Original research

Assessing the impact of the 13 valent pneumococcal vaccine on childhood empyema in Australia

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ABSTRACT

Background Empyema is a serious complication of pneumonia frequently caused by *Streptococcus pneumoniae* (SP). We assessed the impact of the 13-valent pneumococcal conjugate vaccine (13vPCV) on childhood pneumonia and empyema after inclusion in the Australian National Immunisation Program.

Methods For bacterial pneumonia and empyema hospitalisations, we ascertained incidence rates (IRs) using the National Hospital Morbidity Database International Statistical Classification of Disease discharge codes and relevant population denominators, and calculated incidence rate ratios (IRR) comparing the 13vPCV period (June 2012–May 2017) with the 7vPCV period (June 2007–May 2011). Blood and pleural fluid (PF) cultures and PF PCR of 401 children with empyema from 11 Australian hospitals during the 13vPCV period were compared with our previous study in the 7vPCV period.

Findings Across 7vPCV and 13vPCV periods, IRs per million children (95% CIs) were 1605 (1588 to 1621) and 1272 (1259 to 1285) for bacterial pneumonia, and 14.23 (12.67 to 15.79) and 17.89 (16.37 to 19.42) for empyema hospitalisations. IRRs were 0.79 (0.78 to 0.80) for bacterial pneumonia and 1.25 (1.09 to 1.44) for empyema. Of 161 empyema cases with SP serotypes, 147 (91.3%) were vaccine types. ST3 accounted for 76.4% of identified serotypes in the 13vPCV period, more than double than the 7vPCV period (p<0.001); ST19A decreased from 36.4% to 12.4%. No cases of ST1 empyema were identified in the 13vPCV period versus 14.5% in the 7vPCV period.

Interpretation 13vPCV resulted in a significant reduction in all-cause hospitalisations for bacterial pneumonia but empyema hospitalisations significantly increased, with emergence of pneumococcal ST3 as the dominant serotype in empyema.

Trial registration number Australian and New Zealand Clinical Trial Registry ACTRN 12614000354684.

Key messages

What is the key question?

- What was impact following the introduction of the 13-valent pneumococcal conjugate vaccine (13vPCV) on childhood pneumonia and empyema in Australia?

What is the bottom line?

- 13vPCV resulted in a decrease in childhood pneumonia hospitalisations with a contemporaneous increase in admissions for empyema. Although there was a substantial reduction in serotype (ST) 1, ST 3 is now the predominant causative organism of childhood empyema with the suggestion of emergence of non-vaccine STs.

Why read on?

- Childhood bacterial pneumonia and empyema are potentially preventive diseases through vaccination. Our study highlights the potential negative impact of 13vPCV on childhood empyema by potentially causing ST replacement disease, emphasising the need for enhanced molecular surveillance following the introduction of new vaccines onto national programmes.

INTRODUCTION

Empyema, the collection of pus in the pleural cavity, is a complication which affects approximately 1% of children hospitalised with pneumonia.[1–3] The most common bacterial cause of empyema is *Streptococcus pneumoniae* (SP); other bacterial causes include methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pyogenes* and *Haemophilus influenza*.[1]

In January 2005, the 7-valent pneumococcal conjugate vaccine (7vPCV) was introduced onto the National Immunisation Program (NIP) for all Australian children. 7vPCV provides coverage against invasive pneumococcal disease (IPD) caused by serotypes (ST) 4, 6B, 9V, 14, 18C, 19F and 23F, which were responsible for up to 70% of paediatric IPD at the time of introduction.[4] We previously reported a decline in pneumonia hospitalisations in children after the 7vPCV was introduced in Australia, with a contemporaneous increase in empyema, especially in children aged 1–4 years old.[2]

Increases in empyema following the introduction of 7vPCV were also reported in other countries.[5–7] The reason for the increase is uncertain, but it has been speculated that immunisation with 7vPCV resulted in the selective carriage in the nasopharynx of non-vaccine pneumococcal ST with a predilection for invasion of the pleural space, particularly ST1, 3 and 19A.[1 5–7]

In July 2011, the 13-valent pneumococcal conjugate vaccine (13vPCV) replaced the 7vPCV on the Australian NIP, extending coverage to six additional ST 1, 3, 5, 6A, 7F and 19A. Doses of 13vPCV were scheduled at 2, 4 and 6 months, with a booster dose at age 12–18 months only recommended for medically high risk and Indigenous children. At the time of 13vPCV introduction, a time-limited booster dose of 13vPCV was available for children aged 12–35 months of age who had already completed the primary course of 7vPCV.

Most studies of the impact of 13vPCV in Europe and North America have reported declines in IPD, including bacterial pneumonia and empyema.[8–11] International evidence also highlights reductions in the prevalence of IPD caused by 13vPCV ST.[8 9 12–15]

We aimed to investigate the impact of the introduction of 13vPCV on childhood empyema in Australia by (1) examining the rates of pneumonia and empyema hospitalisations in children using national hospitalisation data, and (2) by prospectively identifying the bacterial causes of empyema, in particular strains of SP, through targeted enhanced molecular surveillance.

METHODS

Empyema

We analysed hospitalisations for childhood empyema using data from a whole-of-population national administrative dataset (National Hospital Morbidity Database) compiled by the Australian Institute of Health and Welfare (https://www.aihw.gov.au/). This included data on hospitalisations for all Australian children aged 0–≤19 years from 1 January 2007 to 30 June 2017. The data cubes available were grouped <1 years, 1–4 years, 5–9 years, 10–14 years and 15–19 years. International Statistical Classification of Disease and Related Health Problems (ICD-10-AM) diagnosis codes were used to identify all hospitalisations with principal diagnosis codes associated with empyema (J86.0 and J86.9). Age-specific mid-year population estimates were sourced from Australian Bureau of Statistics 2016 census estimates.[16 17] Incidence rates were calculated for the 13vPCV period (1 June 2012–31 May 2017) and compared with those for the 7vPCV period (1 June 2007–31 May 2011) as per our previous evaluation.[2]

From February 2015 to September 2018, we prospectively identified and enrolled children (0–17 years old) hospitalised to 1 of 11 sentinel paediatric hospitals across Australia with empyema. This was defined as having one or more of the following clinical symptoms: cough, fever or increased work of breathing; in addition to endpoint consolidation on chest X-ray as judged by the treating physician; presumed infective aetiology requiring antibiotic treatment (either planned or commenced) and presence of pus on microscopy on drained pleural fluid or a culture positive pleural fluid result. Children were excluded if their primary reason for admission was not respiratory illness. Consent was obtained from the primary caregiver. We have previously undertaken a similar prospective study using the same methodology in the 7vPCV period era where we recruited children with empyema over a 2-year period (2007–2009).[1]

Demographic and clinical data were obtained from review of the medical record including age, sex, Aboriginal and/or Torres Strait Islander status, area of residence and risk factors for IPD. The vaccination status of enrolled patients was obtained by either review of the child's hand-held records or the Australian Immunisation Registry. Children were considered either fully, partially or not vaccinated with pneumococcal conjugate vaccine at the time of hospitalisation according to the NIP vaccination schedule.

The microbiological methods have been described previously.[1] Briefly, we collected blood and pleural fluid specimens from each enrolled child. Blood and pleural fluid specimens were cultured at local hospitals by standard local laboratory methods. A separate aliquot (ideally 10 mLs) of pleural fluid was stored at −20°C. Specimens were then transported in batches on dry ice by a commercial transport company to the Centre for Infectious Disease and Microbiology Laboratory, Westmead Hospital, New South Wales, for processing.

DNA was extracted from pleural fluid specimens using NucliSENS easyMAG Total Nucleic Acid Extractor (bioMérieux Australia Pty, Sydney, New South Wales, Australia). DNA specimens were tested with real-time quantitative PCR using Rotor-Gene 6000 real time DNA amplification system (Qiagen, Australia) targeting autolysin gene (*lytA*) for pneumococcal DNA detection as described by McAvine *et al*.[18] Standard curves and minimal limit of detection were generated by plotting the cycle threshold values of the qPCR performed on a dilution series of synthetically synthesises of *lytA* (*lytA* gBlock, IDT Technologies, Australia) in triplicate. All assays with each clinical sample were performed in duplicate. A specimen was considered positive if one of the two duplicates gave a positive result within the <40-cycle cut-off.

All samples in which pneumococcus was detected by PCR were further tested to determine the specific pneumococcal ST. Sequetyping PCR was used to amplify and sequence *cps B* capsular gene.[19] Sequencing results were confirmed with ST-specific PCR[20 21] based on ST shown in sequencing.

Pleural fluid samples were also tested for MSSA, MRSA and *H. influenzae* by PCR using the BD MAX StaphSR assay (BD Diagnostics, Québec, Canada) which targets SA (SCC*mec*) and MRSA (*mecA* and *mecC*)-specific genome.[22] *H. influenzae* was detected using conventional PCR methods with primers: Hinf OmP 6F, 5′-AAT GGT GCT GCT CAA ACT TT-3′; and Hinf Omp 6R, 5′-TCT AAG ATT TGA ACG TAT TCA CC-3′ as previously published.[1]

Annual incidence rates (IR) were calculated for each of the age groups (<1, 1–4, 5–9, 10–14 and 15–19 years old) by dividing the year-specific total number of hospitalisations (bacterial pneumonia and empyema) in that specific age group by the total mid-year age-specific population. We calculated an expected number of hospitalisations in the 13vPCV period by applying the estimated rate in the 7vPCV period (1 June 2007–31 May 2011) to the mid-year population in the 13vPCV period (1 June 2012–31 May 2017). Poisson estimation was used to estimate incident rate ratio (IRR) and corresponding 95% CIs in the 13vPCV period compared with the 7vPCV period. We described the frequency of pathogen and ST and compared this to the frequency previously described by us for the 7vPCV era using a χ^2 test.[1]

Pneumonia

We used the same methods described above to analyse hospitalisations for childhood pneumonia. ICD-10-AM diagnosis codes were used to identify all hospitalisations with principal diagnosis codes associated with bacterial pneumonia (J13–J15.9, J17.0, J18.0, J18.0, J18.1, J18.8 and J18.9). As describe above, incidence rates were calculated for the 13vPCV period

Table 1 Paediatric bacterial pneumonia and empyema coded hospitalisation in Australia in the 7-valent pneumococcal conjugate vaccine and 13-valent pneumococcal conjugate vaccine periods

Age group (years), by disease category	June 2007–May 2011 hospitalisation (no.)	Incidence/1 000 000 children per year (95% CI)	June 2012–May 2017 hospitalisations (no.)		Incidence/1 000 000 children per year (95% CI)	Incidence rate ratio (95% CI)
			Expected	Observed		
Bacterial pneumonia						
0–19	36 087	1605 (1588 to 1621)	46 925	37 587	1272 (1259 to 1285)	0.79 (0.78 to 0.80)
<1	3622	3128 (3025 to 3229)	4801	3091	1998 (1927 to 2068)	0.64 (0.60 to 0.67)
1–4	17 595	3968 (3909 to 4026)	24 029	17 641	2870 (2828 to 2913)	0.72 (0.70 to 0.74)
5–9	7780	1437 (1406 to 1470)	10 500	9111	1218 (1193 to 1243)	0.84 (0.82 to 0.87)
10–14	3493	624 (604 to 645)	4370	3773	537 (519 to 554)	0.85 (0.82 to 0.9)
15–19	3597	611 (591 to 631)	4484	3971	540 (523 to 557)	0.88 (0.84 to 0.92)
Empyema						
0–19	320	14.23 (12.67 to 15.79)	409	529	17.89 (16.37 to 19.42)	1.25 (1.09 to 1.44)
<1	49	42.31 (30.46 to 54.15)	64	50	32.31 (23.35 to 41.27)	0.73 (0.51 to 1.13)
1–4	157	35.40 (29.86 to 40.94)	212	255	41.49 (36.39 to 46.58)	1.17 (0.96 to 1.42)
5–9	36	6.65 (4.47 to 8.82)	51	96	12.83 (10.27 to 15.40)	1.92 (1.31 to 2.83)
10–14	27	4.82 (3.00 to 6.64)	35	55	7.82 (5.75 to 9.89)	1.62 (1.02 to 2.56)
15–19	51	8.86 (6.28 to 11.04)	66	73	9.92 (7.65 to 12.20)	1.14 (0.80 to 1.63)

(1 June 2012–31 May 2017) and compared with those for the 7vPCV period (1 June 2007–31 May 2011) as per our previous evaluation.[2]

RESULTS

National hospitalisations

The mean annual incidence rates/1 000 000 children per year (95% CI) in the 7vPCV and 13vPCV periods were 1605 (1588 to 1621) and 1272 (1259 to 1285) for hospitalisations coded as bacterial pneumonia, and 14.23 (12.67 to 15.79) and 17.89 (16.37 to 19.42) for hospitalisations coded as empyema, respectively (table 1).

The mean annual IR of hospitalisations coded as bacterial pneumonia reduced by 21% (IRR 0.79, 95% CI 0.78 to 0.80) and those coded as empyema increased by 25% (IRR 1.25, 95% CI 1.09 to 1.44) in the 13vPCV in comparison to the 7vPCV period (table 1 and figure 1). The age-specific number of hospitalisations and incidence rates with rate ratios are presented in table 1. There was a decline in the observed, compared with expected, number of admissions with bacterial pneumonia-coded hospitalisations in the 13vPCV period across all age groups, with the greatest decline in children <5 years old (table 1). However, the observed, compared with expected, number of empyema coded hospitalisations increased in the 13vPCV period in all age-groups except in children <1 year old (table 1).

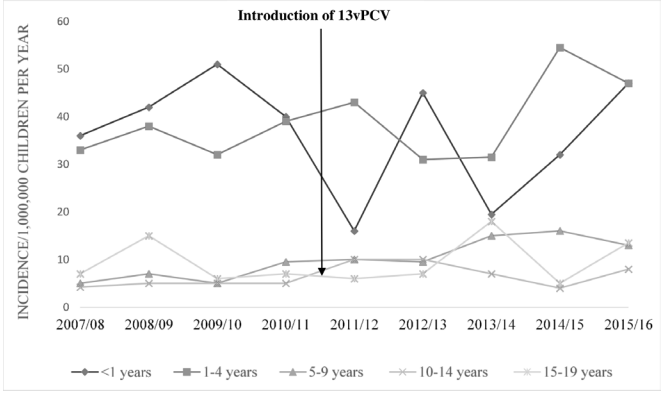

Figure 1 Year-specific and age-specific incidence rates of paediatric empyema hospitalisation in the 7-valent pneumococcal conjugate vaccine (2007–2011) and 13-valent pneumococcal conjugate vaccine (13vPCV; 2012–2016) periods in Australia.

Targeted enhanced surveillance of empyema

A total of 401 children with empyema were enrolled; of these, 208 (52%) were male and the median age was 4.0 (range 0.3–17.3) years (table 2).

Of the 401 with empyema, 300 (75%) had both pleural fluid and blood cultured, 91 (23%) only had pleural fluid cultured, 7 (1.7%) only had blood cultured and 3 (0.7%) participants had neither cultured. Of 307 blood cultures, 35 (11%) were positive for one or more bacterial pathogens; of 391 pleural fluid cultures, 118 (30%) were positive (table 3).

SP was the most common causative organism identified in both blood and pleural fluid. SP was identified in the pleural fluid in 55% by PCR and in 10% by culture and was detected in 5% by blood culture. Other organisms detected included *S. pyogenes*, MSSA, and MRSA (table 3).

Of the 207 children with SP-confirmed empyema, 191 (92%) were fully vaccinated against pneumococcus (mean age 4.0 years; range 0.9–12.8 years), 10 (4.8%) were partially vaccinated (mean age 3.3 years; range 0.8–6.1 years), and 6 (2.9%) were unvaccinated (mean age 9.0 years; range 4.7–15.7 years; figure 2).

Of 207 SP PCR positive samples, ST were identified in 161 (78%) (table 4).

Forty-six (22%) samples were not able to be typed. 13vPCV ST3 accounted for 76% of all identified ST in the 13vPCV period, compared with 33% in the 7vPCV period ($p<0.001$). ST19A accounted for 12% of identified ST, compared with 36% in the 7vPCV era. No cases of ST1 were identified, compared with 15% in the 7vPCV period. A small number of non-13vPCV ST were identified which were not identified in the 7vPCV era (table 4).

Table 2 Characteristics of children with empyema in Australia in the 7-valent pneumococcal conjugate vaccine (7vPCV; 2007–2009) and 13-valent pneumococcal conjugate vaccine (13vPCV) (2015–2018) enhanced surveillance periods

	Participants	
	April 2007–April 2009 (7vPCV period)	February 2015–September 2018 (13vPCV period)
Number	172	401
Age (years; median, range)	3.9 (0.4–15.5)	4.0 (0.3–17.3)
Sex		
Male	93 (54.1)	208 (51.9)
Indigenous status		
Indigenous	8 (4.7)	31 (7.7)
Non Indigenous	160 (93)	366 (91.3)
Not recorded	4 (2.3)	4 (1)
State/territory		
Queensland	59 (34.3)	50 (12.5)
New South Wales	52 (30.2)	127 (31.7)
Victoria	37 (21.5)	132 (32.9)
Western Australia	16 (9.3)	33 (8.2)
South Australia	4 (2.3)	39 (9.7)
Tasmania	2 (1.2)	5 (1.2)
Australian Capital Territory	2 (1.2)	9 (2.2)
Northern Territory	0	6 (1.5)
Chronic respiratory diseases	7	14
Congenital diseases	3	17
Potentially immuno-compromised	6	12
Cardiac disease	1	1

*Values are no. (% of total cases) unless otherwise indicated.

DISCUSSION

After the introduction of 13vPCV in Australia, there was a 25% increase in hospitalisations in children coded as empyema and a 21% decrease in hospitalisations coded as bacterial pneumonia. Our incidence data for childhood empyema hospitalisations are similar to that reported in other countries.[10 23 24] Contemporaneous data from our enhanced surveillance study at sentinel hospitals indicate that pneumococcus remains the most common cause of empyema in Australian children in the 13vPCV period, followed by *Streptococcus pyogenes*, MSSA and MRSA. The 13vPCV ST ST3 now accounts for 76% of pneumococcal empyema in children, compared with 33% in the 7vPCV period. Despite a reduction in the prevalence of ST19A, it remains the second most common identified ST. The 13vPCV ST ST1 appears to have been eliminated as an important cause of empyema among Australian children. Only 9% of pneumococcal ST identified were non-13vPCV ST.

The observed reduction in incidence of bacterial pneumonia coded hospitalisations is consistent with other data from Australia. Jayasinghe *et al* previously reported declines in the rates of overall IPD in the 13vPCV period in Australia, which were greatest in children aged less than 2 years old.[25] Our study contrasts with data reported from some other countries; for example, a decrease in both pneumococcal pneumonia and empyema was observed after the introduction of the 13vPCV in the USA.[8 10] In France, the frequency of pneumococcal pleural effusion and empyema declined from 79% to 36%.[11] Similarly, Spain[9] and Scotland[26] also observed declines in empyema rates; Sweden reported a significant decline in pneumonia hospitalisations of 19%[23] and Argentina reported a 51% decrease in community acquired pneumonia, 39% decrease in empyema and 68% decrease in pneumococcal empyema after the 13vPCV introduction.[24]

We acknowledge that a potential limitation of our empyema data is relatively small numbers which may be subject to natural variations in discrete clusters of ST-specific disease.

In Europe and the USA, a range of changes in specific pneumococcal ST causing pneumonia and empyema have been reported following the introduction of 13vPCV. Greece[15] and Germany[13] have reported a predominance of empyema caused by ST3. Sweden reported a decline in ST6A and ST19A but no change in ST3.[12] Shortly after the introduction of the 13vPCV in Spain, the most common ST causing pneumococcal pneumonia and empyema was ST1 accounting for 42% of cases.[9] A Portuguese study[14] also reported a predominance of ST1, in addition to ST3 and 19A in empyema post 13vPCV, suggesting reduced vaccine effectiveness. In the USA, early reports using a 4+0 schedule suggested a fall in invasive pneumococcal infection caused by ST3 and 19A;[27] however, more recent studies suggest that they were reportedly still responsible for half of pneumococcal pneumonia and empyema cases post 13vPCV.[8] It is worth noting that the limitations of making these international comparisons are the different vaccination schedules as well the time period of analysis following introduction of 13vPCV.

There are several plausible explanations for the observed increase in empyema hospitalisations in our study. While changes in coding practices could account for the increase, targeted molecular surveillance suggests that the rise has been driven by the increased prevalence of ST ST3 which has previously been reported to have a predilection for infection of the pleural space and causes complicated pneumonia worldwide.[13 14] Although included in 13vPCV, there have been reports of suboptimal protection[13] and vaccine failures.[28] We note previous reports of the apparent suboptimal vaccine protection of 13vPCV against ST ST3[14 29] which has been shown to produce and release more capsular polysaccharide than other 13vPCV pneumococcal ST. The capsular polysaccharide is thought to interfere with antibody-mediated killing, reducing the protective efficacy of pre-existing anticapsular antibody,[30] suggesting that higher antibody titres are required for protection than for other strains.[31] This may be particularly relevant in empyema fluid where the bacterial load and thus the amount of capsular polysaccharide is likely to be high.

Furthermore, Zimmerman *et al* reported that children vaccinated with an un-boosted '3+0' schedule at 2, 4 and 6 months of age were found to have waning protective pneumococcal antibody concentrations at 13 months of age.[29] We speculate that waning from the unboosted 3+0 NIP schedule in place in Australia during the period of our study may have contributed to the high prevalence of 13vPCV pneumococcal ST causing empyema cases in our study. The Australian NIP has since moved to a boosted '2+1' (2, 4 and 12 months) schedule in response to persisting rates of 13vPCV ST IPD.[32] However, it is possible that this will have minimal impact on ST3, as demonstrated in countries that have used a 2+1 schedule since inception.[12–15] It is unlikely that the increase in our study is due to lack of vaccination coverage, given only 2.9% of cases in the molecular surveillance arm of the study were unvaccinated.

Our study has several limitations, including the inherent limitation of hospital discharge codes for ascertaining disease

Table 3 Bacteria isolated by culture of blood and pleural fluid samples and by PCR of pleural fluid samples from children with empyema, Australia, in the 7-valent pneumococcal conjugate vaccine (7vPCV) period (2007–2009) and 13-valent pneumococcal conjugate vaccine (13vPCV) period (2015–2018)

	April 2007–April 2009 (7vPCV period)			February 2015–Sept 2018 (13vPCV period)		
	Blood	Pleural Fluid		Blood	Pleural Fluid	
	Culture	Culture	PCR	Culture	Culture	PCR
Organism	(Total number=152) %, (n=)	(Total number=160) %, (n=)	(Total number=145) %, (n=)	(Total number=307) %, (n=)	(Total number=391) %, (n=)	(Total number=337) %, (n=)
Streptococcus pneumoniae	12.5 (19)	7.5 (12)	51 (74)	4.6 (14)	9.7 (38)	54.9 (207)
Streptococcus pyogenes	2.0 (3)	8.8 (14)	–	2.9 (9)	9.5 (37)	–
Streptococcus milleri	–	2.5 (4)	–	–	1.3 (5)	–
Methicillin susceptible *Staphylococcus aureus*	0.7 (1)	6.8 (11)	4.1 (6)	1 (3)	4.1 (16)	6.6 (25)
Methicillin-resistant *Staphylococcus aureus*	0.7 (1)	3.8 (6)	4.8 (7)	0.7 (2)	2.8 (11)	0.3 (1)
Coagulase negative staphylococci	2.6 (4)	1.3 (2)	–	0.7 (2)	1.3 (5)	–
Haemophilus influenzae	0.7 (1)	–	2.8 (4)	0.3 (1)	0.8 (3)	1.8 (7)
Mycobacterium tuberculosis	–	0.6 (1)	–	–	–	–
Pseudomonas aeruginosa	–	0.6 (1)	–	–	–	–
Mycoplasma pneumoniae	–	–	0.7 (1)	–	–	–
Chlamydia pneumoniae	–	–	0.7 (1)	–	–	–
Viridans streptococci	–	–	–	–	0.8 (3)	–
Escherichia Coli	–	–	–	–	0.5 (2)	–
Others*	2.6 (4)	2.5 (4)	–	1.3 (4)	1 (4)	–

7vPCV period.
Blood cultures: one isolate each of *Streptococcus sanguinis*; *Staphylococcus hominis* (from a specimen in which *S. aureus* was also isolated); *Neisseria meningitidis*; and *Actinomyces naeslundii*.
Pleural fluid: one isolate each of *Streptococcus oralis*; *Staphylococcus cohni*; *Eikenella corrodens*; and *Bacteroides fragilis* (the last two from the same specimen, from which *S. milleri* was also isolated). One pleural fluid specimen was culture positive for both MRSA and MSSA.
13vPCV period.
Blood cultures: one isolate each of Gram-positive Bacilli; *Bacillus endoradicus*; Gram-positive staphylococci; and *Micrococcus luteus*.
Pleural fluid: one isolate each of *Brevundimonas diminuta*; *Kocuria kristinae*; *A. odontolyticus* and *Fusobacterium necrophorum*. Both MSSA and MRSA were cultured from one pleural fluid specimen; both *Streptococcus pyogenes* and *H. influenzae* in one specimen; both *S. pneumonia* and *Esherichia coli* in one pleural fluid sample; both *E. coli* and *S. milleri* in one pleural fluid sample and; one pleural fluid sample had MSSA, *A. odontolyticus* and *V. streptococci* isolated.
MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

rates. First, the inclusion of 'principal' diagnosis discharge codes only, and not secondary codes means that we may have underestimated the true rates. Second, we were unable to link all hospitalised cases to microbiology data to validate whether hospitalisations coded as bacterial pneumonia or empyema were truly associated with confirmed bacterial infection; it is known that laboratory test results are not necessarily reflected in hospital coding. However, unlike uncomplicated pneumonia which may be caused by either viruses or bacteria, empyema is thought to be exclusively caused by bacterial infection. Not all

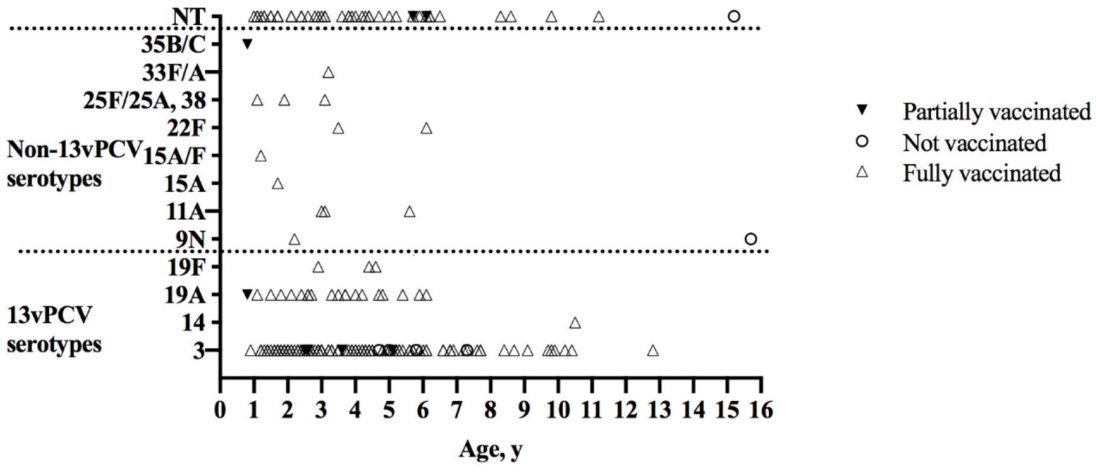

Figure 2 *Streptococcus pneumoniae* serotype distribution in relation to age and vaccination status of children with empyema Australia, in the 13-valent pneumococcal conjugate vaccine (13vPCV) period, 2015–2018. NT, not able to be typed.

Table 4 *Streptococcus pneumoniae* serotypes identified in PCR-positive specimens from children with empyema, Australia, in the 7-valent pneumococcal conjugate vaccine (7vPCV) (2007–2009) and 13-valent pneumococcal conjugate vaccine (13vPCV) periods

	No. (%) specimens	
Serotypes	**April 2007–April 2009 (7vPCV period)**	**February 2015–Sept 2018 (13vPCV period)**
Total number serotypes	55	161
13vPCV serotypes	50 %, (n=)	147 %, (n=)
3	32.7 (18)	76.4 (123)
19A	36.4 (20)	12.4 (20)
19F	–	1.9 (3)
14	1.8 (1)	0.6 (1)
1	14.5 (8)	–
7F/7A	3.6 (2)	–
9V/9A	1.8 (1)	–
Non-vaccine serotypes	5 %, (n=)	14 %, (n=)
11A	–	1.9 (3)
25F/25A, 38	–	1.9 (3)
9N	–	1.2 (2)
22F	–	1.2 (2)
15A	–	0.6 (1)
15A/F	–	0.6 (1)
33F/A	–	0.6 (1)
35B/35C	–	0.6 (1)
22F/22A	3.6 (2)	–
6C	1.8 (1)	–
15F	1.8 (1)	–
21	1.8 (1)	–

*7vPC period: two serotypes were identified in each of three specimens: 19A/3, 19A/1 and 6C/15F. The multiplex PCR reverse line blot assay cannot distinguish some pairs or groups of closely related serotypes, including 7F/7A, 22F/22A, serogroup 6. Individual serotypes within serogroup six were distinguished by using serotype-specific PCR.
*13vPCV period: serotypes 25F, 25A and 38 were grouped together as they could not be individually identified through molecular methods.

childhood empyema cases in Australia were captured by targeted surveillance over the study period, as many children were likely treated outside participating hospitals; we enrolled children from all Australian states and territories to try to obtain a nationally representative sample.

Our results are also in keeping with a recent small Australian study which reported an increase in ST3 empyema in the 13vPCV era in one centre.[33] In further support of our findings, Jayasinghe *et al* studied the impact of 13vPCV on IPD compared with the 7vPCV period across all ages using data from the National Notifiable Disease Surveillance System in Australia.[25] IRRs for ST3 increased in the <2 years (1.35), 2–4 years (4.65), 5–14 years (1.15). ST19A decreased across all paediatric age groups; <2 years (0.23), 2–4 years (0.25), 5–14 years (0.16). Similarly, ST1 was not detected in the <2 year and 2–4 year old groups; the IRR in the 5–14 years was 0.70. National surveillance of IPD in Australia consists primarily of serotyping pneumococcus cultured isolates; enhanced molecular testing of normally sterile sites is not routine. We therefore do not have PCR data for paediatric empyema in the interval between the two prospective cohort periods (from April 2009 to January 2015). We have previously demonstrated that enhanced molecular surveillance using PCR of empyema cases identified a ~sevenfold increase in ST3 and ST1 compared with routine serotyping of cultured pneumococcus isolates from pleural fluid[34]; this study further highlights the value for routine enhanced molecular surveillance.

In summary, the introduction of 13vPCV onto the Australian NIP was associated with a reduction in bacterial pneumonia hospitalisations but an increase in empyema hospitalisations in children. SP continues to be the main bacterial cause. The 13vPCV ST ST3 and 19A remain prevalent, with evidence that an increase in ST3 in particular, with a lesser contribution from non-13vPCV pneumococcus ST, may have driven a true increase in childhood empyema. The recent change in the Australian vaccination schedule to include a dose at 12 months may increase effectiveness of 13vPCV against ST3 and ST19A but ongoing enhanced molecular surveillance will be required to monitor this given that the yield of identifying SP ST in pleural fluid is much higher with PCR compared with bacterial culture.

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