COVID-19 and influenza vaccination in a COVID-19 vaccine effectiveness evaluation using a test-negative design. Vaccine **2023**; 41:7581–6.
18. Cochrane Handbook. 9.5.2 Identifying and measuring heterogeneity. Available at: https://handbook-5-1.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm. Accessed 8 August 2024.
19. WHO. Recommended composition of influenza virus vaccines for use in the 2022 southern hemisphere influenza season. Available at: https://www.who.int/

Downloaded from https://academic.oup.com/ofid/article/12/10/ofaf560/8252015 by guest on 01 December 2025

publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2022-southern-hemisphere-influenza-season. Accessed 1 November 2024.
20. WHO. Recommended composition of influenza virus vaccines for use in the 2022–2023 northern hemisphere influenza season. Available at: https://www.who.int/publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2022-2023-northern-hemisphere-influenza-season. Accessed July 24.
21. WHO. Recommended composition of influenza virus vaccines for use in the 2023–2024 northern hemisphere influenza season. Available at: https://www.who.int/publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2023-2024-northern-hemisphere-influenza-season. Accessed 24 July 2024.
22. Frutos AM, Price AM, Harker E, et al. Interim estimates of 2023–24 seasonal influenza vaccine effectiveness—united States. MMWR Morb Mortal Wkly Rep **2024**; 73:168–74.
23. Whitaker H, Findlay B, Zitha J, et al. Interim 2023/2024 Season influenza vaccine effectiveness in primary and secondary care in the United Kingdom. Influenza Other Respir Viruses **2024**; 18:e13284.
24. Skowronski DM, Zhan Y, Kaweski SE, et al. 2023/24 mid-season influenza and Omicron XBB.1.5 vaccine effectiveness estimates from the Canadian Sentinel Practitioner Surveillance Network (SPSN). Euro Surveill **2024**; 29:2400076.
25. Maurel M, Howard J, Kissling E, et al. Interim 2023/24 influenza A vaccine effectiveness: VEBIS European primary care and hospital multicentre studies, September 2023 to January 2024. Euro Surveill **2024**; 29:2400089.
26. Jones-Gray E, Robinson EJ, Kucharski AJ, Fox A, Sullivan SG. Does repeated influenza vaccination attenuate effectiveness? A systematic review and meta-analysis. Lancet Respir Med **2023**; 11:27–44.
27. CDC. Preliminary Flu Vaccine Effectiveness (VE) data for 2023–2024. Available at: https://www.cdc.gov/flu-vaccines-work/php/effectiveness-studies/2023-2024.html. Accessed 25 March 2024.
28. Maurel M, Mazagatos C, Goerlitz L, et al. Exploring the effect of clinical case definitions on influenza vaccine effectiveness estimation at primary care level: results from the end-of-season 2022–23 VEBIS multicentre study in Europe. Vaccine **2024**; 42:3547–54.
29. WHO. Recommended composition of influenza virus vaccines for use in the 2023 southern hemisphere influenza season. Available at: https://www.who.int/publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2023-southern-hemisphere-influenza-season. Accessed 24 July 2024.
30. Izurieta HS, Chillarige Y, Kelman J, et al. Relative effectiveness of influenza vaccines among the United States elderly, 2018–2019. J Infect Dis **2020**; 222:278–87.
31. Beck CR, McKenzie BC, Hashim AB, Harris RC, Nguyen-Van-Tam JS. Influenza vaccination for immunocompromised patients: systematic review and meta-analysis by etiology. J Infect Dis **2012**; 206:1250–9.
32. Hughes K, Middleton DB, Nowalk MP, et al. Effectiveness of influenza vaccine for preventing laboratory-confirmed influenza hospitalizations in immunocompromised adults. Clin Infect Dis **2021**; 73:e4353–60.
33. Reber AJ, Chirkova T, Kim JH, et al. Immunosenescence and challenges of vaccination against influenza in the aging population. Aging Dis **2012**; 3:68–90.
34. Domnich A, Orsi A, Signori A, et al. Waning intra-season vaccine effectiveness against influenza A(H3N2) underlines the need for more durable protection. Expert Rev Vaccines **2024**; 23:380–8.
35. Young B, Sadarangani S, Jiang L, Wilder-Smith A, Chen MI. Duration of influenza vaccine effectiveness: a systematic review, meta-analysis, and meta-regression of test-negative design case-control studies. J Infect Dis **2018**; 217:731–41.
36. Hoa LNM, Sullivan SG, Mai LQ, et al. Influenza A(H1N1)pdm09 but not A(H3N2) virus infection induces durable seroprotection: results from the Ha Nam Cohort. J Infect Dis **2022**; 226:59–69.

Downloaded from https://academic.oup.com/ofid/article/12/10/ofaf560/8252015 by guest on 01 December 2025