Medical Journal of Australia

MJA The Medical Journal of Australia

RESEARCH

Short-Term Safety and Adverse Event Risk Profiles for SARS-CoV-2 Booster Vaccine Doses in Australian Adults: A Survey Study

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Received: 23 July 2025 | **Revised:** 22 April 2026 | **Accepted:** 4 May 2026

Keywords: SARS-CoV-2 | vaccines | vaccine safety

ABSTRACT

Objective: This study quantifies the short-term risk profiles of seven severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2) vaccines—Comirnaty Bivalent BA.1, Comirnaty Bivalent BA.4-5, Comirnaty XBB.1.5, Spikevax Bivalent BA.1, Spikevax Bivalent BA.4-5, Spikevax XBB.1.5 and Nuvaxovid—administered as booster doses in Australia.

Design: This is a survey study using data collected from online surveys sent via AusVaxSafety, the Australian active vaccine safety surveillance system, 3 days post-vaccination, soliciting reports of adverse events following vaccination.

Participants and Setting: Individuals 18 years and older who received a SARS-CoV-2 vaccine booster at an AusVaxSafety vaccine surveillance site between 1 January 2023 and 31 August 2024.

Main Outcome Measures: Bayesian logistic regression was used to estimate risk of reported adverse events, seeking medical advice and impact on daily activities.

Results: Of 197,476 respondents, 59,089 (29.9%) reported at least one adverse event, of which the most commonly reported symptoms were injection site reaction (23.8% [46,988/197,476]) and fatigue (19.4% [38,352/197,476]). Symptom resolution was reported by 69.9% (41,299/59,089) by day 3 and 5.6% (11,006/197,476) reported any time lost from daily activities. The unadjusted proportion of respondents who sought medical advice was higher in those who received Spikevax XBB.1.5 (1.2% [212/17,551]) than the other vaccines (0.5% [379/69,493] to 0.7% [147/20,271]), but the modelled, adjusted mean risk of medical advice was similar (< 2.5%) across subgroups for vaccine brands, co-administered vaccines, medical conditions, age, sex and Indigenous status. The modelled risk of any adverse event at age 40 years ranged from 35.2% (95% credible interval [CrI], 32.2%–38.5%) for men who had received Comirnaty XBB.1.5 to 75.5% (95% CrI, 71.9%–78.8%) for women who had received Spikevax XBB.1.5. At age 80 years, this risk was lowest across all vaccines, ranging from 12.0% (95% CrI, 11.2%–13.0%) for men who had received Comirnaty BA4-5 to 36.7% (95% CrI, 34.6%–38.7%) for women who had received Spikevax XBB.1.5.

Conclusions: The results of this study confirm the short-term safety and low impact on daily living of SARS-CoV-2 booster vaccine administration to Australian adults.
JEL Classification: Infectious diseases, Environment and public health

1 | Introduction

Severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2) is now endemic and vaccination with further SARS-CoV-2 vaccine doses (hereafter known as boosters) remains recommended for prevention of severe illness among vulnerable groups [1, 2]. Although SARS-CoV-2 vaccines are recommended every 6–12 months for Australians aged 64–75 years, only 28.6% of this age group received a SARS-CoV-2 vaccine in 2024 [2, 3]. Information about expected adverse effects of SARS-CoV-2 boosters on vaccine recipients, such as risk of adverse reactions and impact on daily living, may provide reassurance and thereby increase vaccine uptake.

As SARS-CoV-2 evolved beyond the ancestral strain, formulations of messenger ribonucleic acid (mRNA) platform vaccines were adapted to target the prevailing variants, whereas updates to protein-based vaccine formulations have not been approved in Australia (see Supporting Information). The safety of Nuvaxovid (Novavax-CoV2373) used as a booster has been examined in clinical trials [4, 5]. Post-marketing safety evaluation has been conducted on bivalent SARS-CoV-2 mRNA boosters, supplemented by limited trial data [6–9].

A systematic review of trials comparing SARS-CoV-2 boosters found that mRNA-1273 (Spikevax) vaccines were more reactogenic than the BNT-162b2 (Comirnaty) vaccines but did not include XBB.1.5-adapted COVID-19 vaccines [9]. A recent study of elderly recipients reported less reactogenicity for Comirnaty XBB.1.5 compared with Spikevax XBB.1.5 [10]. Subsequent formulations of mRNA vaccines such as the bivalent Omicron COVID-19 vaccines have been found to have similar safety profiles to earlier vaccines against previous SARS-CoV-2 strains [9, 11].

Safety monitoring of SARS-CoV-2 vaccines by AusVaxSafety, the Australian active vaccine safety surveillance system, commenced February 2021. Data are collected through surveys sent 3 days post-vaccination and summarised in safety reports. Safety profiles of priming doses of Comirnaty, Spikevax and Nuvaxovid have been published [12, 13]. Consultation with a vaccine-focussed consumer group in a face-to-face seminar indicated that information on daily-life impact and symptom resolution is of greater public interest than detailed adverse event (AE) profiles. The figures and information in this study are intended to support consumer-friendly resources, complementary to graphics available on the AusVaxSafety website (https://www.ausvaxsafety.org.au).

This analysis aims to contribute evidence on the safety profiles of mRNA and protein-based SARS-CoV-2 vaccines used in Australia. We provide novel visualisation of data on what to expect in the days following SARS-CoV-2 boosters.

2 | Methods

This study was conducted as a longitudinal survey study. The Consensus-Based Checklist for Reporting of Survey Studies (CROSS) was employed and is included in the Supporting Information [14]. As part of the AusVaxSafety active vaccine safety surveillance, vaccine safety surveys were sent to individuals aged 18 years and older who received a Comirnaty Bivalent BA.1, Comirnaty Bivalent BA.4-5, Comirnaty XBB.1.5, Spikevax Bivalent BA.1, Spikevax Bivalent BA.4-5, Spikevax XBB.1.5 or Nuvaxovid SARS-CoV-2 vaccine dose at an AusVaxSafety vaccine surveillance site (participating general practices, Aboriginal community-controlled health organisations, pharmacies and government vaccination clinics) between 1 January 2023 and 31 August 2024, inclusive. It was assumed that adult vaccine doses received within this period were boosters given the high uptake of priming doses in Australian adults unless indicated otherwise [15].

The AusVaxSafety SARS-CoV-2 vaccine safety survey has previously been administered to about 5 million individuals [12, 13]. Surveys were delivered by links to one of two web-based surveys (Vaxtracker [https://www.vaxtracker.net] and SmartVax [https://www.smartvax.com.au]) via SMS or email, including a link to a webpage informing vaccinees of usage of their de-identified data and that participation is voluntary (https://www.ausvaxsafety.org.au/vaccine-safety-surveillance/information-immunisation-recipients). Survey participation served as implied consent. Only de-identified responses, received on secure servers within 7 days post-vaccination, were included for analysis to reduce errors in recall. Where multiple responses per unique individual were identified, only the first response was included in the analysis.

Demographic information (date of birth, biological sex, Indigenous status) and immunisation details (vaccine/s received, date of vaccination) were obtained from clinical records from the vaccination provider via the surveillance tools. Responses with complete demographic information were included for analysis. Survey recipients were asked whether they had an AE following vaccination and, if so, whether they experienced specific symptoms (e.g., headache) and impact on daily activities. Additional questions included if they sought medical advice and, if so, the type of medical advice (phone advice, primary healthcare worker, emergency department). Participants were asked about underlying medical conditions and symptom resolution. Details of the AusVaxSafety SARS-CoV-2 vaccine survey, including a full list of self-reported underlying medical conditions, are provided in the Supporting Information.

2.1 | Measured Outcomes

We analysed the following outcomes reported within 3 days of vaccination as binary outcomes: (i) medical advice sought following any AE, (ii) any AE, (iii) specific solicited AE (injection

Plain Language Summary

The Known: SARS-CoV-2 booster vaccine uptake is suboptimal in recommended groups in Australia. The safety of these vaccines has largely been extrapolated from post-marketing surveillance of ancestral strain formulations or limited trial data.

The New: We provide short-term safety and risk profiles of adverse events for SARS-CoV-2 boosters from active vaccine safety survey data in Australia. There was a low impact of booster vaccination on activities of daily life in the survey respondents.

The Implications: This confirmation of the safety and low impact on normal activities following SARS-CoV-2 booster vaccination adds to available data on safety to encourage uptake.

site reaction, headache, fatigue, fever, myalgia, arthralgia, chills, gastrointestinal symptoms) and (iv) any days of work, study or daily activities lost.

2.2 | Statistical Analysis

All analyses were performed on de-identified survey data in R version 4.5.2. Descriptive statistics describe the demographic characteristics of the survey respondents as well as the proportions of those who reported each of the above binary outcomes. Bayesian logistic regression [16] was used to model the probability of the outcomes. The model was adjusted for age (using B-splines stratified by sex, Indigenous status and vaccine received), self-reported underlying medical condition, co-administration with specific vaccines and time epoch of survey response (using a Bayesian time machine approach) [16, 17]. All covariates together with their coding schemes are specified in the Supporting Information. Modelled risks for each outcome are summarised as probabilities with 95% credible intervals (95% CrIs), marginalised over the appropriate covariates. Estimated effects of categorical variables are presented in Table S1. Posterior distributions for model parameters were estimated using STAN [18] via the cmdstanr package (version 0.9.0) [19]. Each model was run with four chains of 1000 iterations. Sensitivity analyses were conducted assuming all respondents with missing data were (i) male and non-Indigenous and (ii) female and non-Indigenous. A reduced model was implemented for the analysis of Nuvaxovid data due to the low frequencies for some covariates (Table 1), which did not allow for inclusion of demographic subgroups. Further details of the statistical modelling are provided in the Supporting Information.

2.3 | Ethics Statement

This study was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee (HREC/16/SCHN/19). AusVaxSafety operates under the governance and infrastructure support of Kids Research, Sydney Children's Hospitals Network.

3 | Results

3.1 | Sample Characteristics

Between 1 January 2023 and 31 August 2024, 433,626 SARS-CoV-2 vaccine surveys were sent from AusVaxSafety surveillance sites and 251,949 responses were received. The response rates were similar for Comirnaty (58.3% [188,746/323,647]), Spikevax (57.5% [62,667/108,934]) and Nuvaxovid (51.3% [536/1045]). Responses from priming doses (0.05% [122/251,949]), multiple response from the same individual (13.7% [34,614/251,949]) and those reporting sex as 'other' (< 0.01% [2/251,949]) were excluded, leaving 217,211 included survey responses.

For some participants, data were missing for Indigenous status (0.5% [1033/217,211]), sex (8.6% [18,745/217,211]) or both Indigenous status and sex (0.02% [43/217,211]). Sex was missing in 28.9% (18,627/64,393) of respondents vaccinated at pharmacies and in 0.1% (118/173,478) of those vaccinated at general practices, leaving 197,476 survey responses in the complete case analysis. Of these respondents, 76.6% (151,332/197,476) received a Comirnaty vaccine, 23.2% (45,876/197,476) Spikevax and 0.1% (268/197,476) Nuvaxovid. Overall, 57.7% (113,852/197,476) of survey respondents in the complete case analysis were women and the median age of respondents was 69.0 years (interquartile range [IQR], 61.0–76.0 years). A total of 1.5% (2920/197,476) of respondents identified as Aboriginal and Torres Strait Islander, 29.2% (57,647/197,476) self-reported as having an underlying medical condition and 30.7% (60,680/197,476) had at least one co-administered vaccine. Proportions by vaccine are presented in Table 1.

3.2 | Medical Advice Sought and Impact on Routine Activities

Medical advice sought and impact on routine activities by vaccine are reported in Table 2. The unadjusted proportion seeking medical advice (0.5% [379/69,493] to 0.7% [147/20,271]) was similar across all vaccines except for Spikevax XBB.1.5 (1.2% [212/17,551]). Across various age strata and by sex, there was a consistently low mean modelled risk of medical advice of < 2.0% after receiving the Comirnaty and Spikevax vaccines, except for women who received Spikevax XBB.1.5 (< 2.5%) (Figure 1). A similar pattern was observed for Aboriginal and Torres Strait Islander people, albeit with less precision. Across all ages for all underlying medical conditions, the mean risk of medical advice sought following Comirnaty and Spikevax boosters was consistently low (women, < 2.5%; men, < 1.5%). The most recent formulations, Comirnaty XBB.1.5 and Spikevax XBB.1.5, were used to assess the risk of seeking medical advice following vaccination with a SARS-CoV-2 booster when co-administered with another vaccine. The mean risk of seeking medical advice was low (< 2.5%) across age and sex, irrespective of whether the SARS-CoV-2 vaccine was given alone or co-administered with another vaccine (Figure S1). There was a low risk of about 2.0% for seeking medical advice following Nuvaxovid, although poor precision was evident in the younger age range (Figure S2). Overall, 30.5% (397/1301) of those who sought medical advice consulted a primary healthcare worker and 10.6% (138/1301) attended an emergency department (Table 2).

TABLE 1 | Demographic characteristics of respondents to the AusVaxSafety day 3 vaccine safety survey, 1 January 2023 to 31 August 2024, by vaccine.[a]

	Comirnaty Bivalent BA.1 (Pfizer)	Comirnaty Bivalent BA.4-5 (Pfizer)	Comirnaty XBB.1.5 (Pfizer)	Spikevax Bivalent BA.1 (Moderna)	Spikevax Bivalent BA.4-5 (Moderna)	Spikevax XBB.1.5 (Moderna)	Nuvaxovid (Novavax)
Number of respondents	14,741	67,098	69,493	8054	20,271	17,551	268
Sex							
Male	6508/14,741 (44%)	28,384/67,098 (42%)	29,560/69,493 (43%)	3444/8054 (43%)	8287/20,271 (41%)	7340/17,551 (42%)	101/268 (38%)
Female	8233/14,741 (56%)	38,714/67,098 (58%)	39,933/69,493 (57%)	4610/8054 (57%)	11,984/20,271 (59%)	10,211/17,551 (58%)	167/268 (62%)
Age (years), median (interquartile range)	69 (60–76)	68 (59–75)	71 (64–77)	68 (59–75)	65 (55–73)	70 (63–76)	63 (49–69)
Age group							
< 20 years	70/14,741 (< 1%)	292/67,098 (< 1%)	156/69,493 (< 1%)	20/8054 (< 1%)	88/20,271 (< 1%)	63/17,551 (< 1%)	6/268 (2%)
20 to < 30 years	336/14,741 (2%)	1355/67,098 (2%)	763/69,493 (1%)	165/8054 (2%)	568/20,271 (3%)	247/17,551 (1%)	12/268 (4%)
30 to < 40 years	566/14,741 (4%)	2475/67,098 (4%)	1453/69,493 (2%)	386/8054 (5%)	1040/20,271 (5%)	489/17,551 (3%)	19/268 (7%)
40 to < 50 years	783/14,741 (5%)	4204/67,098 (6%)	2442/69,493 (4%)	512/8054 (6%)	1636/20,271 (8%)	773/17,551 (4%)	34/268 (13%)
50 to < 60 years	1677/14,741 (11%)	9058/67,098 (13%)	6071/69,493 (9%)	1063/8054 (13%)	3433/20,271 (17%)	1806/17,551 (10%)	42/268 (16%)
60 to < 70 years	4048/14,741 (27%)	19,285/67,098 (29%)	18,432/69,493 (27%)	2325/8054 (29%)	5972/20,271 (29%)	4884/17,551 (28%)	90/268 (34%)
70 to < 80 years	5168/14,741 (35%)	22,026/67,098 (33%)	28,458/69,493 (41%)	2534/8054 (31%)	5500/20,271 (27%)	6706/17,551 (38%)	51/268 (19%)
≥ 80 years	2063/14,741 (14%)	8301/67,098 (12%)	11,673/69,493 (17%)	1029/8054 (13%)	1974/20,271 (10%)	2560/17,551 (15%)	14/268 (5%)
Indigenous status							
Aboriginal and Torres Strait Islander	310/14,741 (2%)	1026/67,098 (2%)	975/69,493 (1%)	100/8054 (1%)	293/20,271 (1%)	214/17,551 (1%)	2/268 (1%)
Non-Indigenous	14,431/14,741 (98%)	66,072/67,098 (98%)	68,518/69,493 (99%)	7954/8054 (99%)	19,978/20,271 (99%)	17,337/17,551 (99%)	266/268 (99%)
Underlying medical condition							
No	10,488/14,741 (71%)	48,657/67,098 (73%)	47,629/69,493 (69%)	5786/8054 (72%)	15,015/20,271 (74%)	12,078/17,551 (69%)	176/268 (66%)
Yes	4253/14,741 (29%)	18,441/67,098 (27%)	21,864/69,493 (31%)	2268/8054 (28%)	5256/20,271 (26%)	5473/17,551 (31%)	92/268 (34%)

(Continues)

TABLE 1 | (Continued)

	Comirnaty Bivalent BA.1 (Pfizer)	Comirnaty Bivalent BA.4-5 (Pfizer)	Comirnaty XBB.1.5 (Pfizer)	Spikevax Bivalent BA.1 (Moderna)	Spikevax Bivalent BA.4-5 (Moderna)	Spikevax XBB.1.5 (Moderna)	Nuvaxovid (Novavax)
Co-administered vaccine							
No	11,307/14,741 (77%)	42,053/67,098 (63%)	49,060/69,493 (71%)	7160/8054 (89%)	14,263/20,271 (70%)	12,713/17,551 (72%)	240/268 (90%)
Yes	3434/14,741 (23%)	25,045/67,098 (37%)	20,433/69,493 (29%)	894/8054 (11%)	6008/20,271 (30%)	4838/17,551 (28%)	28/268 (10%)

[a]The number of respondents in each subgroup is expressed as a percentage of the total number for each vaccine.

The following unadjusted proportions are reported by vaccine in Table 2. 5.6% (11,006/197,476) reported any time lost from daily activities, with 4.5% (6800/151,332) of Comirnaty recipients and 9.1% (4189/45,879) of Spikevax recipients having made such reports. Of these survey respondents, 64.2% (7053/10,989) reported at most 1 day lost. A total of 69.9% (41,299/59,089) of those who reported an AE reported symptom resolution by 3 days post-vaccination across the Comirnaty and Spikevax formulations. The most recently available formulations, Comirnaty XBB.1.5 and Spikevax XBB.1.5, are used to illustrate the risk of solicited AE and risk of any time loss from daily activities. There was a similar risk profile of reporting any time loss from work or daily activities between the sexes, with an age-dependent peak between 20 and < 30 years of age and a lower risk for those who received Comirnaty XBB.1.5 compared with Spikevax XBB.1.5 (Figure 2).

3.3 | Any AE Following Immunisation

Unadjusted proportions by vaccine of AEs within 3 days after vaccination are reported in Table S2. The overall unadjusted proportion of respondents reporting any AE across the vaccines was 29.9% (59,089/197,476). Across the Comirnaty formulations, 26.4% (39,899/151,332) of Comirnaty recipients reported any AE. These proportions for the Spikevax vaccines were 37.6% (3028/8054) for the BA.1 formulation, 38.2% (7737/20,271) for BA4-5 and 47.6% (8350/17,551) for XBB.1.5. The proportion of Nuvaxovid recipients who reported any AE was 28.0% (75/268). The most commonly reported AEs were injection site reaction (23.8% [46,988/197,476]), fatigue (19.4% [38,352/197,476]) and myalgia (14.2% [27,956/197,476]). Across all vaccines, 34.8% (39,574/113,852) of women and 23.3% (19,515/83,624) of men reported any AE. The overall unadjusted proportion of reported AEs was 48.8% (4817/9874) in adults aged 20 to < 40 years and 18.4% (5070/27,600) in adults aged ≥ 80 years across the Comirnaty and Spikevax vaccines (< 0.1% for Nuvaxovid recipients aged ≥ 80 years). The unadjusted proportion of reported AEs in those with an underlying medical condition was 34.3% (19,793/57,647). Reported AE proportions were similar among those who received a co-administered vaccine, across all co-administered vaccines, except for the herpes zoster vaccine (Shingrix) where the overall proportion of AEs was 47.9% (1754/3659) across SARS-CoV-2 vaccine brands.

There was an age-dependent modelled risk of any reported AE across all vaccines and sexes, with peak risk between 20 and < 40 years of age (Figure 3, Figure S2). The modelled risk of any AE at age 40 years ranged from 35.2% (95% CrI, 32.2%–38.5%) for men who had received Comirnaty XBB.1.5 to 75.5% (95% CrI, 71.9%–78.8%) for women who had received Spikevax XBB.1.5. At age 80 years, this risk was lowest across all vaccine brands, ranging from 12.0% (95% CrI, 11.2%–13.0%) for men who had received Comirnaty BA4-5 to 36.7% (95% CrI, 34.6%–38.7%) for women who had received Spikevax XBB.1.5. The mean risk of any reported AE for all three Comirnaty vaccines appeared consistently lower than that for the Spikevax vaccines. Risk of any AE was similar for Spikevax BA.1 and Spikevax BA.4-5, but the risk appeared higher for Spikevax XBB.1.5. There was less precision in the modelling of any AE risk for Aboriginal and Torres Strait Islander people, but a similar age-dependent pattern of modelled risk was observed.

TABLE 2 | Impact of any adverse event within 3 days after immunisation on the daily activities and medical review by vaccine.[a]

	Comirnaty Bivalent BA.1 (Pfizer)	Comirnaty Bivalent BA.4-5 (Pfizer)	Comirnaty XBB.1.5 (Pfizer)	Spikevax Bivalent BA.1 (Moderna)	Spikevax Bivalent BA.4-5 (Moderna)	Spikevax XBB.1.5 (Moderna)	Nuvaxovid (Novavax)
Number of responses	14,741	67,098	69,493	8054	20,271	17,546	268
Any time lost from work, study or daily activities							
Yes	770/14,741 (5.2%)	3378/67,098 (5.0%)	2652/69,493 (3.8%)	645/8054 (8.0%)	1726/20,271 (8.5%)	1818/17,551 (10.4%)	17/268 (6.3%)
Unknown	13/14,741 (0.1%)	60/67,098 (0.1%)	94/69,493 (0.1%)	11/8054 (0.1%)	21/20,271 (0.1%)	36/17,551 (0.2%)	2/268 (0.7%)
Number of days missed							
< 1 day	88/770 (11.4%)	502/3378 (14.9%)	373/2652 (14.1%)	97/645 (15.0%)	278/1726 (16.1%)	279/1818 (15.3%)	3/17 (17.6%)
1 day	365/770 (47.4%)	1726/3378 (51.1%)	1263/2652 (47.6%)	333/645 (51.6%)	870/1726 (50.4%)	879/1818 (48.3%)	8/17 (47.1%)
2 days	215/770 (27.9%)	801/3378 (23.7%)	734/2652 (27.7%)	164/645 (25.4%)	430/1726 (24.9%)	471/1818 (25.9%)	2/17 (11.8%)
≥ 3 days	93/770 (12.1%)	318/3378 (9.4%)	261/2652 (9.8%)	48/645 (7.4%)	139/1726 (8.1%)	175/1818 (9.6%)	4/17 (23.5%)
Unknown	9/770 (1.2%)	31/3378 (0.9%)	21/2652 (0.8%)	3/645 (0.5%)	9/1726 (0.5%)	14/1818 (0.8%)	4/17 (23.5%)
Medical advice sought	87/14,741 (0.6%)	425/67,098 (0.6%)	379/69,493 (0.5%)	48/8054 (0.6%)	147/20,271 (0.7%)	212/17,551 (1.2%)	3/268 (1.1%)
Highest level of medical advice sought							
Phone	20/87 (23.0%)	100/425 (23.5%)	79/379 (20.8%)	16/48 (33.3%)	35/147 (23.8%)	61/212 (28.8%)	—
Primary healthcare worker	31/87 (35.6%)	148/425 (34.8%)	93/379 (24.5%)	20/48 (41.7%)	48/147 (32.7%)	57/212 (26.9%)	—
Emergency department	12/87 (13.8%)	50/425 (11.8%)	36/379 (9.5%)	8/48 (16.7%)	16/147 (10.9%)	16/212 (7.5%)	—
Unknown	24/87 (27.6%)	127/425 (29.9%)	171/379 (45.1%)	4/48 (8.3%)	48/147 (32.7%)	78/212 (36.8%)	—
Any adverse event	4118/14,741 (27.9%)	17,984/67,098 (26.8%)	17,797/69,493 (25.6%)	3028/8054 (37.6%)	7737/20,271 (38.2%)	8350/17,551 (47.6%)	75/268 (28.0%)
Symptom resolution by day 3	2883/4118 (70.0%)	12,240/17,984 (68.1%)	12,841/17,797 (72.2%)	2158/3028 (71.3%)	5260/7737 (68.0%)	5876/8350 (70.4%)	41/75 (54.7%)

[a]The number of reports is expressed as the number and percentage of the responses for the respective subgroup except for where the denominator is < 100. We do not report the proportions where there are five or fewer respondents in the denominator (represented by an em dash).

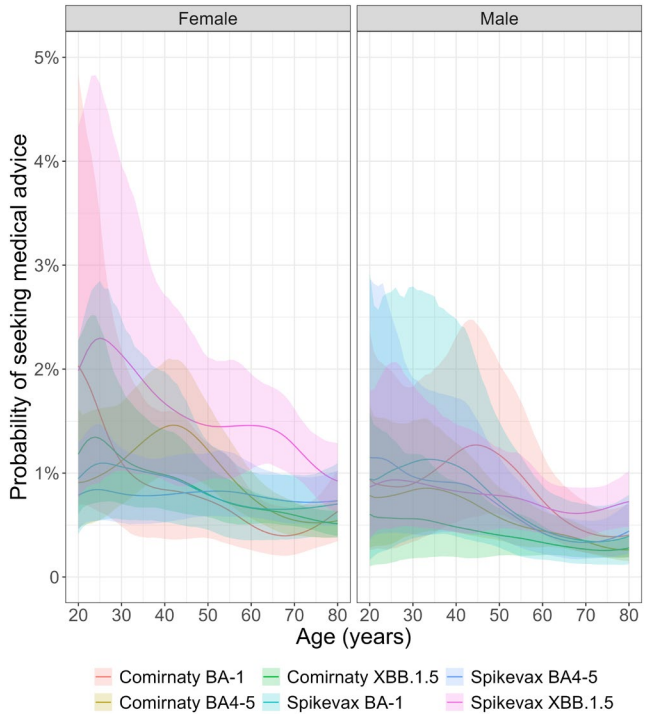

FIGURE 1 | Mean risk (solid line), with 95% credible intervals (shaded regions), of seeking medical advice 3 days after vaccination reported by survey respondents by age for sex, marginalised over Indigenous status, co-administered vaccines and underlying medical conditions.

Risk profiles of injection site reaction, fatigue, myalgia and headache are presented in Figure 4 (see Figure S3 for the risk of chills, fever, arthralgia and gastrointestinal symptoms). There was a consistent pattern overall across these AEs of an age-dependent symptom risk peaking at 30 to < 40 years of age. The risk of reporting an AE with Comirnaty XBB.1.5 appeared lower across all symptoms.

Sensitivity analyses assuming all respondents with missing data had complete records produced similar results to the complete case analyses. For the key model parameters, each model converged as demonstrated by acceptable R-hat values (all less than 1.1), effective sample sizes (ratios greater than 0.1) and well-mixed trace plots. Figure S4 shows the trace plots for 20 randomly selected key parameters from the medical advice model.

4 | Discussion

This analysis of post-immunisation survey responses from almost 200,000 people in Australia confirms an acceptable reactogenicity profile of Nuvaxovid and different variant-based mRNA SARS-CoV-2 boosters. Commonly reported AEs, while not necessarily determined to be causally related to vaccination, were found to have a short duration and mainly resulted in at most 1 day lost of normal activities. The risk of seeking medical advice after vaccination was consistently low, generally < 2.0%, and still < 2.5% for more reactogenic vaccines such as Spikevax XBB.1.5, with no unusual patterns in event types observed. Individuals were more likely to consult a primary healthcare worker than attend an emergency department when seeking medical advice.

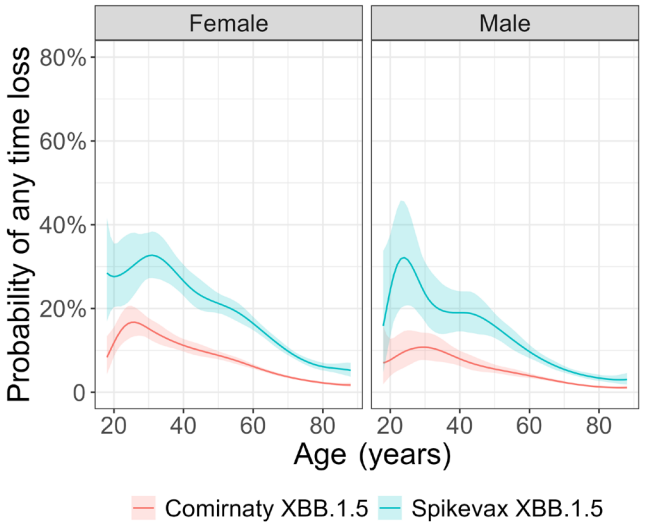

FIGURE 2 | Mean risk (solid line), with 95% credible intervals (shaded regions), of any time loss from work or daily activities 3 days after vaccination with Comirnaty XBB.1.5 or Spikevax XBB.1.5 reported by survey respondents, marginalised over co-administered vaccines and underlying medical conditions.

There was a slight increase (about 0.5%) in risk of seeking medical advice in people with an underlying medical condition when compared with those without, after adjustment for age and sex effects. However, it was not possible to exclude coincidental medical advice seeking that was unrelated to vaccination, which is likely to be more frequent in people with an underlying medical condition. There may also be complex relationships concerning the propensity for seeking medical advice in such subgroups.

These SARS-CoV-2 boosters can be safely co-administered with influenza, diphtheria–tetanus–pertussis, Prevenar 13 and Shingrix vaccines. These data provide further evidence for vaccination providers and the public that the risk of seeking medical advice following co-administration with these vaccines is similar to that for administration of the SARS-CoV-2 boosters alone. Comparably, clinical trials and post-marketing studies conclude no safety concerns of co-administration of SARS-CoV-2 mRNA boosters with any of these vaccines [20–23].

Higher proportions of women than men reported any AE across all vaccine formulations, and there was some evidence of an elevated risk of seeking medical advice in women compared with men after SARS-CoV-2 boosters, but with low precision. There is an acknowledged difference in reporting patterns observed in previous health surveys [24]. Higher rates of reported AEs among women have been observed across multiple vaccines and may reflect sex-based differences in immune response [25, 26], health-seeking behaviour and reporting behaviour [27, 28] rather than increased vaccine-related risk [29].

There was no apparent age-related pattern of seeking medical advice following SARS-CoV-2 boosters, although there was low precision in the younger age groups. This has not previously been reported in other studies. The proportions of any reported AE and both the expected risks of any AE and the specific solicited AE showed an age-dependent pattern across all vaccine

brands, peaking between 30 and <40 years of age. This age-dependent pattern is consistent with those previously reported for Nuvaxovid, Comirnaty and Spikevax SARS-CoV-2 vaccine priming doses [12, 13] and the findings of regulatory trials of these vaccines [30–32].

The proportion of reporting for any AE was lower for boosters compared with the SARS-CoV-2 vaccine priming doses (Comirnaty, 26.1% vs. 43.7%; Spikevax, 40.8% vs. 51.3%; Nuvaxovid, 26.3% vs. 44.6%) [12, 13]. However, these are non-concurrent comparisons and both the Comirnaty and Spikevax SARS-CoV-2 vaccines given as priming doses in Australia were monovalent formulations developed against the ancestral SARS-CoV-2 virus. While the survey methods are the same, we note that this cohort is older due to Australian vaccine policy, recommending SARS-CoV-2 boosters for older and high-risk individuals [3]. The median age for a first priming dose of Comirnaty vaccine in Australia was 42 years (IQR, 33–49 years) [12], compared with 70 years for a Comirnaty booster (IQR, 63–77 years).

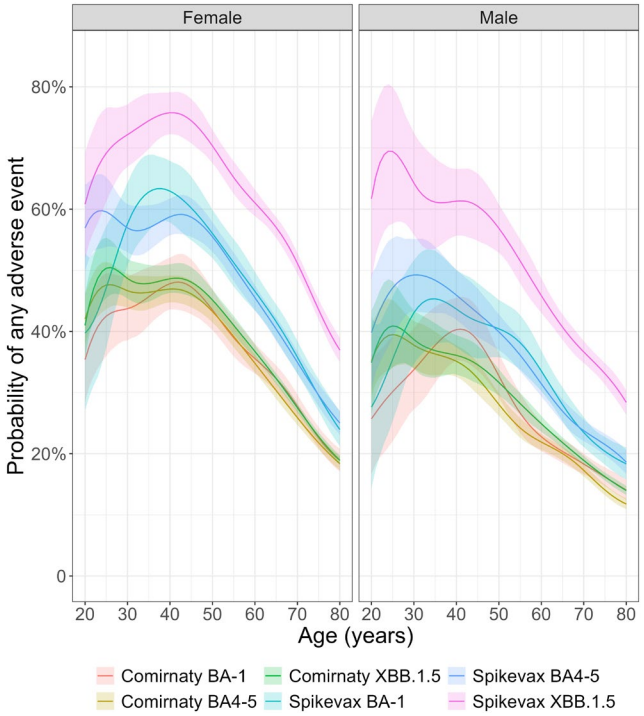

FIGURE 3 | Mean risk (solid line), with 95% credible intervals (shaded regions), of any adverse event 3 days following vaccination for each vaccine formulation reported by survey respondents by age for sex, marginalised over Indigenous status, co-administered vaccines and underlying medical conditions.

Reported risks of AEs appear lower after Comirnaty boosters compared with Spikevax. While we caution that this observation is based on non-randomised comparisons, it is in keeping with a systematic review which concluded that Comirnaty vaccines are associated with lower reactogenicity than Spikevax vaccines [1]. While there were similar proportions of reported AEs across the Comirnaty vaccine formulations (25.6% [17,797/69,493] to 27.9% [4118/14,741]), these proportions appear higher after Spikevax XBB.1.5 (47.6% [8350/17,551]) compared with the respective Bivalent BA.1 (37.6% [3028/8054]) and Bivalent BA.4-5 (38.2% [7737/20,271]) formulations. Higher reactogenicity of Spikevax XBB.1.5 than Comirnaty XBB.1.5 was reported in a small study among elderly vaccine recipients [10]. Further post-marketing studies comparing these and subsequent formulations of SARS-CoV-2 vaccines are warranted.

While the overall safety profile of these vaccines is not in doubt, the anticipated impact of AEs through lost days of daily activity may concern consumers. Most survey respondents who reported any lost days of work or normal daily activity reported no more than one lost day. Across all boosters and age groups, 69.9% (41,299/59,089) of survey respondents who reported any AE reported symptom resolution within 3 days of vaccination with a SARS-CoV-2 booster.

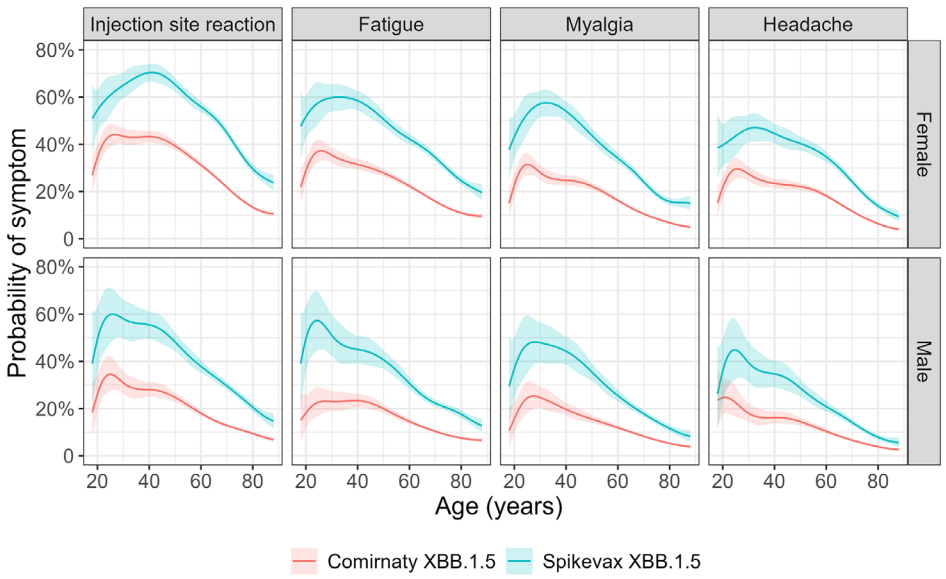

FIGURE 4 | Mean risk (solid lines) with 95% credible intervals (shaded regions) of solicited symptoms within 3 days after vaccination with Comirnaty XBB.1.5 or Spikevax XBB.1.5 by age for sex, marginalised over co-administration vaccines and underlying medical conditions.

SARS-CoV-2 boosters provide protection for at-risk groups against morbidity, hospitalisation and death [1, 33, 34]. While not the only factor, the short duration of reactogenicity profiles and information about the limited impact on daily life may encourage individuals undecided about booster immunisation.

4.1 | Limitations

In comparison with Australian population demographics, the survey population was older (median, 69.0 years [IQR, 61.0–76.0 years]), but this is consistent with the Australian recommendation for annual SARS-CoV-2 vaccination in chiefly the 64- to 75-year age group [2]. The response rates (51.3% [536/1045] to 58.3% [188,746/323,647]) are in the range for published health-related survey studies (40%–75%) [35–37]. Respondent bias is inherent in active safety vaccine surveys as those who have experienced an AE are more likely to respond, thus inflating AE reporting [12, 13]. Those who have experienced very severe AEs may not have been able to respond to the survey within the time limit. There is lack of clinical verification of self-reported medical conditions and of AEs, as well as of causal attribution of AEs. We also caution against comparison of the modelled risks of AEs between vaccines as these are non-randomised comparisons. Survey responses were excluded due to missing information on sex (8.6% [18,702/217,211], the majority of which were missing from respondents who were vaccinated at pharmacies), however, similar sex distributions were observed between respondents from these sites. Sensitivity analyses assuming all respondents with missing data were (i) male and non-Indigenous and (ii) female and non-Indigenous produced similar estimates to the complete case analysis. The choice of study start date, 1 January 2023, assumes that any SARS-CoV-2 vaccine administered after that date in Australia was a booster, given the high uptake of SARS-CoV-2 priming vaccinations (> 95%). The proportion of respondents who self-identified as Aboriginal and Torres Strait Islander in this study was only 1.5% (2920/197,476), as opposed to the estimated proportion in the Australian population of 3.8% [38]. While the rates of seeking medical advice between non-Indigenous and Aboriginal and Torres Strait Islander peoples were similar, the sparsity of data resulted in poor precision in risk estimates. This may be partly explained by lower SARS-CoV-2 vaccine coverage in Aboriginal and Torres Strait Islander peoples, which has been reported previously [39]. Understanding factors for this discrepancy by consultation with Aboriginal and Torres Strait Islander advisory groups may lead to improved coverage in this vulnerable population [39, 40]. Similarly, poor precision in risk estimates was obtained for Nuvaxovid due to low survey response frequency. The statistical analysis focussed on separate risk profiles for each formulation. As such, whether we can extrapolate these findings to future formulations is unknown. While the AE profiles of the Comirnaty vaccines were similar, the apparent increase in reactogenicity for Spikevax XBB.1.5 suggests that ongoing safety surveillance is warranted across all SARS-CoV-2 boosters.

5 | Conclusion

Australian surveillance of SARS-CoV-2 booster vaccines confirms their short-term safety, including in people with underlying medical conditions and when co-administered with other vaccines. We report overall and specific AE risk profiles, along with data on time lost from daily activities and symptom resolution. These findings may support undecided consumers considering booster vaccination, helping improve protection in vulnerable groups.

Author Contributions

Conceptualisation and methodology: Evelyn Tay, Julie A. Marsh, Thomas L. Snelling, Lucy Deng, Michael Dymock, Kristine Macartney and Nicholas Wood. Data curation: Lucy Dawes, Thuy Nguyen and Alan Leeb. Formal analysis: Evelyn Tay and Michael Dymock. Project administration: Julie A. Marsh, Thomas L. Snelling and Lucy Deng. Visualization: Evelyn Tay and Michael Dymock. Writing – original draft: Evelyn Tay. Writing – review and editing: Evelyn Tay, Michael Dymock, Lucy Dawes, Thuy Nguyen, Lucy Deng, Julie A. Marsh, Alan Leeb, Nicholas Wood and Kristine Macartney. All authors have read and agreed to the final version of the manuscript.

Acknowledgements

We acknowledge the participants and staff at the AusVaxSafety surveillance sites and the contribution of Vaxtracker and SmartVax. We thank all the Aboriginal and/or Torres Strait Islander people who provided advice to ensure Aboriginal cultural perspective in the development and conduct of the survey, as well as the reporting of these results. We also wish to thank the Vaccines and Infectious Diseases Advisory Group for providing a consumer perspective on this study.

Funding

This research was funded by the Australian Government Department of Health, Disability and Ageing. Grant number: Health/20-21/PH20/17578. The project was designed, implemented, analysed and reported independent of the funder.

Disclosure

Not commissioned; externally peer reviewed.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

De-identified individual participant data underpinning the findings of this study may be made available upon request, pending approval from the data owner. Requests for data, accompanied by a methodologically sound proposal, can be submitted to AusVaxSafety. The study group will review all applications for data access. Upon approval, the data will be shared exclusively for the purposes outlined in the approved proposal. Data requesters must sign a data access agreement before gaining access.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** mja270227-sup-0001-supinfo.pdf.