Original Article

Diagnostic testing in influenza and pertussis-related paediatric intensive care unit admissions, Queensland, Australia, 1997-2013

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Abstract

Severe respiratory infections make up a large proportion of Australian paediatric intensive care unit (ICU) admissions each year. Identification of the causative pathogen is important and informs clinical management.

Methods

We investigated the use of polymerase chain reaction (PCR) in the ICU-setting using data collated by the Australian and New Zealand Paediatric Intensive Care (ANZPIC) Registry from five ICUs in Queensland, Australia. We reviewed diagnostic testing among all pertussis and influenza-related paediatric ICU admissions between 01 January 1997 and 31 December 2013.

Results

There were 177 influenza-related and 78 pertussis-related ICU admissions. Overall, 157 (89%) influenza-related admissions had an influenza-specific diagnostic test conducted, of which 129 (82%) had a PCR test requested. Patients that were tested for influenza using non-PCR tests all occurred prior to 2007. An influenza-positive result was recorded for 130 (82%) of the tested influenza-related ICU admissions – 73% of all ICU admitted influenza-related cases. Among pertussis-related admissions, 63 (81%) had a pertussis-specific diagnostic test ordered, of which 60 (95%) were tested using PCR. A pertussis-positive result was recorded for 53 (86%) of those tested, and 68% of all ICU admitted pertussis-related admissions.

Conclusions

PCR has become the preferred diagnostic method to test influenza and pertussis-related ICU admissions, largely replacing other methods. This finding mirrors trends observed across other health care settings, but appears to have occurred earlier among ICU admissions. The move to PCR testing, has allowed more sensitive and rapid diagnosis of severe pertussis and influenza infections among children.

Keywords: pertussis, influenza, intensive care, paediatric, polymerase chain reaction, diagnostic testing

Introduction

Severe respiratory infections among infants and young children make up approximately one-third of all Australian paediatric intensive care unit (ICU) admissions each year.[1, 2] Respiratory infections can be caused by a range of viral and bacterial pathogens, and given that infants and children can manifest a broad array of non-specific symptoms, identifying the aetiology based on clinical presentation alone is difficult.[3-5] Identification of the causative pathogen is important, particularly in severe cases, in order to inform clinical and infection control management.[5] As such, infants and children that are hospitalised or admitted to ICU are likely to be tested for a broad range of respiratory pathogens.[6]

In the last decade, polymerase chain reaction (PCR) has largely replaced traditional diagnostic methods, such as culture and immunofluorescence, for routine testing of respiratory samples.[7, 8] In Australia, influenza and pertussis are notifiable conditions under public health legislation, and all cases that meet the case definitions must be reported to state and territory health departments.[9, 10] Influenza and pertussis are the two most common vaccine preventable notifiable diseases in Australia,[8, 11] and the increasing use of PCR has, in part, been linked to better case recognition and magnification of the number of notifications.[8, 12]

The incidence of paediatric influenza and pertussis-related ICU admissions has increased in recent years.[13, 14] It is unclear whether there has been a true increase in severe disease over this time period, or whether a shift in diagnostic methods (to PCR) has led to improved case detection and therefore more accurate coding of admissions. To date, only two Australian studies have reported diagnostic testing use among pertussis and influenza hospitalisations, however these studies focused on overall laboratory findings and not changes to laboratory methods over time.[3, 15] The aim of this study was to investigate the use of PCR in the ICU-setting by reviewing the diagnostic testing of pertussis and influenza-related paediatric ICU admissions in Queensland, Australia, over a 17-year period.

Methods

We conducted a retrospective cohort study using data collated by the Australian and New Zealand Paediatric Intensive Care (ANZPIC) Registry on ICU admissions between 01 January 1997 and 31 December 2013. Data relating to the admission of paediatric patients aged 0 to 16 years was extracted. The ANZPIC Registry collects paediatric intensive care patient episode information from contributing specialist paediatric ICUs (PICUs) as well as general ICUs (which admit mainly adult and some paediatric patients) across Australia and New Zealand.[2] Ethics approval for this study was obtained from the Children's Health Services Queensland Human Research Ethics Committee.

For this study, only admissions to contributing ICUs located in the state of Queensland were extracted. Data from two hospitals with PICUs located in Brisbane ('PICU A' and 'PICU B'), and three hospitals with general ICUs located in regional areas ('General ICU A', 'General ICU B', and 'General ICU C') were used. The two Brisbane-based PICUs, PICU A and PICU B, contributed data for the full study period (1997-2013), during which time they treated 10,264 and 13,158 all-cause admissions, respectively. The other three ICUs began contributing admission data for 0 to 16 year old patients to the ANZPIC Registry later: General ICU A from 2002 (1,028 all-cause paediatric ICU admissions 2002-2013), General ICU B from 2006 (331 all-cause paediatric ICU admissions 2006-2013), and General ICU C from 2009 (97 all-cause paediatric ICU admissions 2009-2013). Participating ICUs collect data in real-time and a single record is created for each ICU admission.[2]

Admissions are defined using ANZPIC Registry-specific standardised diagnosis codes,[16] and include 'principal diagnosis' (the diagnosis most directly responsible for the ICU admission), 'underlying diagnosis' (the principal underlying diagnosis contributing to the need for ICU

admission), and up to seven 'associated diagnoses'. Associated diagnoses are conditions additional to the principal and underlying reasons that contributed to the ICU admission, and can include other syndromes, diseases, abnormalities, or diagnoses identified on or during ICU admission. For this study, we extracted ANZPIC Registry data for all Queensland paediatric ICU admissions with diagnosis codes of 470 – Pertussis Syndrome, 720 – Pertussis, or 715 – Influenza Virus occurring in any of the diagnosis fields. The line-listed data extract included patient demographic variables and ICU admission details, as well as a hospital identification number. Immunisation history, medications/treatments prescribed during admission, and laboratory data used to support the diagnosis coding are not collected in the ANZPIC Registry.

Using the hospital identification number for each ICU admission, we searched for any respiratory diagnostic tests occurring from 14 days prior to ICU admission to seven days after ICU discharge (based on specimen collection date) in appropriate pathology databases (the Pathology Queensland Laboratory Information System, Auslab, and/or the Mater Pathology Laboratory Information System, Kestral). Where tests were found, we recorded the sample date, sample method (e.g. nasopharyngeal swab or aspirate), diagnostic method (e.g. PCR, serology, culture, antigen detection), and result for each test. Diagnostic method was coded as PCR (≥1 test done, where at least one PCR-based), non-PCR (≥1 test done, none PCR-based), or no tests found. The test results were coded as influenza positive only, pertussis positive only, other respiratory pathogen positive (influenza and pertussis negative), influenza and other respiratory pathogen positive, pertussis and other respiratory pathogen positive, or negative (no respiratory pathogen identified). Co-detection was defined as a respiratory test positive for another respiratory pathogen, in addition to a positive influenza/pertussis result. Where another respiratory pathogen was detected, the organism was recorded.

Descriptive statistics are presented as frequency (percentage) or median (range) as appropriate. Comparisons between groups were calculated using the non-parametric Mann-Whitney U-test. We calculated the proportion of ICU admissions tested using any testing modality, as well as the proportion of admissions with a matching positive diagnostic test result. All analyses were conducted using Stata statistical software v.12 (StataCorp, College Station, TX, USA).

Results

From 1997 to 2013, there were 177 influenza-related paediatric ICU admissions and 78 pertussis-related paediatric ICU admissions in the five participating hospitals (Table 1). Admissions predominantly occurred in Brisbane (PICU A, 52%; n=133 and PICU B, 40%; n=103). Children with influenza-related admissions were older than children with pertussis-related admissions (median age: 2.0 years vs. 51 days, respectively, $p<0.001$), and had a shorter median length of ICU stay (2.6 days vs. 4.3 days, respectively, $p=0.049$). A total of 16 deaths were recorded, 8 (5%) influenza-related admissions and 8 (10%) pertussis-related admissions.

Influenza-related admissions were highest in 2011 (n=26 admissions), and 119 (67%) occurred between 2007 and 2013 (Figure 1). Overall, 157 (89%) influenza-related admissions had an influenza-specific diagnostic test conducted. An influenza positive result was recorded for 130 (83%) of those tested and 73% of all influenza coded admissions (Table 2). Prior to 2007, 28 influenza-related admissions were tested using non-PCR diagnostic tests, which included one or a combination of: immunofluorescence, antigen detection, culture, or serology. From 2008 onwards, all tested influenza-related admissions included a PCR test (10 in combination with antigen detection, serology, or immunofluorescence).

Pertussis-related admissions between 2009 and 2012 accounted for 62% (n=48) of total pertussis-related admissions during the study period (Figure 2). Among pertussis-related admissions, 62 (80%) had a pertussis-specific diagnostic test ordered. A pertussis-positive result was

recorded for 53 (86%) of those tested and for 68.0% of all pertussis coded admissions. Only three pertussis-related ICU admissions, all prior to 2002, were tested using a non-PCR diagnostic method (immunofluorescence) and all three had negative results. Serology, antigen detection, culture, or immunofluorescence were used, in combination with PCR, for 17 of the remaining 59 tested pertussis-related admissions.

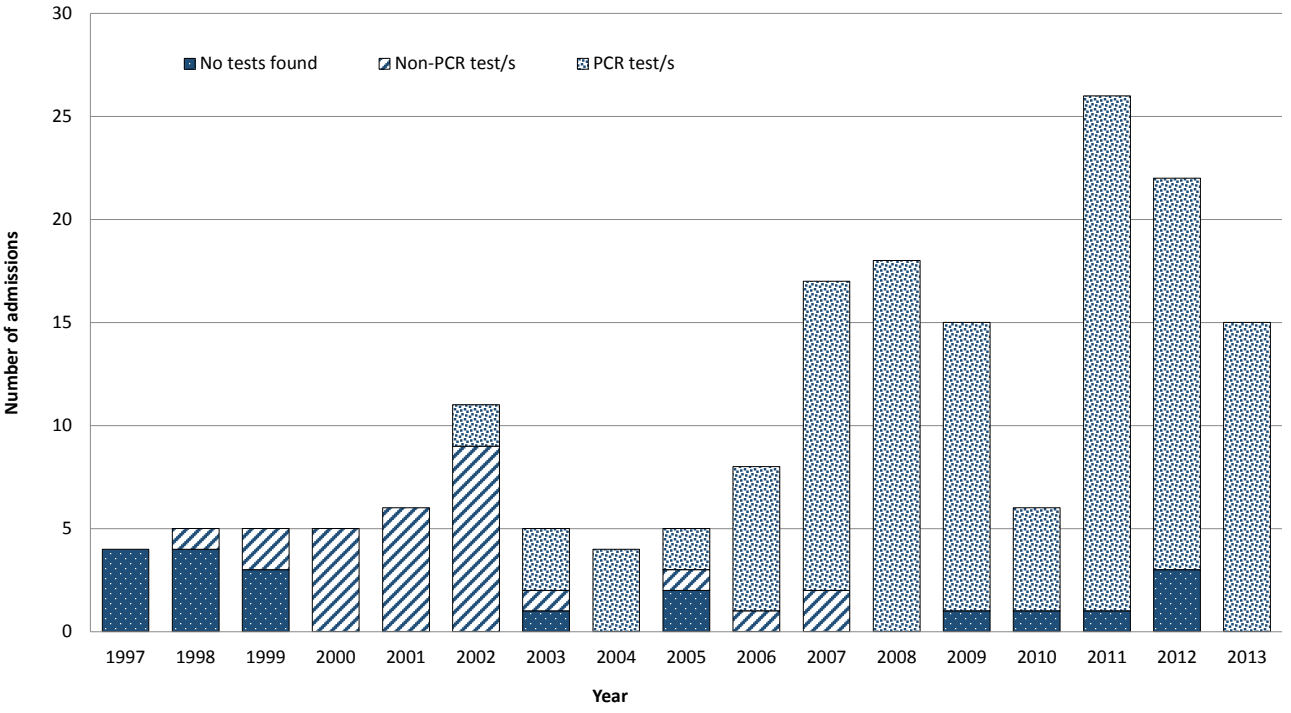
Co-detection of another respiratory pathogen was identified in 14% (n=24) influenza-related admissions and 19% (n=15) pertussis-related admissions (Table 1). Additionally, there were 18 ICU admissions coded as influenza-related, that tested negative for influenza but positive for one or more respiratory pathogens, including: parainfluenza (type 2 n=1, type 3 n=9), rhinovirus (n=5), *Haemophilus influenzae* type

Table 1: Influenza and pertussis admissions, 1997-2013, Queensland Australia

	Influenza	Pertussis
Total admissions	**177**	**78**
Admitting ICU [n (%)]		
PICU A	105 (59%)	28 (36%)
PICU B	63 (36%)	40 (51%)
General ICU A	8 (5%)	2 (3%)
General ICU B	1 (1%)	4 (5%)
General ICU C	0 (0%)	4 (5%)
Sex - Male [n (%)]	97 (55%)	42 (54%)
Age [median (range)]	2.0 years (16 days – 14.6 years)	51 days (16 days – 8.4 years)
Length of stay [median (range)]	2.6 days (0.2 - 57.7)	4.3 days (0.3 - 120.3)
Deaths [n (%)]	8 (5%)	8 (10%)
Tested for coded illness [n (%)]	157 (89%)	62 (80%)
Number of coded pathogen specific tests performed per admission [a] [median (range)]	2 (1 - 10)	3 (1 - 21)
Admissions with relevant positive laboratory test [n (%)]	130 (73%)	53 (68%)
Co-detection of other respiratory pathogen [n (%)]	24 (14%)	15 (19%)
RSV-positive	12 [b]	4
adenovirus-positive	6 [b]	3
rhinovirus-positive	3 [c]	6 [d]
parainfluenza type 3-positive	2	2 [d]
human metapneumovirus-positive	3 [c]	1

a. where one or more diagnostic tests conducted. Cases with no test identified were excluded.
b. one case positive for influenza, RSV, and adenovirus – counted in both rows.
c. two cases positive of influenza, rhinovirus, and human metapneumovirus – counted in both rows.
d. one case positive for pertussis, rhinovirus, and parainfluenza type 3 – counted in both rows.

Figure 1: Influenza admissions by test method and year, 1997-2013, Queensland Australia



B (HiB, n=2), and respiratory syncytial virus (RSV, n=2). Among these 18 admissions, only one HiB-positive admission and both RSV-positive admissions had relevant HiB or RSV-specific ICU diagnosis codes in addition to the influenza ICU diagnosis code. There were no influenza/pertussis co-detections.

Discussion

The vast majority of paediatric ICU admissions for influenza and pertussis in Queensland, Australia, between 1997 and 2013 had at least one pathogen-specific diagnostic test conducted. This aligns with the clinical imperative to identify the aetiology of severe respiratory illness. For both illnesses, PCR largely replaced other methods over time and became the predominant diagnostic test, mirroring what has previously been observed among national influenza and pertussis notifications.[8] Interestingly, the move to PCR testing appears to have occurred earlier among ICU admissions (from approximately 2001-2002 onwards) than among notifications (from approximately 2007 onwards).[8] As PCR testing was still relatively novel in 2001-2002, its use at that time will have been expensive, limited to larger laboratories, and run as one-off diagnostic tests rather than mass routine testing.[17] However the benefits of PCR compared to culture, such as much higher sensitivity (94% vs. ~15%, respectively) and faster results,[18] likely still made it a preferable choice for clinicians treating infants with severe respiratory infections. It was only in 2005 that public funding commenced, under the Australian Government-funded Medicare Benefits Schedule, for laboratories to test clinical specimens using PCR.[19] Additionally, during the 2009 H1N1 influenza pandemic, public funding was allocated to laboratories to purchase equipment (notably PCR suites) to enhance capacity.[20] While funding facilitated the expansion of PCR availability, the development and use of large-scale, multiplex PCR assays has allowed testing and identification of a broader range of respiratory pathogens, including the detection of co-infections.[21-25]

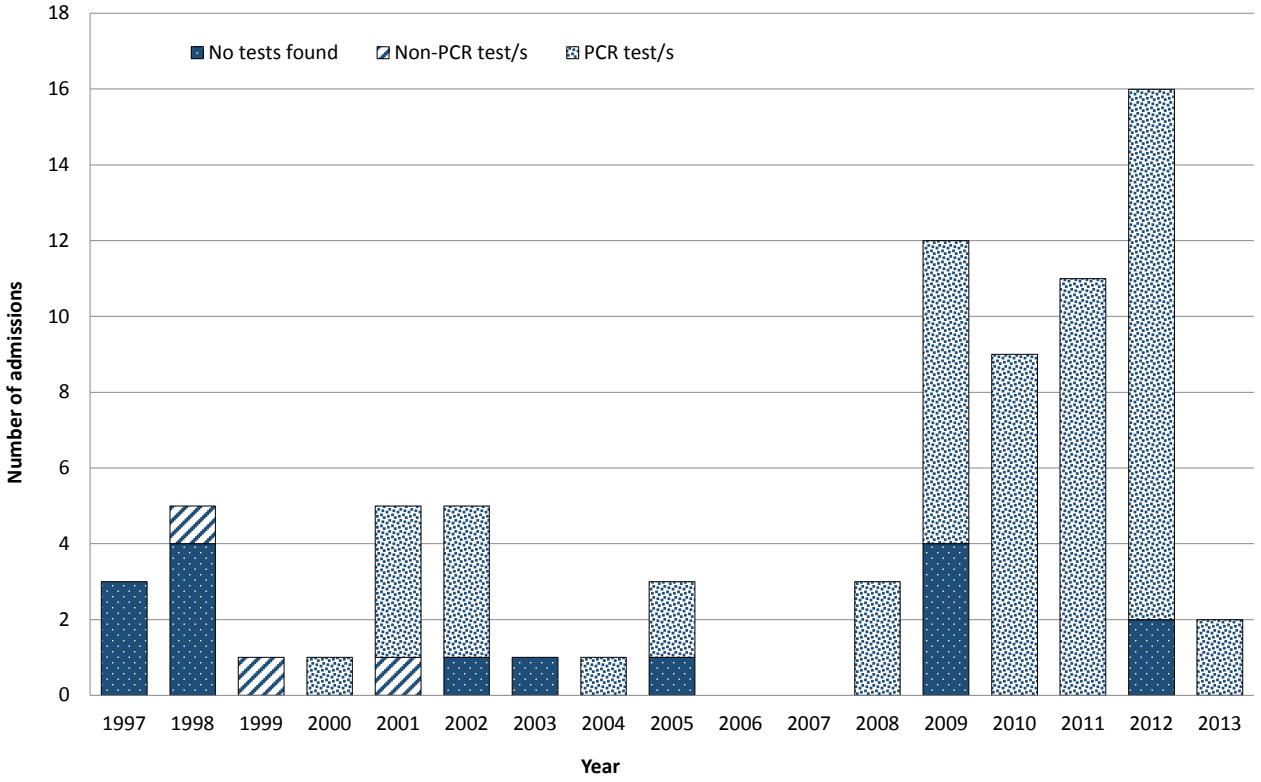
The ANZPIC Registry is a well-established dataset, and has been collating data from participating ICUs since 1997. A particular strength of the Registry is that it captures data from the two large dedicated PICUs in Queensland, as well as from three smaller general ICUs in more regional areas, therefore capturing the vast majority of paediatric ICU admissions across the state

Table 2: Influenza and pertussis paediatric ICU admissions by test type and result, 1997-2013, Queensland Australia

Year	Influenza						Pertussis					
	Total admissions n	Non-PCR test/s n (% positive)[a]	PCR test/s n (% positive)[a]	Not tested n	Tested % [b]	Test positive % [a]	Total admissions n	Non-PCR test/s n (% positive)[a]	PCR test/s n (% positive)[a]	Not tested n	Tested % [b]	Test positive % [a]
1997	4	0 (-)	0 (-)	4	0	0	3	0 (-)	0 (-)	3	0	0
1998	5	1 (100)	0 (-)	4	20	20	5	1 (0)	0 (-)	4	20	0
1999	5	2 (50)	0 (-)	3	40	20	1	1 (0)	0 (-)	0	100	0
2000	5	5 (100)	0 (-)	0	100	100	1	0 (-)	1 (100)	0	100	100
2001	6	6 (100)	0 (-)	0	100	100	5	1 (0)	4 (75)	0	100	60
2002	11	9 (100)	2 (100)	0	100	100	5	0 (-)	4 (100)	1	80	80
2003	5	1 (0)	3 (100)	1	80	60	1	0 (-)	0 (-)	1	100	0
2004	4	0 (-)	4 (100)	0	100	100	1	0 (-)	1 (100)	0	100	100
2005	5	1 (100)	2 (100)	2	60	60	3	0 (-)	2 (100)	1	67	67
2006	8	1 (100)	7 (86)	0	100	88	0	-	-	-	-	-
2007	17	2 (100)	15 (100)	0	100	100	0	-	-	-	-	-
2008	18	0 (-)	18 (83)	0	100	83	3	0 (-)	3 (100)	0	100	100
2009	15	0 (-)	14 (79)	1	93	73	12	0 (-)	8 (88)	4	67	58
2010	6	0 (-)	5 (80)	1	83	67	9	0 (-)	9 (100)	0	100	100
2011	26	0 (-)	25 (72)	1	96	70	11	0 (-)	11 (89)	0	100	89
2012	22	0 (-)	19 (84)	3	86	73	16	0 (-)	14 (88)	2	88	75
2013	15	0 (-)	15 (53)	0	100	53	2	0 (-)	2 (100)	0	100	100
Total	177	28 (93)	129 (81)	20	89	73	78	3 (0.0)	59 (90)	16	80	68

a. percentage of admissions positive for specific pathogen
b. percentage of admissions tested for specific pathogen using any testing modality

Figure 2: Pertussis admissions by test method and year, 1997-2013, Queensland Australia



and allowing generalisability of the findings. Additionally, by keeping data definitions largely consistent over a 17-year period, it provides the opportunity to analyse trends over a long time frame. A limitation of the ANZPIC Registry is that laboratory results are not captured, and the diagnosis codes have not previously been validated. We found that for approximately 70% of influenza and pertussis-related ICU admissions there was a corresponding relevant positive influenza or pertussis laboratory test result. When limited to only those admissions that had a diagnostic test conducted (89% of influenza-related admissions, 80% of pertussis-related admissions), approximately 85% had a matching positive result. We were unable to locate any previous studies, specifically validating coding for ICU admissions, with which to compare our results. Our findings however, were consistent with a previous study which validated the ICD-10 coding of influenza and pertussis hospitalisations in Western Australia.[15]

Our results likely represent minimum values as we were reliant on the accuracy and completeness of the databases that we used. We included all ICU admissions coded as influenza and pertussis, however any admissions that were due to, but not coded as, 'influenza' or 'pertussis' would have been missed. Similarly, as we did not include a medical chart review, we will have included any admissions incorrectly coded as influenza or pertussis-related. For example, we identified 18 influenza-coded ICU admissions that were negative for influenza, but positive for other respiratory pathogens. While these ICU admissions may have been diagnosed as influenza-related based on clinical symptoms, it is possible that there was some misclassification with the ANZPIC Registry coding, particularly influenza coded admissions where parainfluenza or *Haemophilus influenzae* type B were laboratory diagnosed. Additionally, although we conducted an extensive search of the pathology datasets, any diagnostic tests not contained within the database, for example, tests conducted by a private pathology provider or outside of our search criteria (between 14 days before ICU admission through to 7 days after ICU discharge), will have been missed. However, it is reassuring that the majority of ICU admissions had at least one diagnostic test identified.

The move to PCR testing in the ICU setting, allowing more sensitive and rapid diagnosis of respiratory pathogens compared to earlier diagnostic methods, may have improved clinical management of severe paediatric pertussis and influenza infections and led to a reduction in overall health care costs. Compared to bacterial pathogens, viruses are more commonly responsible for acute respiratory infections in children.[7, 26] Therefore rapid detection of a bacterial pathogen may aid a clinician's decision to prescribe and/or continue appropriate antibiotics, thus likely improving clinical management.[26] Although detection of a viral pathogen in a general practice setting would allow a GP to withhold antibiotic treatment, in the ICU setting, viral detection may not alter antibiotic use due to concerns of secondary bacterial infection.[7, 26] However additional (often unnecessary) laboratory tests or diagnostic imaging, pursued where the illness aetiology is not yet established, may be avoided due to the fast turn-around of PCR results, contributing to an overall reduction in health care costs.[7, 27] Furthermore, rapid diagnosis in a hospital/ICU setting would allow appropriate infection control measures to be enforced, limiting the likelihood of nosocomial infections.[7]

In conclusion, PCR has become the preferred diagnostic method in influenza and pertussis-related ICU admissions. This finding mirrors the trends observed more broadly across other health care settings.

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Conflicts of interest

SBL reports not having shares, paid employment, or consultancies with any influenza vaccine manufacturer; he has been an investigator on vaccine and epidemiological studies sponsored by bioCSL, Merck, GSK, Novartis, and Sanofi; his institute has received honoraria from Merck for talks he has given on rotavirus epidemiology and vaccines. Authors MCK, SS, RSW, JAM, and MGC declare that they have no competing interests.

Author contributions

All authors (MCK, SS, RSW, JAM, MGC and SBL) contributed to the study design. MCK and SS obtained the data. MCK conducted the data analysis and drafted the manuscript. All authors (MCK, SS, RSW, JAM, MGC and SBL) contributed to the interpretation of the results and revision of the manuscript. All authors (MCK, SS, RSW, JAM, MGC and SBL) read and approved the final manuscript.

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