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Has the incidence of empyema in Scottish children continued to increase beyond 2005?

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What is already known. Empyema is a complication of pneumonia and usually caused by pneumococcal infection. Childhood empyema incidence in many countries increased during the 1990s and early 2000s. The introduction of routine pneumococcal vaccination in 2006 has reduced pneumonia incidence (presumably reflecting reduced pneumococcal disease).

What this paper adds. More children were admitted to hospitals in Scotland between 2006 and 2013 than the period 1981 to 2005. Between 2006 and 2010, after the introduction of routine heptavalent pneumococcal vaccination empyema incidence doubled but after 13-valent vaccination was introduced in 2010, empyema incidence has fallen modestly.

ABSTRACT (word count 221)

Background. The incidence of empyema increased dramatically in children during the 1990s and early 2000s. We investigated the relationship between changes in the incidence of childhood empyema in Scotland following the 2006 introduction of routine heptavalent conjugate pneumococcal vaccination (PCv-7) and the 2010 introduction of the 13-valent (PCV-13) vaccine.

Methods. This was a whole population study of Scottish hospital admissions between 1981 and 2013 using ICD-9 and -10 diagnostic codes for empyema. The number of admissions for pneumonia and croup was also captured to give insight into secular trends in admissions with other related and unrelated respiratory presentations.

Results. There were 217 admissions with empyema between 1981 and 2005 (mean incidence 9 cases/million/year) and 323 between 2006 and 2013 (mean incidence 47 cases/million/year), p<0.001. The introduction of conjugate vaccines in 2006 was associated with an overall increase in admissions for empyema of 2.0 (95% CI 1.4-2.8) per 100,000 children however the incidence rate ratio for empyema admission between 2010-2013 was lower relative to 2006-2009 (0.78 [95% CI 0.63, 0.98]. Secular changes in pneumonia, but not croup, were comparable to those for empyema.

Conclusion. The incidence of empyema in Scottish children initially rose in children aged 1 to 9 years after the introduction of routine conjugate pneumococcal vaccination however empyema incidence has fallen since 2010 when the 13-valent pneumococcal vaccine was introduced.

INTRODUCTION

Empyema is a serious complication of pneumonia in children. A number of studies reported an increasing incidence of paediatric empyema during the 1990s and early 2000s[1-6]. *Streptococcus pneumoniae* (pneumococcus) is a common cause of pneumonia and the most common pathogen isolated in empyema[7, 8] but our previous data suggested that changes in the epidemiology of empyema occurred at a time when pneumonia incidence was static [1]. One explanation for the increasing incidence of empyema might be changes in pneumococcal virulence or serotype distribution.

Routine vaccination beginning in infancy with a 7 valent pneumococcal conjugate vaccine (PCV-7) containing antigen against serotypes 4, 6B, 9V, 14, 18C, 19F and 23F was introduced in the USA in 2000 and subsequently into the UK paediatric schedule in 2006. In the UK, this programme appears to have been effective in reducing the frequency of hospital admissions for pneumonia [8, 9]. In April 2010, PCV-7 was superseded by a 13-valent vaccine (PCV-13) providing coverage for six additional serotypes (1, 3, 5, 6A, 7F and 19A); these serotypes are responsible for a significant proportion of invasive pneumococcal disease in UK children [2] and the PCV-13 might therefore be expected to lead to a reduction in the incidence of empyema.

We have previously reported data on the incidence of empyema for the childhood population of Scotland from 1981 to 2005 [1] and here we extend our observations to 2013 to include the period when PCV-7 and -13 vaccinations were introduced. Given the dissociation between the relative incidence of empyema and pneumonia[1] we hypothesised that the incidence of empyema might continue to rise between 2006 and 2013.

METHODS

Study design

Hospital admission data were provided by the Scottish Government Information Services Division (ISD) in Edinburgh. The ISD is part of NHS Scotland and provides health information to researchers and to NHS Scotland and the Scottish Government. Inclusion criteria were children aged up to 14 years admitted over the time period 1st January 1981 to 31st December 2013 inclusive with a diagnostic coding for empyema in four groups (<one year, one to four, five to nine and ten to 14 years old). As previously [1], paediatric admissions for pneumonia and croup were also obtained to allow comparison between secular trends in empyema incidence and related and unrelated respiratory conditions. Pneumococcal serotype data from children admitted to hospitals in Scotland between 2006 and 2010 were provided by the Health Protection Agency [2].

Definitions

As previously [1], international classification of diseases -09 and -10 were used. Empyema codes were ICD-9 510.0, ICD-9 and 466.0 and ICD-10 J86.9 and A156-165. Pneumonia codes were ICD-9 480-486 and ICD-10 J12-18. Croup was defined as an ICD-9 code 464.4 or 466.0 or ICD-10 code J05.0 or J20.9.

Analysis

Incidence rate for admission was given per million children in the population as previously [1]. For the purposes of examining the impact of pneumococcal vaccine the data were divided into three periods of similar length – pre-vaccine (2000-5), PCV-7 era (2006-9), PCV-13 era (2010-13). Relative change in admission incidence (Incidence rate ratios) was estimated using standard Poisson methods for comparisons between eras.[10] An interrupted time series analysis was carried out for the period 2000

and 2013 to measure the absolute change in admissions associated with the introduction of the 2006 pneumococcal vaccine to the routine immunization schedule on the incidence of the three conditions. There were insufficient empyema data available to perform vaccine specific analyses. Similar techniques have been used to assess the impact of vaccination on pneumonia and empyema.[11, 12] Standard statistical software was used (SPSS version 20.0.0 and R version 3.0.1 –nLME & epiR packages) and significance was assumed when $p<0.05$.

RESULTS

Between 1st January 1981 and 31st December 2013 540 children were admitted to hospital in Scotland with empyema, 32,996 with pneumonia and 41,885 with croup. The online supplement presents the absolute number of admissions for empyema, pneumonia and croup by year 1981-2013. The total number of cases for the period 1981 and 2005 are marginally higher compared to our previous report [1], reflecting late cases added to the ISD database since 2005.

Empyema admissions

There were 217 admissions with empyema between 1981 and 2005 and 223 between 2006 and 2013, equivalent to a rise in the mean annual incidence of 11 admissions per million children (SD 9) for 1981 to 2005 to 47 (SD 14) after 31st December 2005 (figure 1). Interrupted time series analysis demonstrated an increase in empyema admission incidence of 1.97 extra admissions per 100,000 children associated between 2000 and 2013 (95% CI 1.39-2.79); age group specific differences were seen, with an increase focussed in the 1-4 and 5-9 years age groups (data not presented). Admission incidence for empyema across all age groups combined, increased in the PCV-7 period (incidence rate ratio, IRR, 2.14 [95% CI 1.65, 2.80]). Within age groups, this increase was seen in the 1-4 and 5-9 year old age groups (IRR 2.26

[1.52, 3.42] and 2.88 [1.59, 5.47] respectively) but not others (table 1). There was a fall in admissions between 2006 and 2013 (IRR 0.78 [0.63, 0.98]) when all age groups were considered (table 1).

Pneumonia admissions

Admissions for pneumonia increased in Scotland when PCV-7 was introduced, IRR 1.08 [95% CI 1.03, 1.13] when all age groups were considered (table 2) Within age groups admissions in infants fell (IRR 0.87 [95% CI 0.78, 0.96]), remained static in 1-4 year olds and rose in the 5-9 year olds (IRR 1.18 [95% CI 1.07, 1.29]) and 10-14 year olds (IRR 1.16 [95% CI 1.02, 1.32]) (table 2). Admissions for pneumonia fell in all age groups apart from infants during the PCV-13 period when compared with the PCV-7 period (table 2). There was no change in pneumonia admission incidence between2006 and 2013 in the interrupted time series analysis

Croup admissions

Total croup admissions increased in the PCV-7 era (IRR 1.18 [95% CI 1.13, 1.23]) but remained unchanged during the PCV-13 era (table 3). Croup admission incidence for infants and 1-4 year olds rose during the PCV-7 era but did not fall during the PCV-13 era (table 3). Admission incidence for 10-14 year olds fell during the PCV-13 era compared to the PCV-7 era (table 3). There was no change in croup admission incidence between 2000 and 2013 in the interrupted time series analysis.

Pneumococcal serotype data

Pneumococcal serotype data were available in 41 children admitted between 2006 and 2010 (4 from blood and the remainder from pleural fluid samples) during which time a total of 223 children were admitted. Molecular testing at the Scottish reference laboratory did not recover a serotype in 21 cases. There were six cases of serotype 1, two of serotype 14A, two of serotype 19A, 4 of serotype 3 and four cases of serogroup 7A/F. Two non typeable serotypes were recovered (Multi-locus sequence types - 4119 and 4122).

DISCUSSION

The incidence of empyema in children was still rising abruptly in Scotland in 2005 when we published our previous study[1] and the present study demonstrates that this rise continued after introduction of routine pneumococcal vaccination in 2006 but fell after 13-valent vaccination was introduced in 2010. Where serotype data were available for the PCV-7 vaccination era, all cases were infected with non PCV-7 serotypes suggesting that by extrapolation, the 13-valent conjugate vaccines may be effective in preventing invasive disease from the serotypes covered. Non-vaccine serotypes continue to cause morbidity in the UK as has been previously reported[2,13]. Empyema incidence now seems to be falling following the introduction of the PCV-13 vaccine (figure 1) but incidence in 2013 remains considerably higher than 2000.

Our results are generally consistent with reports of increasing empyema incidence during the 2000s from the UK and other countries. Two studies from the US [5, 14] have observed rises in empyema incidence of a very similar order as we report here although in the US studies, pneumonia incidence had fallen several years before the reduction seen in our population (table 2). Between 1996-2007, Grijalva *et al*[5] report a

doubling of empyema admissions in these age ranges (to 70 and 103 cases/million children/year for <2 and 1.4 year olds respectively) in the context of a33% fall in pneumonia admissions in children aged <2 years and a 24% fall for 2-4 year olds. Su-Ting *et al*[14] report empyema admissions in <5 year olds increasing from 38/million/year in 1997 to 76/million/year in 2006; during this period, pneumonia admissions fell by 29% for the <2 year age group. In a two-centre study from Spain, Obando *et al*[15] report a 13-fold increase in the numbers of children admitted with empyema between 1998 and 2006. Data from England and Wales also demonstrate a rise in empyema admissions 1997-2006 which was highest in the under 5s[9]. This latter study did however find a 22% fall in empyema admissions for all children between 2006 and 2008 which was mostly explained by falling admissions in infants[9]; here we report a 22% reduction in incident rate ratio after 2010 (table 1) for all children with the largest fall also being seen in infants. The greatest fall might be expected in infants since this age group will all have had the opportunity for vaccination, whereas children born before 2010 will not have received protection of 13-valent vaccination.

There are a number of mechanisms which might explain changing empyema admissions and these include (non-exclusively) changes in referral patterns, pneumonia incidence, exposure to environmental factors (e.g. second hand smoke) and antibiotic prescribing. Changes in admission incidence for croup between 2000 and 2013 do indicate changing drivers for referral to hospital with paediatric respiratory conditions *per se* but the changes in incidence for croup and empyema were different and we imagine that very few cases of paediatric empyema will be managed in the community. Changes in empyema admissions were different to those of pneumonia, suggesting that the mechanism for the changes in empyema do not directly reflect changes in pneumonia incidence as we have previously observed[1]. We do not believe that increasing empyema admission incidence is secondary to a reduction in threshold for referral or an increase in pneumonia.

The 2005 legislation preventing smoking in the workplace and public spaces has been associated with reduced childhood asthma admissions in the UK [16] but does not appear to have reduced empyema incidence, although our study is underpowered to definitively explore this association. Our study design did not include an assessment of changes in antibiotic prescribing in children but primary care prescribing of broad spectrum antibiotics in children in the UK rose between 2000 and 2007[17] , and in secondary care there is an increasing preference for oral versus intravenous antibiotic treatment for pneumonia[18].

A further mechanism which might explain changing empyema incidence is "serotype replacement disease" where, following the introduction of a vaccine, non-vaccine serotypes become important pathogens. A recent study from England and Wales following introduction of the heptavalent vaccine concluded that herd immunity was well established providing uptake was good but also found evidence of serotype replacement with non-vaccine organisms [19]. In Alaska, non vaccine type organisms were responsible for a significant rise in invasive pulmonary infections in a small population of Alaskan children [20] and in the UK, there has been a rise in serotype 19A invasive disease since the introduction of the 13 valent conjugate vaccine [2]. What remains to be seen is whether in future, empyema incidence rises again due to infections with Pneumococcal serotypes not included in the 13-valent.

There are a number of limitations to this study which should be considered when interpreting the results. First, we report admission incidence and not the number of children admitted and a single child admitted twice during an empyema illness would count as two admissions and therefore falsely inflate the incidence of empyema, but we believe that this is unlikely to be a significant factor. Secondly,

changes in clinical practice following the 2005 publication of guidelines [21] may have increased the detection rate for empyema; in this scenario, earlier incidence would have been an underestimate however this is unlikely to explain the rise in empyema incidence. Third, we have relied on hospital coding for diagnosis and this may not be accurate in every case although in Denmark, ICD-10 coding had a positive predictive value of 95% for case note confirmed empyema in 15-39 year olds [22]. Fourth, we obtained PCR data in less than 20% of cases admitted between 2006 and 2010 and, although missing data is likely to be independent of serotype, our serotype results are at best indicative of the actual serotype profile. Finally, although we suggest that there has been a fall in empyema incidence since 2010, our experience is that there may be some delay between admission and notification to ISD and therefore incidence may be underestimated.

In summary, empyema incidence continued to dramatically rise in children following the introduction of PCV-7 but has fallen slightly since the PCV-13 vaccine was introduced in 2010. The absolute numbers of admissions with empyema are very small (approximately 50 cases/million in Scotland and North America) compared to pneumonia and croup, but empyema remains a serious condition associated with significant morbidity. Case control studies are now required to give insight into why some children with pneumonia go on to develop empyema.

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Table 1. Incidence rate ratios comparing incidence of empyema in the pre-vaccine, heptavalent (PCV-7) and 13-valent (PCV-13) vaccination eras. SE = standard error, CI = confidence interval, *p<0.05

PCV-7 versus pre vaccine era	**Incidence Rate Ratio**	**SE**	**95 % CI**	
All ages	2.14*	1.14	1.65	2.80
Infants	1.72	1.51	0.73	4.38
1-4 yrs	2.26*	1.22	1.52	3.42
5-9 yrs	2.88*	1.34	1.59	5.47
10-14 yrs	1.44	1.30	0.84	2.53
PCV-13 versus PCV-7 era				
All ages*	0.78	1.12	0.64	0.98
Infants	0.47	1.54	0.17	1.14
1-4 yrs	0.92	1.16	0.68	1.26
5-9 yrs	0.65	1.26	0.40	1.06
10-14 yrs	0.63	1.33	0.34	1.12

Table 2. Incidence rate ratios comparing incidence of pneumonia in the pre-vaccine, heptavalent (PCV-7) and 13-valent (PCV-13) vaccination eras. SE = standard error, CI = confidence interval, *p<0.05

PCV-7 versus pre vaccine era	**Incidence Rate Ratio**	**SE**	**95% CI**	
All ages	1.08*	1.02	1.03	1.13
Infants	0.87*	1.06	0.78	0.96
1-4 yrs	1.01	1.03	0.95	1.07
5-9 yrs	1.18*	1.05	1.07	1.29
10-14 yrs	1.16*	1.07	1.02	1.32
PCV-13 versus PCV-7 era				
All ages	0.93*	1.02	0.89	0.97
Infants	0.94	1.06	0.84	1.04
1-4 yrs	0.88*	1.03	0.83	0.93
5-9 yrs	0.90*	1.05	0.82	0.99
10-14 yrs	0.98	1.07	0.87	1.11

Table 3. Incidence rate ratios comparing incidence of croup in the pre-vaccine, heptavalent (PCV-7) and 13-valent (PCV-13) vaccination eras. SE = standard error, CI = confidence interval, *p<0.05

PCV-7 versus pre vaccine era	**Incidence Rate Ratio**	**SE**	**95% CI**	**95 % CI**
All ages	1.18*	1.02	1.13	1.23
Infants	1.13*	1.05	1.03	1.24
1-4 yrs	1.11*	1.03	1.06	1.17
5-9 yrs	1.04	1.06	0.93	1.17
10-14 yrs	1.24	1.15	0.94	1.65
PCV-13 versus PCV-7 era				
All ages	1.02	1.02	0.98	1.06
Infants	1.06	1.04	0.97	1.16
1-4 yrs	0.96	1.02	0.91	1.00
5-9 yrs	0.96	1.06	0.86	1.07
10-14 yrs	0.64*	1.17	0.46	0.87

FIGURE LEGENDS

Figure 1. Incidence of empyema admissions for children in Scotland between 1980 and 2013. The vertical dashed lines correspond with the introduction of the heptavalent pneumococcal vaccination (PCV-7) and 13-valent (PCV-13).

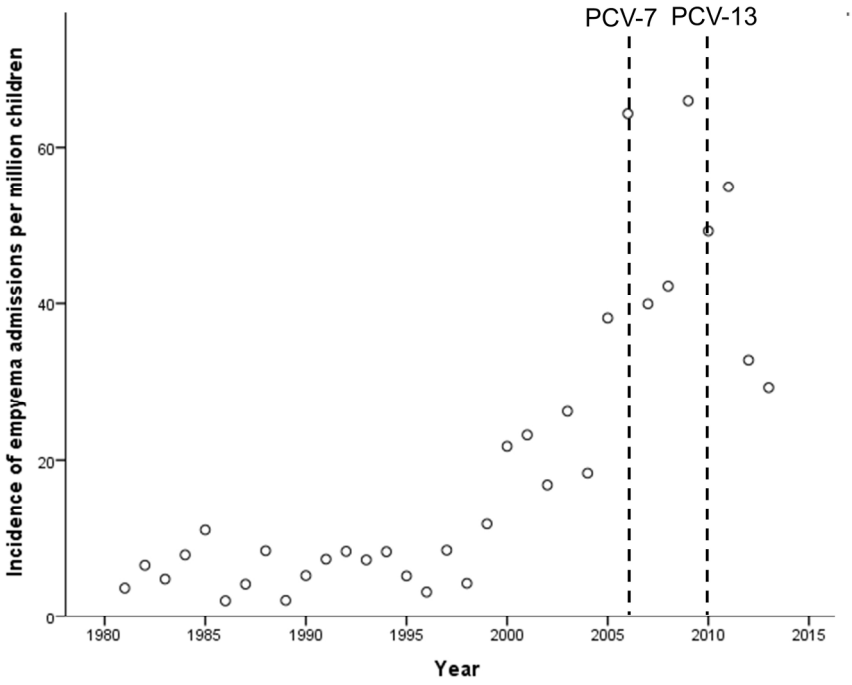

Figure 1. Incidence of empyema admissions for children in Scotland between 1980 and 2013. The vertical dashed lines correspond with the introduction of the heptavalent pneumococcal vaccination (PCV-7) and 13-valent (PCV-13).
190x142mm (300 x 300 DPI)

Year	Number of empyema admissions	Number of pneumonia admissions	Number of croup admissions	Number of children in the population
1981	4	964	1,079	1098333
1982	7	1,040	1,008	1070635
1983	5	974	1,667	1043756
1984	8	831	1,014	1018845
1985	11	819	1,335	998068
1986	2	763	793	979521
1987	4	907	1,391	964725
1988	8	880	988	955009
1989	2	682	1,454	954826
1990	5	997	919	955908
1991	7	1,028	1,582	957724
1992	8	882	1,364	963963
1993	7	1,022	1,463	968931
1994	8	1,069	1,542	969615
1995	5	1,272	1,454	963364
1996	3	982	1,416	952790
1997	8	1,016	1,522	946649
1998	4	1,231	1,253	940477
1999	11	881	1,180	933380
2000	13	955	997	919439
2001	11	1,026	1272	904997
2002	8	1,062	933	890242
2003	21	969	1280	877685
2004	15	970	873	871907
2005	32	1,222	1501	865091
2006	55	1,315	1038	856083
2007	34	1,065	1662	851334
2008	36	1,060	952	850206
2009	56	986	1604	850477
2010	42	983	1120	851621
2011	47	1,248	1414	854752
2012	28	1,061	959	853009
2013	25	834	1856	852005

Table E1. Number of children admitted to hospitals in Scotland per year with empyema, pneumonia and croup.