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Varicella vaccine effectiveness over 10 years in Australia; moderate protection from 1-dose program

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SUMMARY

Objectives: To examine the impact of Australia's single dose infant varicella vaccination program, we assessed single dose varicella vaccine effectiveness (VE) in preventing hospitalised disease using two methods.

Methods: Clinically confirmed varicella cases from the Paediatric Active Enhanced Disease Surveillance (PAEDS) sentinel network were age-matched to 20 controls obtained from the Australian Immunisation Register. Conditional logistic regression models were used to estimate VE and compared with estimates obtained using our second approach.

Results: There were 78 hospitalised varicella cases during the post vaccine introduction period from January 2008 to December 2015, who were eligible for funded varicella vaccination. Median age at onset was 4.5 years and more than half (59%) were vaccinated. The majority of children received one vaccine brand (Varilrix, GSK). The estimated case-control VE for one dose of vaccine against hospitalised varicella was 64.7% (95% CI: 43.3–78.0%); estimates using the screening method were not significantly different. Exclusion of children who were immunocompromised did not significantly alter VE estimates.

Conclusions: Although Australia's program has impacted on the burden of varicella disease, single dose VE against varicella hospitalisation is only moderate. Greater reductions in varicella disease could potentially be achieved by incorporation of a second vaccine dose into the program to minimise breakthrough disease and interrupt virus circulation.

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Introduction

Prior to the availability of varicella vaccine approximately 1500 hospitalisations and 7–8 deaths occurred in Australia each year due to varicella (chickenpox).[1] To combat this burden, Australia introduced publicly funded one-dose varicella vaccination under Australia's National Immunisation Program (NIP) more than a decade ago. From November 2005, varicella vaccine (either Varivax® (Seqirus/Merck and Co) or Varilrix® (GlaxoSmithKline, (GSK)) was provided for all non-immune infants aged 18 months. A single adolescent catch-up dose for those not previously immunised or infected was offered to a single cohort (aged 12–13 years) via the school-based vaccination program from 2006.[2,3] Provision of funded catch-up for children aged 2–11 years was not included in the NIP. Prior to this both vaccines had been available in Australia on the private market for approximately 5 years but uptake was very low at approximately 6%.[4] Following NIP introduction, uptake of varicella vaccination measured at 24 months of age was 72% by September 2006, rising to 82% by the end of 2009, where it remained largely unchanged until December 2013.[5] In 2013, the combination measles-mumps-rubella-varicella vaccine (MMRV, Priorix-Tetra®, GSK) replaced the monovalent vaccine at the 18 month of age schedule point,[6] which resulted in increased coverage of 92% by December 2015.[5] Reductions in congenital and neonatal varicella, and varicella hospitalisations, particularly among vaccine eligible children (73% decline in cases), as well as older children and adults, have been reported.[7–10] However, despite these ecological studies showing an impact on severe disease, evidence of ongoing varicella zoster virus (VZV) transmission in the form of school-based outbreaks,[11] notifications among school aged children[12] and varicella hospitalisations, including in immunocompetent children,[10] have occurred.

Similarly, a decade after implementation of a single dose vaccine program in the United States (US), a significant impact on varicella morbidity and mortality was reported.[13] However, outbreaks continued to occur in highly vaccinated populations[14] and vaccine effectiveness was observed to be lower (73–85%)[15,16] than expected from clinical trials.[17,18] In response to this a second dose of varicella vaccine was included in the US schedule from 2007,[19] with a similar transition occurring from one- to two-dose programs in other countries, including Germany, Canada and Spain.[20–22] In Australia, one previous assessment of the addition of a second dose of varicella vaccine (given as MMRV vaccine) to the NIP in 2008 showed unfavourable incremental cost-effectiveness based on assessment of direct costs only,[23] resulting in no change to the single dose schedule. From 2008, the Australian Immunisation Handbook recommended that parents could self-fund a second dose of varicella vaccine for their children to increase protection against varicella.[24]

In order to better examine the impact of Australia's policy of single dose varicella vaccination, data on vaccine effectiveness is required. The aim of this study was to assess single dose varicella vaccine effectiveness (VE) against hospitalised varicella disease in Australia, using two methods involving confirmed varicella cases from an established sentinel surveillance system, the Paediatric Active Enhanced Disease Surveillance (PAEDS) network.[25]

Method

Case ascertainment

Active surveillance for hospitalised varicella was conducted in major tertiary paediatric hospitals in five Australian states in the PAEDS network[25]; Royal Children's Hospital, Victoria; The Children's Hospital at Westmead, New South Wales; Women's and Children's Hospital, South Australia; Princess Margaret Hospital for Children, Western Australia and Lady Cilento Children's Hospital (formerly Royal Children's Hospital), Queensland. Ethical approval was obtained at each hospital to conduct this surveillance.

Hospital admissions for any possible cases of varicella and laboratory testing for varicella were prospectively monitored by PAEDS surveillance nurses at each site for an 8 year period from January 1, 2008 to December 2015 (only 3.5 year period from July 1, 2012 to December 2015 in Queensland). Eligible cases were children aged <15 years of age hospitalised with clinical and/or laboratory-confirmed varicella (with or without complications). Patients who were only treated in the emergency department were excluded. For the purpose of assessing vaccine effectiveness, we only included cases eligible for vaccination under the NIP-funded program (born from 1 May 2004) aged 19 months (1 month older than the age at which single dose vaccination was routinely provided) to <11 years. We excluded potential (age-eligible) recipients of the adolescent catch-up dose because data confirming receipt of this vaccine dose was not accessible. The clinical characteristics of all hospitalised varicella cases is reported separately.[26] Demographic and clinical data and medical history were obtained from medical records. Immunocompromised cases were defined on the basis of their underlying disease (e.g. cancer) and/or immunosuppressive medication. Vaccination history was obtained from the Australian Immunisation Register (AIR; formerly the Australian Childhood Immunisation Register). The AIR is a population-based register of citizens and permanent residents enrolled in the national publicly funded health care system, Medicare, regardless of vaccination status (99% enrolment of all Australian children by 12 months of age).[27] During the study period the AIR included the vaccination history of children until they reached 7 years of age. For estimates of VE, a vaccine dose was considered valid if received ≥28 days before disease onset.

Control ascertainment for case control study

Controls were randomly sampled for each PAEDS case from a de-identified dataset of individual records extracted from the AIR, following restriction of the database to those states included in the PAEDS network to ensure sampling from a similar population. Controls were matched to cases by date of birth. Because the analysis relies on discordance in vaccination status between cases and matched controls, and the AIR provided a readily available source of controls, we sampled 20 age-matched controls for each case to maximise precision. Vaccination status of controls was ascertained from the register after selection and vaccination considered valid if received ≥28 days before the date of disease onset in the matched case. There were no 2-dose recipients among selected controls. This method of control ascertainment has been used previously to assess VE of pertussis and measles vaccines in Australia.[28,29]

Statistical analysis

Conditional logistic regression models were generated in Stata to estimate VE for a range of scenarios; (a) all cases; (b) cases who were immunocompetent at the time of their varicella hospitalisation; (c) cases born from 2008 when vaccination coverage had risen to 80% and disease circulation had declined[8]; and (d) cases aged <7 years at onset of illness for whom all vaccinations should be recorded on the AIR. An exploratory analysis also included children who were vaccinated prior to commencement of the funded NIP program. The models estimated the odds ratio (OR) for receipt of 1 vaccine dose for varicella cases compared with their matched controls. VE estimates and 95% CIs were based on the OR using the formula $VE = 1 - OR \times 100\%$.

To further explore the validity of our results we used the screening method to assess VE, where VE = 1 – [PCV/(1-PCV)][(1-

Table 1
Proportion of population vaccinated (PPV) estimates by year, used to model VE using the screening method.

Year of birth	PPV-base case[a]	PPV-alternate[b]
2004–2005	0.755	0.839
2006	0.796	0.867
2007	0.819	0.887
2008	0.830	0.889
2009	0.836	0.906
2010–2013	0.810	0.919

[a] measured at 24 months of age.
[b] measured at 60 months of age, except for 2011 (48 months of age), 2012 (36 months of age) and 2013 (24 months of age) as birth cohort had not yet reached 60 months of age.

PPV)/PPV].[30] PPV was the proportion of the population vaccinated (Table 1) and PCV was the proportion of varicella cases that were vaccinated. PPV was calculated using the population weighted average of vaccine coverage assessed at the routinely reported milestone of 24 months of age for states included in the PAEDS network, by individual annual birth cohort years of 2006, 2007, 2008 and 2009 and grouped (due to low case numbers) for the period 2004–2005 and the later period of 2010–2013 (Table 1). VE was calculated for the same scenarios as the case control study, with the exception of including children vaccinated prior to commencement of the funded NIP program, as accurate coverage data were not available to estimate a PPV for this period. Recognising that some children were vaccinated against varicella later than the recommended age, a sensitivity analysis was conducted using alternate PPVs estimated from coverage data at 60 months of age (Table 1), representing an upper limit for varicella coverage.

Results

Characteristics of study cases

There were 231 children hospitalised with varicella for the period 2008 to 2015. Of these 84 (36%) were <19 months of age and 23 (10%) were aged ≥11 years. A further 46 (37%) were vaccinated prior to the commencement of the NIP-funded program and 4 (3%) had a history of varicella, leaving 74 cases eligible for inclusion in the main VE analyses. Of the 74 cases, 36 (48.6%) were laboratory confirmed.

Demographic characteristics of the 74 cases included in the VE analysis are summarised in Table 2. The median age of varicella onset was 4.5 years (IQR: 3.0–6.4). The median length of stay was 3 days and 3 children required intensive care admission for complications from their illness. Unvaccinated children were slightly younger (median = 3.7) than vaccinated children (median = 4.7; $P = 0.09$). The percentage of cases who identified as Aboriginal or Torres Strait Islander (4.1%) was similar to that in the same aged Australian population[31] during the study period (5.7%; $p = 0.54$). Of the 74 cases, 44 (59.5%) were vaccinated and the majority had received Varilrix® (90.9%, $n = 40$), 2 cases had received Varivax®, and 2 cases received Priorix-Tetra®. No cases received 2 doses of varicella vaccine. The distribution of cases by year during the study period is shown in Fig. 1. The percentage of cases who were immunocompromised at the time of their varicella hospitalisation was significantly higher in the latter part of the study period (2014–2015: 42.3%) than in the first year (16.7%).

Vaccine effectiveness estimates

Case control study

Twenty controls were matched to each case, giving a total of 1480 controls. There was no significant difference between cases and controls for characteristics including gender ($P = 0.87$), Indigenous status ($P = 0.98$), age at vaccination ($P = 0.66$) and vaccine brand received ($P = 0.62$).

Table 2
Demographic characteristics of varicella cases included study.

Characteristic	*N* (%) *N* = 74
Gender	
Male	38 (51.4)
Female	36 (48.6)
Age at onset (years)	
Median (IQR)	4.5 (3.0–6.4)
Aboriginal or Torres Strait Islander	
No	71 (95.9)
Yes	3 (4.1)
Length of stay (days)	
Median (IQR)	3 (2–5)
Intensive care admission	
Yes	3 (4.1)
No	71 (95.9)
Vaccinated	
Yes	44 (59.5)
No	30 (40.5)
Age at vaccination (years)	
Median (IQR)	1.6 (1.5–1.6)
Time from vaccination to onset (years)	
Median (IQR)	3.0 (2.0–4.8)
Vaccine brand ($n = 44$)	
Varilrix® (monovalent)	40 (90.9)
Varivax® (monovalent)	2 (4.5)
Priorix-Tetra® (MMRV)	2 (4.5)

VE estimations are summarised in Table 3. The estimated VE for one-dose of vaccine against hospitalised varicella was 64.2% (95% CI: 41.7–78.1%). Effectiveness remained similar for the majority of explored scenarios. When cases were restricted to birth cohorts from 2008–2013, the point estimate declined, however the confidence intervals are wide and include the other point estimates. In the exploratory analysis that included children who were vaccinated prior to commencement of the funded NIP program, the VE estimate was no different to that obtained for the main analysis (64.2%, 95% CI: 45.0–76.7%).

Screening method

Estimates obtained using the screening method were similar to those from the case control study (Table 3). Use of the alternate PPV (Table 1) to measure the VE against all cases resulted in a higher estimate of 80.8% (95% CI: 69.3–88.0).

Discussion

This study is the first to report nationally representative VE estimates of single dose varicella vaccine under the NIP in preventing hospitalisation for varicella. Although publicly-funded vaccination has led to high coverage in pre-school aged children for a decade and resulted in a decline in disease,[8,32,33] VE estimates of 64–69% for the prevention of confirmed hospitalised varicella among children aged 19 months to 10 years suggest less than complete protection against severe varicella. A recent study of varicella VE conducted in one Australian state found a higher VE estimate against hospitalised disease (81.9%; 95% CI: 61.8–91.4%), however this study used administrative ICD-coded hospitalisation data with no clinical confirmation of varicella.[34] We obtained similar results using both methodological approaches, however the use of alternative PPV values for the screening method gave a higher VE estimate similar to that obtained in the study by Sheridan et al.[34]

The VE seen in our study is also lower than pooled one-dose VE estimates reported in a meta-analysis of 42 studies from 10 countries including either vaccine against both moderate/severe varicella (98%; 95% CI: 97–99%) and all varicella (81%; 95% CI:

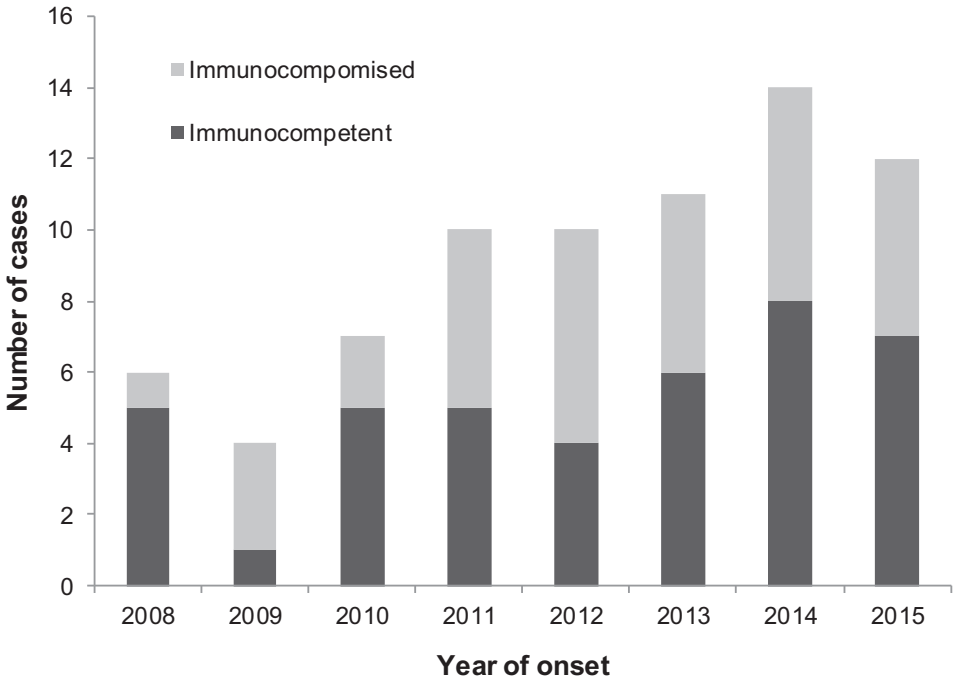

Fig. 1. Number of cases, by year of study.

Table 3
Estimated vaccine effectiveness against hospitalised varicella.

Analysis cohort	Cases (%)[a]	Controls (%)	Case control VE (95% CI)	Screening VE (95% CI)
All cases	*N*=74	*N*=1480		
Unvaccinated	30 (40.5)	301 (20.3)	Reference	Reference
Vaccinated	44 (59.5)	1179 (79.7)	64.2 (41.7–78.1)	64.8 (43.8–77.9)
Immunocompetent cases	*N*=41	*N*=820		
Unvaccinated	17 (41.5)	174 (21.2)	Reference	Reference
Vaccinated	24 (58.5)	646 (78.8)	64.1 (30.9–81.3)	65.6 (35.7–81.5)
Birth cohort 2008–2013	*N*=34	*N*=680		
Unvaccinated	11 (32.3)	136 (20.0)	Reference	Reference
Vaccinated	23 (67.6)	544 (80.0)	51.8 (−4.8–77.8)	55.8 (9.2–78.5)
Aged <7 years at onset of illness	*N*=63	*N*=1260		
Unvaccinated	25 (39.7)	255 (20.2)	Reference	Reference
Vaccinated	38 (60.3)	1005 (79.8)	66.9 (−10.3–90.9)	63.8 (40.0–78.2)
All cases, including those from unfunded period	*N*=132	*N*=2285		
Unvaccinated	82 (62.1)	1199 (52.5)	Reference	–
Vaccinated	50 (37.9)	1441 (63.1)	64.2 (45.0–76.7)	–

[a] PCV for screening method analysis.

78–84%).[35] Several definitions of moderate/severe varicella were used in these studies, including: >500 lesions; complications of varicella; hospitalisation; or a combination of these, resulting in heterogeneity among estimates. Even when comparing estimates derived from studies of hospitalised varicella cases only, this may be complicated by differences in case ascertainment due to variations in admission policies and/or referral patterns. One potential explanation for the lower VE obtained in our study could have been the method of case ascertainment used: the sentinel sites in our study are all specialist paediatric hospitals, with patients admitted from both the local community and via hospital-referral (11% of this study cohort), and thus may include a higher proportion of complex cases. However, of note, exclusion of children who were immunocompromised at the time of hospitalisation for varicella did not result in an increase in the VE estimation.

Our study contributes further data on the effectiveness of Varilrix®. The majority of post-licensure studies of 1-dose varicella vaccine effectiveness have been for Varivax®. Many studies did not specify or include both vaccines brands, although most were conducted in the US, where only Varivax® has been used. A study by Spackova et al.[36] was able to perform a side by side comparison of VE for Varivax® and Varilrix®, with point estimates for 1-dose effectiveness of 86% (95% CI: 56–96%) and 56% (95% CI: 29–72%), respectively. In the meta-analysis by Marin et al.[35] stratification by brand showed a higher 1-dose point estimate of 82% (95% CI: 79–85%) for Varivax® compared to 77% (95% CI: 62–85%) for Varilrix®, although confidence intervals were overlapping. The recent prospective randomised controlled clinical trial of Prymula et al.[37] provides valuable additional evidence to these observational studies; over the 3 year study period 1-dose efficacy of Varilrix® against all-severity varicella (65.4%; 97.5% CI: 57.2–72.1%) was low, increasing to 90.7% (97.5% CI: 85.9–93.9%) against moderate to severe varicella (defined using the scoring system of Vazquez et al.).[38] In this study,[37] 2-dose efficacy of Priorix-Tetra® against all varicella was 94.9% (97.5% CI: 92.4–96.6%), which was similar to the pooled 2-dose VE against all varicella reported in the meta-analysis (92%; 95% CI: 88–95%) and significantly higher than the protection derived from 1 dose.[35] It remains unclear if

these suggestions of brand-specific differences in effectiveness have implications on program impact. In Australia we are now using both registered MMRV vaccine brands (GlaxoSmithKline and Merck and Co, respectively) on the NIP and plan to compare brand specific VE in future analyses.

Despite the success of the Australian 1-dose varicella program in reducing disease among children and adults, including hospitalisations,[8,9] VZV circulation continues to occur, as evident by the continued hospitalisation and notification of cases in children. A limitation of the Australian program was the lack of funded catch-up vaccination for children aged 18 months to 11 years. This has meant that multiple birth cohorts of susceptible school-aged children have contributed to ongoing pre-school and primary school based outbreaks. Under this persistent force of infection, and with sub-optimal effectiveness of a single vaccine dose, unvaccinated and vaccinated Australian children continue to suffer from varicella. Although the majority of breakthrough disease in 1-dose vaccinated children is mild,[39] as demonstrated in our study one third of children hospitalised with varicella were healthy prior to admission and of these, half were vaccinated. Breakthrough disease is also costly to families in lost time from work and education. Another important consideration is that ongoing varicella infections will continue to put people at risk of herpes zoster later in life. With the moderate VE estimates obtained in our study, and noting coverage of a single dose measured at age 2 years has now reached 92.4% (December 2015),[5] any further reduction in disease burden associated with varicella may be difficult to achieve in Australia with the current 1-dose program. This finding is supported by modelling of Australia's varicella zoster virus epidemiology, which showed incremental benefits from adding a second vaccine dose, once high 1-dose uptake was achieved.[40] The modelling study demonstrated that an initial increase in zoster incidence would occur for up to 30 years with either a 1-dose or 2-dose program; however the 2-dose strategy would lead to a more rapid decline and an overall lower incidence of zoster in the long term.

Countries vary in their approach to the use of varicella vaccine. Some have moved from 1-dose to 2-dose varicella vaccination programs.[19–22] Others such as New Zealand and some Canadian jurisdictions also recommend only one dose, and a number of high and middle income countries, including England and Sweden, have not included varicella vaccine in their national schedules at all. While the Australian Immunisation Handbook recommends a second dose of varicella vaccine,[6] this second dose is not NIP-funded and 2-dose coverage (assessed at 5 years of age) is only 4% (B Hull, NCIRS, personal communication). The potential incorporation of a second varicella vaccine dose into Australia's NIP requires consideration of a number of factors, including demonstration of incremental cost effectiveness (which should consider both direct and indirect costs) and vaccine choice.[41] A number of countries preference the use of separate measles-mumps-rubella (MMR) and varicella (V) vaccines, rather than the combination MMRV vaccine for the first measles vaccine administration point, due to an increased risk of febrile seizures in measles-vaccine naive children related to MMRV.[42]

A strength of this study was our ability to obtain detailed clinical information for all cases and conduct a sensitivity analysis excluding children significantly immunocompromised at the time of acquiring varicella (45%) in whom VE could be expected to have been reduced. This study sourced de-identified controls from the national immunisation register, and as such, there is the possibility that a case may have been matched by DOB to his/her self. However, due to the availability of numerous eligible matches (of which 20 were randomly selected) and the large annual birth cohort (~300,000), the possibility of this occurring was considered rare. There is also the potential for misclassification bias due to the inability to definitively exclude cases from register derived controls. We were unable to exclude controls with a prior history of varicella. These are more likely to be unvaccinated and would lower the VE estimate. Of note, analysis restricted to birth cohorts from 2008 onward, a period when less varicella was likely to be circulating, did not result in an increased VE estimate. Another potential source of bias is the use of population controls instead of hospital-based controls. This would particularly be an issue if hospital patients have different characteristics to the wider population, related to the exposure, which in this case is vaccination. Our study did include a subset of immunocompromised patients who potentially have different vaccination recommendations to the general population. Reassuringly, restriction of the analysis to immunocompetent cases did not change the VE estimate. Socioeconomic data were not available for adjustment in this study; however cases and controls were not significantly different for any of the variables that were assessed. VE estimates obtained by the screening method (using coverage at age 24 months) were similar to and provide reassurance of the validity of the case control study results. When higher estimated proportions of the population that were vaccinated were used, based on vaccine coverage at 5 years of age (albeit much higher than the median age of 1.6 years at vaccination of included cases), a higher point estimate for VE was obtained. This was not unexpected as the screening method is known to be very sensitive to changes in PPV in high coverage settings, and this estimate remains compatible with both the meta-analysis and recent Australian study.[34,35] The AIR was used as the source of vaccination data for both cases and controls. As this register only records doses given up to the age of 7 years, there is the possibility that late doses were missed; however such misclassification would have applied to both cases and controls. Reassuringly, restriction of the analysis to those aged <7 years did not change the VE estimate.

Although the Australian 1-dose varicella vaccination program has impacted on the overall burden of disease, we have shown that VE against hospitalisation due to varicella is suboptimal. After a decade of a 1-dose strategy in Australia and particularly in light of the cessation of the single cohort catch-up for 12–13 year olds, these data, and additional evidence obtained via enhanced varicella surveillance and/or outbreak investigations, would assist assessment of potential inclusion of second vaccine dose on the NIP to improve varicella control. Our experience, and the consistently demonstrated lower VE of one compared with two doses of varicella vaccine, suggests that countries wishing to gain maximal reductions in varicella disease should consider either a 1-dose program that achieves high uptake across multiple birth cohorts simultaneously and/or be willing to incorporate a second vaccine dose to minimise breakthrough disease and interrupt virus circulation to achieve herd immunity.

Authors' contributions

HQ cleaned and analysed the data, drafted the manuscript and revised the manuscript; HG cleaned and analysed the data and revised the manuscript; HM, RB, EE, PR, NC and KM designed the study and revised the manuscript; KM designed the study, cleaned the data and revised the manuscript.

HM, NC and KM are members of the Australian Government ATAGI (Australian Technical Advisory Group on Immunisation). HM, RB and NC have conducted research studies sponsored by vaccine manufacturers (including Seqirus, Roche, Sanofi Pasteur, GlaxoSmithKline, Novartis, Baxter and Pfizer) and received travel support to present at scientific meetings. Any funding received has been directed to accounts held by their respective institutions and not personally accepted. PR is a member of the Vaccine Trials Group, which has received funding from vaccine manufacturers, including Sanofi Pasteur, Seqirus, and GlaxoSmithKline.

Conflict of interest

The authors do not have any conflicts of interest.

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