Short term adverse event profile of COVID-19 mRNA vaccines in children aged 5–15 years in Australia

Nicholas Wood,[a,b,*] Laura K. Lopez,[a] Catherine Glover,[a] Alan Leeb,[c,d] Patrick Cashman,[e] Lucy Deng,[a,b] and Kristine Macartney[a,b]

[a]National Centre for Immunisation Research and Surveillance, Westmead, New South Wales, Australia
[b]The University of Sydney Children's Hospital Westmead Clinical School, Westmead, New South Wales, Australia
[c]SmartVax, Ballajura, Western Australia, Australia
[d]Illawarra Medical Centre, Ballajura, Western Australia, Australia
[e]Hunter New England Population Health, Newcastle, New South Wales, Australia

The Lancet Regional Health - Western Pacific 2023;31: 100684

Published Online xxx https://doi.org/10.1016/j.lanwpc.2023.100684

Australia commenced its COVID-19 vaccine program for children aged 12–15 years from July 2021 and for children aged 5–11 years from January 2022 with two primary doses of either Comirnaty (Pfizer–BioNTech BNT162b2, 10 μg for 5–11 years and 30 μg for 12–15 years) or Spikevax (Moderna mRNA-1273, 50 μg for 6–11 years and 100 μg for 12–15 years), 8 weeks apart. A booster dose is recommended for those aged 5–15 years with complex health conditions or severe immunocompromise.

Data on the safety of Comirnaty and Spikevax in children aged 5–15 derive predominantly from clinical trials.[1,2] Post-marketing surveillance, particularly of Comirnaty, has mainly come from v-safe,[3] a US smartphone-based active COVID-19 vaccine safety surveillance system.[4,5] Among 48,795 children aged 5–11 years enrolled in v-safe, most reported reactions were mild-to-moderate, mostly in the day after vaccination, and more common after dose 2.[5] However, pediatric vaccine safety surveillance data outside the US are lacking.

Australia's active safety surveillance system AusVaxSafety monitors the safety of COVID-19 vaccines. We report on the short-term adverse event profile of mRNA COVID-19 vaccines in >390,000 children aged 5–15 years by age, dose, brand and pre-existing comorbidity.

Children aged 5–15 years who received a COVID-19 vaccine at vaccination sites (state-run vaccination hubs, pharmacies, or primary healthcare practices) were included in our analysis, with active prospective survey-based methods as previously described.[6]

Three days after vaccination, the child's parent/guardian was automatically sent an SMS or email with a link to opt into an online survey with defined response options about adverse events following immunisation (AEFI) including solicited local adverse events (pain, redness, swelling, and itching) and systemic adverse events (myalgia, arthralgia, headache, fever, chills, fatigue, and gastrointestinal symptoms), any medical care or advice sought, and impact on daily activities. Vaccination details (vaccine brand, batch, dose, date) and demographic details (age, sex, Indigenous status, underlying medical conditions) were obtained.[6]

We examined the proportions of respondents reporting any AEFI 0–3 days post-vaccination, medical review for AEFI, and impact on daily activities. All analyses were conducted in R version 4.1.0.[7] The study was conducted with ethics approval from Sydney Children's Hospitals Network (HREC/16/SCHN/19).

We analysed 396,920 survey responses for children aged 5–15 who received a COVID-19 vaccine between July 2021–September 2022: 216,140 following Comirnaty 10μg (5–11 years) and 173,874 following Comirnaty 30 μg (12–15 years) and 6,906 following Spikevax 100 μg (12–15 years) (Table 1). Due to changing vaccine recommendations, availability, and local COVID-19 epidemiology, small numbers of responses were received for Comirnaty 10 μg dose 3 (n = 91), Spikevax 100 μg dose 3 (n = 62), and Spikevax 50 μg (any dose, n = 94); these were excluded from analysis. AEFI rates were similar across sex and Indigenous status but higher for children with parent-reported chronic medical conditions (Table 1). Overall, medical review rates were low (0.7%) as was impact on daily activities (8.9%). However, a higher proportion of children with chronic medical conditions reported medical review and impact on daily activities compared to children without (Supplementary Table S1).

The proportion of children with a reported AEFI (any, local or systemic) trended upwards with age (Supplementary Fig. S1). The prevalence of fever was lowest in children aged 5–11 years (2.9% after dose 1 and 4.9% after dose 2) and was higher in older adolescents (Table 1). AEFI rates were higher following dose 2 compared to dose 1 (Table 1 and Supplementary Fig. S2), though the difference between dose 1 and 2 was lower in the 5–11 years group than the 12–15 years group. AEFI rates were highest following dose 2 of Spikevax in the 12–15 years group, and impact on routine activities was also more common after dose 2 of either vaccine in this age group (Table 1).

*Corresponding author. National Centre for Immunisation Research and Surveillance, Children's Hospital at Westmead, Westmead, New South Wales, Australia.
E-mail address: nicholas.wood@health.nsw.gov.au (N. Wood).

	Comirnaty (Pfizer–BioNTech BNT162b2, 10 µg) 5–11 years		Comirnaty (Pfizer–BioNTech BNT162b2, 30 µg) 12–15 years			Spikevax (Moderna mRNA-1273, 100 µg) 12–15 years	
	Dose 1[a]	Dose 2[a]	Dose 1[a]	Dose 2[a]	Dose 3[a]	Dose 1[a]	Dose 2[a]
Any adverse event rate (all respondents)	33,854/133,670 (25%)	22,833/82,470 (28%)	30,265/94,670 (32%)	38,732/78,460 (49%)	361/744 (49%)	1220/3580 (34%)	2119/3326 (64%)
Local adverse event rate[b]	29,193 (22%)	19,134 (23%)	25,889 (27%)	28,980 (37%)	297 (40%)	1059 (30%)	1633 (49%)
Local pain	28,320 (21%)	18,365 (22%)	25,097 (27%)	27,815 (35%)	289 (39%)	1018 (28%)	1540 (46%)
Local itching	2107 (1.6%)	1293 (1.6%)	1915 (2.0%)	2064 (2.6%)	24 (3.2%)	89 (2.5%)	158 (4.8%)
Local redness	3393 (2.5%)	2764 (3.4%)	2565 (2.7%)	3914 (5.0%)	56 (7.5%)	183 (5.1%)	456 (14%)
Local swelling	3266 (2.4%)	3479 (4.2%)	3834 (4.0%)	5698 (7.3%)	83 (11%)	271 (7.6%)	540 (16%)
Systemic adverse event rate[b]	13,181 (9.9%)	10,614 (13%)	16,241 (17%)	30,729 (39%)	283 (38%)	731 (20%)	1834 (55%)
Myalgia/Arthralgia	6937 (5.2%)	6304 (7.6%)	9393 (9.9%)	19,200 (24%)	194 (26%)	442 (12%)	1248 (38%)
Headache	9715 (7.3%)	7670 (9.3%)	12,204 (13%)	26,262 (33%)	236 (32%)	545 (15%)	1634 (49%)
Fever[c]	3879 (2.9%)	4002 (4.9%)	2953 (3.1%)	13,377 (17%)	135 (18%)	174 (4.9%)	1112 (33%)
Chills	2508 (1.9%)	2632 (3.2%)	3561 (3.8%)	13,917 (18%)	124 (17%)	198 (5.5%)	1126 (34%)
Fatigue	14,636 (11%)	10,676 (13%)	15,784 (17%)	29,337 (37%)	262 (35%)	708 (20%)	1756 (53%)
Gastrointestinal[d]	3901 (2.9%)	3126 (3.8%)	3327 (3.5%)	8492 (11%)	86 (12%)	180 (5.0%)	704 (21%)
Any adverse event rate (by respondent characteristics)							
Sex							
Female	17,665/64,208 (28%)	11,694/39,646 (29%)	15,452/47,288 (33%)	19,416/38,855 (50%)	169/341 (50%)	492/1425 (35%)	764/1214 (63%)
Male	15,733/67,448 (23%)	10,747/41,280 (26%)	14,646/46,821 (31%)	19,060/39,077 (49%)	177/350 (51%)	427/1330 (32%)	766/1187 (65%)
Another Term	25/88 (28%)	15/36 (42%)	74/234 (32%)	83/169 (49%)	1/2 (50%)	0/1 (0%)	2/2 (100%)
Unknown	431/1926 (22%)	378/1522 (25%)	93/327 (28%)	171/359 (48%)	14/51 (27%)	301/824 (37%)	587/923 (64%)
Indigenous status							
Aboriginal and Torres Strait Islander	789/3376 (23%)	523/2058 (25%)	1022/3353 (30%)	1104/2553 (43%)	14/31 (45%)	41/112 (37%)	47/91 (52%)
Not Indigenous	32,104/125,931 (25%)	21,952/78,907 (28%)	28,660/89,261 (32%)	36,953/74,379 (50%)	340/692 (49%)	1155/3392 (34%)	2040/3174 (64%)
Unknown	961/4363 (22%)	359/1519 (24%)	583/2056 (28%)	675/1534 (44%)	7/21 (33%)	24/76 (32%)	32/61 (52%)
History of anaphylaxis[e]							
Yes	1008/3254 (31%)	638/2083 (31%)	1079/2957 (36%)	1419/2470 (57%)	14/37 (38%)	25/70 (36%)	44/71 (62%)
No	32,846/130,416 (25%)	22,196/80,401 (28%)	29,186/91,713 (32%)	37,313/75,996 (49%)	347/707 (49%)	1195/3510 (34%)	2075/3255 (64%)
Any chronic medical condition							
Yes	1350/3719 (36%)	831/2140 (39%)	1670/3717 (45%)	1724/2757 (63%)	129/247 (52%)	40/82 (49%)	60/78 (77%)
No	32,504/129,951 (25%)	22,003/80,344 (27%)	28,595/90,953 (31%)	37,008/75,709 (49%)	232/497 (47%)	1180/3498 (34%)	2059/3248 (63%)
Specific chronic medical condition[f]							
Chronic cardiorespiratory, renal or hepatic disease[g]	138/446 (31%)	81/252 (32%)	220/498 (44%)	198/326 (61%)	16/27 (59%)	3/5 (60%)	3/4 (75%)
Diabetes	79/234 (34%)	51/131 (39%)	151/389 (39%)	157/293 (54%)	8/15 (50%)	1/8 (12%)	2/5 (40%)
Haematological/Oncological condition	37/140 (26%)	28/100 (28%)	29/91 (32%)	40/87 (46%)	20/42 (48%)	–	–
Neurological condition	81/234 (35%)	51/145 (35%)	88/202 (44%)	80/149 (54%)	10/17 (59%)	–	1/2 (50%)
Immunological condition	61/164 (37%)	45/129 (35%)	123/268 (46%)	134/212 (63%)	35/68 (51%)	5/6 (83%)	3/3 (100%)
Obesity	11/32 (34%)	6/21 (29%)	27/53 (51%)	23/35 (66%)	2/4 (50%)	1/1 (100%)	2/3 (67%)
Other[h]	1024/2711 (38%)	620/1503 (41%)	1152/2470 (47%)	1189/1808 (66%)	57/108 (53%)	32/63 (51%)	49/62 (79%)
Medical review rate (all respondents)	708/133,670 (0.5%)	608/82,470 (0.7%)	573/94,670 (0.6%)	1116/78,460 (1.4%)	15/744 (2%)	35/3580 (0.9%)	103/3326 (3%)
Highest level of medical review[i]							
Phone advice line	177/708 (25%)	159/608 (26%)	113/573 (20%)	238/1116 (21%)	5/15 (33%)	6/35 (17%)	27/103 (26%)
Primary healthcare[j]	330/708 (47%)	292/608 (48%)	266//573 (46%)	485/1116 (43%)	4/15 (27%)	6/35 (17%)	41/103 (40%)
Visit to emergency department	168/708 (24%)	122/608 (20%)	159//573 (28%)	357/1116 (32%)	6/15 (40%)	15/35 (43%)	23/103 (22%)
Unknown	33/708 (4.6%)	35/608 (5.8%)	35/573 (6%)	36/1116 (3.2%)	0/15 (0%)	8/35(23%)	12/103 (12%)

(Table 1 continues on next page)

	Comirnaty (Pfizer-BioNTech BNT162b2, 10 µg) 5–11 years		Comirnaty (Pfizer-BioNTech BNT162b2, 30 µg) 12–15 years			Spikevax (Moderna mRNA-1273, 100 µg) 12–15 years	
	Dose 1[a]	Dose 2[a]	Dose 1[a]	Dose 2[a]	Dose 3[a]	Dose 1[a]	Dose 2[a]
(Continued from previous page)							
Impact on daily activities (all respondents)[k]	4035/133,670 (3%)	6059/82,470 (7%)	5778/94,670 (6%)	17,562/78,460 (22%)	143/744 (19%)	315/3580 (8.7%)	1276/3326 (38%)
Number of days impacted[l]							
<1 day	603/4035 (15%)	696/6059 (11%)	920/5778 (16%)	2238/17,562 (13%)	12/143 (8%)	26/315 (8.3%)	83/1276 (6.5%)
1 day	2016/4035 (50%)	3224/6059 (53%)	2932/5778 (51%)	9746/17,562 (55%)	58/143 (41%)	184/315 (58%)	695/1276 (54%)
2 days	1019/4035 (25%)	1464/6059 (24%)	1484/5778 (26%)	4461/17,562 (25%)	48/143 (34%)	71/315 (23%)	378/1276 (30%)
≥ 3 days	395/4035 (9.8%)	651/6059 (11%)	438/5778 (7.6%)	1112/17,562 (6.3%)	25/143 (17%)	34/315 (11%)	119/1276 (9%)

[a]n/N (%). [b]Denominator is the number of respondents who reported any adverse event. [c]Fever defined as a temperature >38 °C. [d]Gastrointestinal symptoms include nausea, vomiting, diarrhoea and abdominal pain. [e]Includes people who report having a history of anaphylaxis or carry an Epipen. [f]Sum of denominators of medical condition groups exceeds the total denominator of chronic medical condition as respondents may select more than one condition. [g]Chronic cardiorespiratory, renal or hepatic disease includes heart disease, poorly controlled hypertension, chronic lung disease, chronic kidney disease, chronic liver disease. [h]Other includes autoimmune conditions, allergies and sleep disorders, among other conditionals self-reported in free text. [i]Denominator is the number of respondents who reported a medical review. [j]Primary healthcare includes general practitioner or Aboriginal healthcare worker. [k]Impact defined as vaccination event causing respondent to miss work, study, or normal/routine duties. [l]Denominator is the number of respondents who reported impact on daily activities.

Table 1: **Rates of adverse events, medical review and impact on daily activities reported by age, sex, underlying medical conditions and vaccine brand and dose.**

Active safety surveillance data from Australia found lower AEFI reporting rates in the days following mRNA COVID-19 vaccination of children aged 5–15 years compared to clinical trial safety data, and similar rates compared to those reported from v-safe.[2,3,5] Lower reported AEFI rates in younger children (aged 5–11 years) compared to older children are potentially related to the use of reduced dose mRNA vaccines. AEFI rates were slightly higher in children with chronic medical conditions and following dose 2. Importantly fever, which is a concern in children under 5 years old due to the potential for febrile seizures, was low in the youngest children (5 years, any dose; 1117/27,653 (4%)) and similar to the reported rate following seasonal influenza vaccination.[8] While the data reflect self-reported AEFI from survey respondents only and include respondents who reported no adverse event, respondents with AEFI are possibly more likely to complete the survey. Vaccine doses for individuals were not linked for this analysis and we therefore cannot comment the effects of dose interval or mixed schedules on adverse event rates. Active safety surveillance confirms the short-term safety profile following mRNA COVID-19 vaccination of children aged 5–15 years. Future surveillance of lower dose mRNA vaccines in children under 5 years old is needed to better understand safety in this population.

Contributors

Professor Wood, Dr Deng, Ms Glover and Dr Lopez conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Leeb and Mr Cashman designed the data collection instruments and reviewed and revised the manuscript.

Professor Macartney conceptualized and designed the study and critically reviewed the manuscript for important intellectual content.

Dr Lopez, Ms Glover and Dr Deng have directly accessed and verified the data.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of interests

Dr Leeb reports grants/contracts from SmartX data and is a member of WA Vaccine Safety Advisory Committee. Professor Macartney reports support for attendance as consultant/facilitator for WHO regional meetings.

Acknowledgements

We acknowledge the participants and staff at the surveillance sites, state and territory health departments, and the contribution of the surveillance tools SmartVax, Vaxtracker, and Microsoft COVID-19 Vaccine Management System.

Funding/Support: AusVaxSafety surveillance is funded under a contract with the Australian Department of Health and Aged Care. The funder had no role in the analysis of the data.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100684.

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