Long term trends introduce a potential bias when evaluating the impact of the pneumococcal conjugate vaccination programme in England and Wales

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A pneumococcal conjugate vaccine (PCV7) was introduced into the United Kingdom's childhood immunisation schedule in September 2006. Evaluation of its impact on the incidence of invasive pneumococcal disease (IPD) as assessed by routine reports of laboratory-confirmed cases should take into account possible long-term trends due to factors like changes in case ascertainment. To this end, we compared pre-PCV7 trends in reported IPD incidence in England and Wales identified by blood culture with those for two other bacteraemias, *Escherichia coli* and non-pyogenic streptococci, for which there has not been any public health intervention. While no trend was detected in the age group 65 years and older, there was an annual increase of 3% and 11% in those aged under five years and between five and 64 years, respectively, which was similar for IPD and the other two pathogens. After PCV7 introduction, a continuing trend was only found for non-pyogenic streptococci in under five year-olds. These trends in the incidence for bacteraemias for which there has been no intervention could suggest that there have been changes in case ascertainment because of increased reporting or blood culturing. Accounting for them will improve the evaluation of the impact of PCV7 on IPD.

Introduction

Streptococcus pneumoniae, also called pneumococcus, is a common cause of mortality and morbidity worldwide. It causes a variety of disease presentations, the most serious, invasive pneumococcal disease (IPD), associated with spread via the blood stream resulting in septicaemia, meningitis, bacteraemic pneumonia or invasion of other normally sterile sites such as pleural or synovial fluid. A seven-valent pneumococcal conjugate vaccine (PCV7) became available in the United States in 2000 offering protection against both carriage [1,2] and disease [3] from the seven most common serotypes causing IPD in children in developed countries. In September 2006 PCV7 was introduced into the immunisation schedule in the United Kingdom

as a 2/4/13 month routine schedule (one dose at two and four months plus a booster dose at 13 months of age) with a catch-up for children up to two years of age.

Most pneumococcal surveillance systems focus on IPD and have shown large reductions in the numbers of cases infected with vaccine-type strains (VT cases) in the targeted age groups, irrespective of vaccine schedule [4,5]. However differences have been reported between countries in the percentage reduction of VT disease and the induced herd effect in older age groups as well as in non-vaccine-type (NVT) replacement disease. Comparison of the incidences of VT and NVT IPD cases before and after the introduction of PCV7 implicitly assumes that the reported disease incidence in the absence of vaccination has not changed, that a similar level of ascertainment has been maintained, and that there were no secular trends in individual serotypes. A recent World Health Organization (WHO) meeting that reviewed the post-PCV7 experience in different countries identified changes in the sensitivity of the surveillance systems due to alterations in clinical awareness, reporting techniques and blood culturing practice as

Figure 1

Age distribution of invasive pneumococcal disease and control infections, England and Wales, 2001/02 to 2005/06
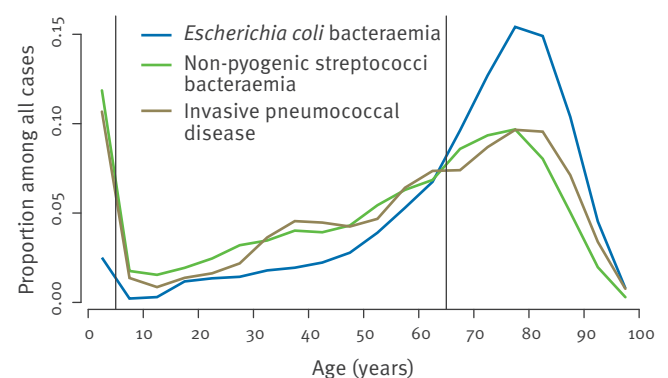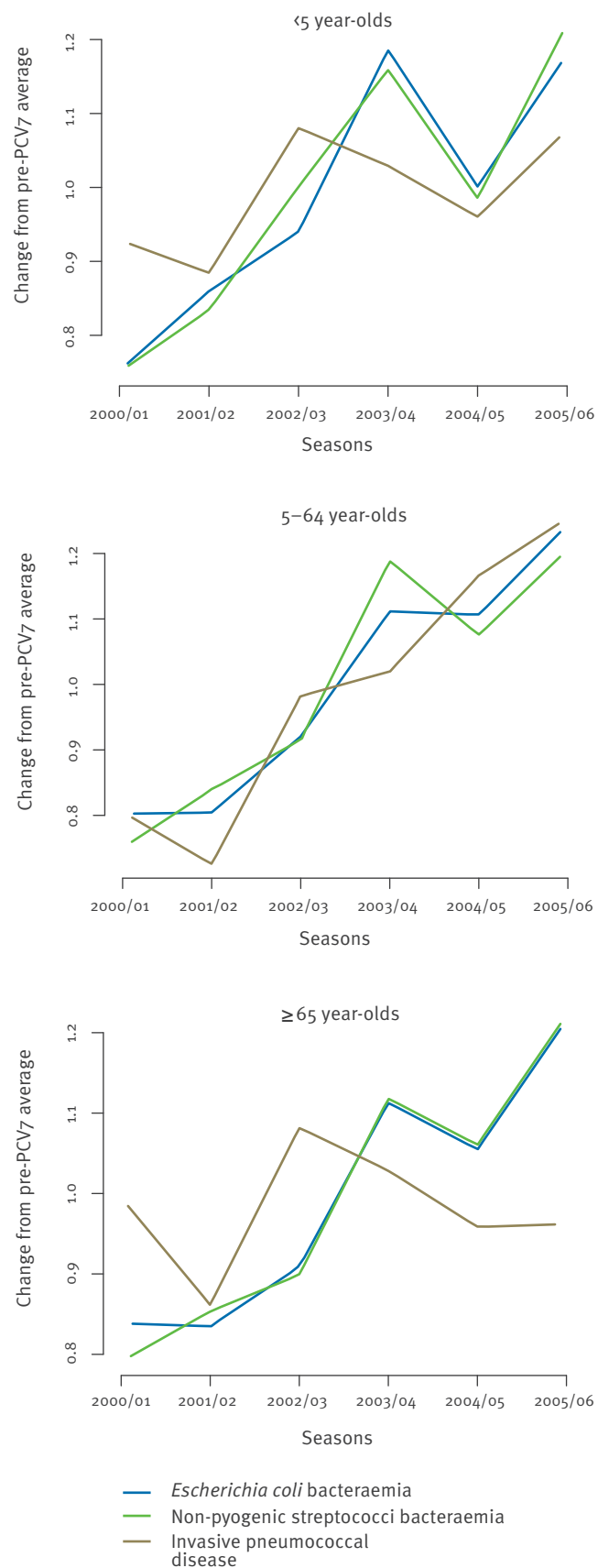
PCV7: seven-valent pneumococcal vaccine.
For the ease of comparison trends for all pathogens are plotted after scaling by the respective average incidence.

potential important confounders when making such comparisons over time and between countries [6].

Given the severity of IPD and the continuing universal access to the National Health System (NHS) it is reasonable to assume that care seeking behaviour of IPD patients in England and Wales has remained constant in recent years. However, this might not be the case for laboratory investigation or reporting behaviour which may have been subject to changes in practice over time. Reporting rates for IPD in hospitalised cases have been shown to vary with blood culturing rates which may have changed as clinical practice has evolved [7], while recent technical developments may have improved reporting of laboratory-confirmed cases [8].

In order to interpret changes in the incidence of IPD after the introduction of PCV7 into the routine childhood vaccination scheme in England and Wales we assessed trends in reported IPD cases before introduction of PCV7 and related them to changes observed before and after that date in a control group of pathogens that similarly depend on blood culturing practice and reporting, but for which there have been no public health or other interventions. Our findings are relevant to the evaluation of the impact of PCV7 in England and Wales.

Methods

Pathogens
Control pathogens selected for the comparison with IPD were those of the most commonly reported bacteraemias that fulfilled the following inclusion criteria: (i) endemic in England and Wales and not solely outbreak-related, (ii) not influenced by vaccination or any other interventions during the time period of the comparison, (iii) sufficiently common to provide statistically robust numbers in each age group, (iv) mainly diagnosed through blood culture. The two pathogens identified that fulfilled these criteria were *Escherichia coli* and non-pyogenic streptococci (*Streptococcus acidominimus, S. bovis, S. gordonii, S. intermedius, S. mitis, S. mutans, S. oralis, S. parasanguinis, S. salivarius*, and not further typable: alpha-haemolytic Streptococcus *sp.*, non-haemolytic *Streptococcus sp.*, *S. anginosus* group, *S. milleri* group, *S. mitis* group, *S. sanguinis* group).

Data on all infections reported between July 2000 and June 2010 (between 2000 and 2007 for pneumococcus) and identified by blood culture were obtained from the national routine laboratory surveillance system of England and Wales (LabBase) [8]. Only one isolate per disease episode was included in the analysis. More than one isolate from the same person where the interval between specimens was less than 14 days and the same pathogen was isolated were assumed to represent the same illness episode. As part of the enhanced surveillance [9] episodes of IPD were checked for duplicates using personal identifiers.

Statistical analysis

For each of the pathogens a negative binomial regression model was fitted to the observed number of cases per 100,000 population. We regressed the number of cases with a linear trend and a five-level factor to indicate the period before and the four seasons after PCV7 introduction, 2006/07, 2007/08, 2008/09, 2009/10 and included a population offset. The (anti-logged) slope of this model indicates the pre-PCV7 trend, i.e. a slope >1 indicates a positive trend and a slope <1 a negative trend in a negative binomial model. To test for differences in slopes we tested their confidence intervals for overlap which provides conservative estimates [10]. Each of the post-PCV7 factors indicates the deviation of the post-2005/06 data from the extrapolated pre-2005/06 trend. No adjustment for multiple comparisons was made.

Data for all analyses were stratified into three age groups (<5, 5–64, ≥65 years) with missing age information being imputed from the age distribution observed for the pathogens, and were performed in R version 2.11 [11].

Results

More than 150,000 disease episodes before PCV7 introduction were considered. They were differently distributed amongst the age groups (Figure 1). While IPD and non-pyogenic streptococci showed similar patterns, most of the *E. coli* episodes were reported in the elderly population. In the population under five years of age 27% of disease episodes were due to *E. coli*, 49% to IPD and 25% to non-pyogenic streptococci. In the 5–64 year-olds the respective distribution was 50%, 34% and 16%, and for those 65 years and older it was 70%, 21% and 9%.

The regression model found a positive trend in IPD incidence prior to the introduction of PCV7 in the age groups under five years and between five and 64 years. The trend was most pronounced in the 5–64 year-olds with an average yearly increase of about 11% (p<0.001). In the under five year-olds reports of IPD increased about 3% per year (p=0.031). In the over 65 year-olds we estimated this trend to be not significantly different from zero (p=0.91) (Table 1).

TABLE 1

Estimated slopes in models of the pre-PCV7 trend in invasive pneumococcal disease and control infections, England and Wales, 2000/01–2005/06

Age group	Invasive pneumococcal disease slope [95% CI]	*Escherichia coli* slope [95% CI]	Non-pyogenic streptococci slope [95% CI]
<5 years	1.030 [1.002–1.058]	1.091 [1.052–1.132]	1.093 [1.051–1.138]
5-64 years	1.106 [1.075–1.138]	1.095 [1.075–1.114]	1.097 [1.061–1.134]
≥65 years	0.999 [0.972–1.027]	1.074 [1.055–1.193]	1.087 [1.063–1.111]

CI: confidence interval; PCV7: seven-valent pneumococcal vaccine.

TABLE 2

Percentage difference between the incidence of control infections and the incidence predicted by two different models, England and Wales, 2000/01–2008/09

Age group	Season	*Escherichia coli*		Non-pyogenic streptococci	
		Model A[a]	Model B	Model A	Model B
<5 years	2006/07	-15.5% [-27.2 to -2.0]	-8.1%	-16.7% [-27.2 to -2.0]	-9.2%
	2007/08	-13.8% [-26.8 to 1.6]	5.1%	-5.2% [-19.6 to 11.8]	15.9%
	2008/09	-19.5% [-33 to -3.2]	8.7%	-8.3% [-23.9 to 10.4]	24.3%
	2009/10	-25.5% [-39.4 to -8.4]	9.5%	-17.3% [-32.9 to 2.0]	22.3%
5-64 years	2006/07	-7.4% [-14.1 to -0.2]	4.4%	-10.9% [-22.5 to 2.6]	0.7%
	2007/08	-5.9% [-13.4 to 2.4]	15.9%	-15.8% [-28.0 to -1.5]	4.0%
	2008/09	-12.3% [-20.1 to -3.6]	18.0%	-23.1% [-35.6 to -8.3]	3.9%
	2009/10	-16.1% [-24.4 to -6.8]	23.3%	-31.9% [-44.1 to -17.1]	-0.8%
≥65 years	2006/07	-8.6% [-15.4 to -1.3]	2.3%	-11.1% [-18.7 to -2.8]	0.7%
	2007/08	-8.3% [-15.9 to 0.0]	10.8%	-7.5% [-16.2 to 2.1]	14.3%
	2008/09	-12.2% [-20.3 to -3.3]	15.0%	-18.0% [-26.7 to -8.3]	11.0%
	2009/10	-11.9% [-20.9 to -1.9]	25.2%	-25.0% [-33.8 to -15.0]	11.5%

PCV7: seven-valent pneumococcal vaccine.
Model A: extrapolation of the trend in the period before introduction of PCV7.
Model B: assuming the trend to discontinue from the season 2005/06 onwards.
[a] For model A 95% confidence intervals are presented.

For *E. coli* and non-pyogenic streptococci the trends were significantly positive in all age groups (all p<0.001). Pre-PCV7 trends in IPD were not significantly different from those in *E. coli* and non-pyogenic streptococci (Table 1) in the under 65 year-olds, although in the children trends in IPD were slightly smaller than in the other pathogens (Table 1, Figure 2). However, in the age group 65 years and older no significantly positive trend was found for IPD, while reports for *E. coli* and non-pyogenic streptococci increased by 7–9% per year.

In the youngest age group (under five years of age) the reported incidence of non-pyogenic streptococci closely followed the prediction extrapolated from the trend before the season 2006/07 (Figure 3). However, the prediction for *E. coli* significantly overestimated the actual incidence (Table 2) although the reported incidences were still higher then before the date of PCV7 introduction. In the 5–64 year-olds the pre-PCV7 trend of non-pyogenic streptococci diminished in the seasons after introduction of PCV7 and the incidence remained at the level of the incidence observed in the season 2005/06. Again *E. coli* differed: the observed incidences were in between the predictions that

assumed the pre-PCV7 to continue and those assuming no trend after introduction of PCV7. In the oldest age group the reports for both *E. coli* and non-pyogenic streptococci were in between these two prediction scenarios.
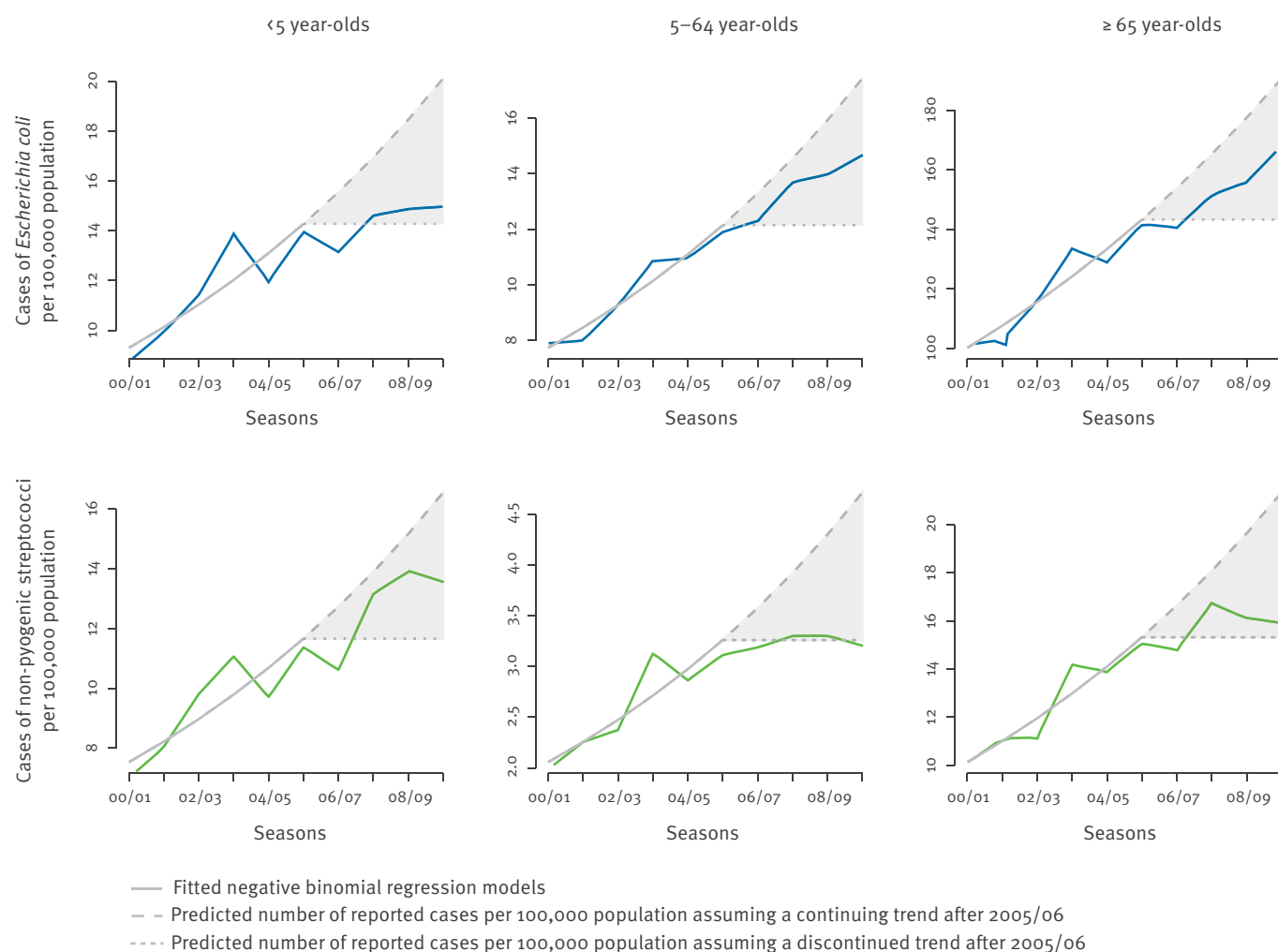
Discussion and conclusion

Upward trends in the annual numbers of some bacteraemias have been reported previously [12]. The similarity of the trends for IPD and the two control pathogens in the age groups under 65 years before 2005/06 suggests that the sensitivity of the national surveillance system in England and Wales was increasing prior to introduction of PCV7. While the trends for the control pathogens extrapolated from the period before PCV7 introduction were not entirely consistent with the observed incidence in the period after 2005/06, they may nevertheless provide an equally likely indication of the expected numbers of bacteraemia reports in the post-PCV7 period compared to those assuming the trend to discontinue after 2005/06.

The data sources introduced some limitations to our analysis. While we employed the data from the national

Figure 3

Pre-and post-PCV7 trends in control infections stratified by pathogen and age group, England and Wales, 2000/01–2008/09

— Fitted negative binomial regression models
– – Predicted number of reported cases per 100,000 population assuming a continuing trend after 2005/06
····· Predicted number of reported cases per 100,000 population assuming a discontinued trend after 2005/06

laboratory-based surveillance for *E. coli* and non-pyogenic streptococci the data on *S. pneumoniae* was further enhanced and controlled for duplicates due to inconsistencies specific to IPD in the national laboratory-based surveillance dataset in the years 2002 and 2003 when duplicates had been included in error; such duplicates were removed from the enhanced IPD dataset (which contains an extra 10–20% of cases identified solely from referral of isolates for serotyping). A further limitation which may have affected the data was the migration in mid-2001 of the national surveillance database to a new platform which could have caused inconsistencies for all pathogens if data deduplication was compromised. Non-pyogenic streptococci are sometimes associated with contamination. This could artificially increase the reported incidence of bacteraemias caused by non-pyogenic streptococci. However, this is unlikely to alter the trend estimates for increasing ascertainment since these would be equally reflected by the contaminated samples.

We assessed the goodness of fit of the regression models in the pre-PCV7 era (goodness of fit is not an issue for the post PCV7 period since the model is saturated there, i.e. the model is set up to exactly fit the data). For all six models (three age groups for both *E. coli* and non-pyogenic streptococci) the root mean square error was between 1.29 and 1.34. Also, considering the logarithm of time rather than time as a linear variable did not improve the Akaike information criterion.

Secular trends in the reports of laboratory-confirmed IPD in the absence of vaccination have been observed for some serotypes [13,14]. These trends are poorly understood, cannot be predicted and are likely to affect the estimates of the vaccine impact. However, in the younger age groups our pre-PCV7 trend estimates for IPD and the other pathogens were similar, which suggest that these trends were more pronounced in that period than any pathogen-specific secular trends.

The similar trends prior to 2005/06 between pneumococcus and the other pathogens in the age groups under five years and between five and 64 years could reveal a common source causing this trend; increasing ascertainment of cases. This could be due to numerous reasons including increasing blood culturing practice and an increasing number of laboratories choosing to report these non-notifiable diseases to the national database. Additional factors might have contributed to the observed trends, such as increasing automation of detection techniques or improved survival of people with underlying conditions, which could have increased the numbers of vulnerable people in the population. However, in the population aged 65 years and older, the trends in IPD were different from the other pathogens. This could possibly be attributed to the step-wise introduction of a vaccination programme with the 23-valent pneumococcal polysaccharide vaccine (PPV) from August 2003 for this age group. A

detailed evaluation of the effectiveness of PPV in the elderly and the likely impact of the universal vaccination programme for this age group is currently being undertaken by the Health Protection Agency.

To assess the probable development of reported cases of IPD in the absence of vaccination we compared two predictions, continuing pre-PCV7 trend (Model A) and no trend (Model B), to the actual reports for *E. coli* and non-pyogenic streptococci. Although we have no clear evidence that one of the predictions was more correct than the other, the reported number of cases was in between both predictions in all age groups. While Model A might provide the better prediction for the under five year-olds, Model B seemed to provide more reliable estimates in the age group between five and 64 years.

These findings do have important implications for analysing the effect of the introduction of PCV7 to the childhood immunisation scheme: We find that by ignoring the pre-PCV7 trend, one is likely to underestimate the reduction in IPD and overestimate the degree of replacement disease. However, allowing for trends introduces the risk to overestimate the reduction in VT IPD and underestimate possible replacement especially in the 5–64 year-olds. This analysis helps to estimate the uncertainty introduced by changing ascertainment when analysing the effects of PCV in England and Wales. Similar analyses from other countries would be valuable to improve the comparability of the vaccine effects.

Conflicts of interest

Acknowledgments

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