Invasive Pneumococcal Disease (IPD) in England & Wales after 7-valent conjugate vaccine (PCV7); potential impact of 10 and 13-valent vaccines

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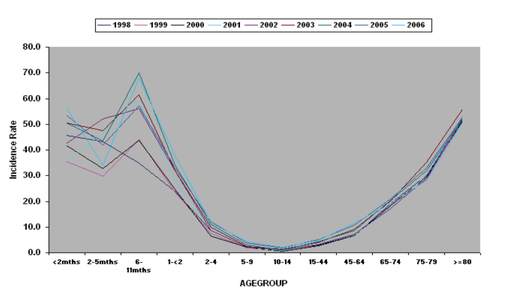
Background

Invasive pneumococcal disease (IPD) is a leading cause of morbidity and mortality in children in England and Wales causing septicaemia, meningitis and pneumonia. Approximately 5,000-6,000 cases of invasive pneumococcal disease (IPD) are reported annually to the Health Protection Agency (HPA), Centre for Infections (CfI) from laboratories in England and Wales.

The age specific incidence rates for IPD have remained broadly unchanged over the periods shown in the graph.

Incidence of Invasive pneumococcal disease per 100,000 population by age. England & Wales 1998-2006



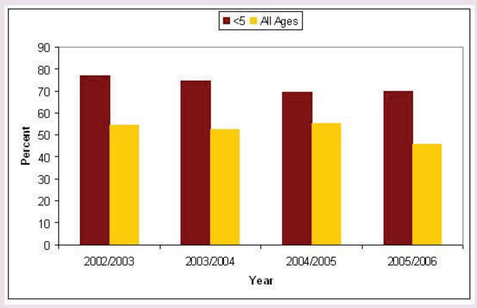
There are currently two licensed pneumococcal vaccines used in the UK; the 23-valent pneumococcal polysaccharide vaccine (PPV23, Pneumovax™) and the 7-valent pneumococcal conjugate vaccine (PCV7, Prevenar™). In England and Wales PPV23 has been recommended since 1992 for people aged 2 years and over in whom pneumococcal disease was considered to be more common or more serious. In August 2003 PPV23 was recommended for all adults aged 80 years and over, this was extended to those 75 years and over in April 2004 and all adults 65 years and over in April 2005.

PCV7 received marketing authorisation in the European Union in February 2001 and in 2002 was recommended for use in at-risk children under 5 years of age in the UK. In 2004 PCV7 use was extended to cover at risk children up to 5 years of age.From 4 September 2006 PCV7 was introduced into the routine childhood immunisation programme (As a 2+1 schedule: 2,4 and 13 months) with a catch-up campaign up to 2 years of age.

PCV7 contains the serotypes

14 , 18C , 19F , 23F , 4, 6B , 9V

From enhanced surveillance data the percentage of the total cases of invasive pneumococcal disease (IPD) with a serotype contained in the PCV7 prior to the introduction of PCV7 can be see in the graph



The impact to date of PCV7 on Invasive Pneumococcal Disease

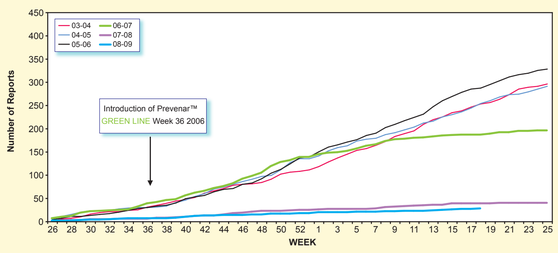
The Health Protection Agency (HPA) is monitoring the impact of the programme by actively following up every case of IPD in England, Wales and Northern Ireland, in children eligible for vaccination. This enables :

- Evaluation of the effectiveness of the current PCV7 schedule
- Identification of risk factors for vaccine failure
- Monitoring for evidence of serotype replacement since the vaccines' introduction
- Provision of individual clinical management of cases by offering serological testing after completion of the vaccination course.

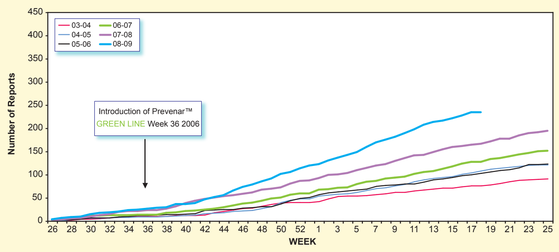
Since referral of cultures to HPA for serotyping by the primary laboratory usually occurs soon after isolation, data on serotype changes since PCV introduction can be monitored in "real time". The impact of the PCV programme on serotype distribution is being monitored by plotting the cumulative weekly number of isolates referred for serotyping from laboratories in England and Wales. Separating IPD cases due to any one of the seven serotypes present in PCV7 and due to serotypes not included in the vaccine for targeted age groups shows that since the introduction of PCV7 there has been a marked reduction in the rate of cumulative increase of cases of disease caused by the vaccine serotypes since the end of 2006 and some herd immunity in older age groups.

<2 years

Cumulative weekly number of reports of Invasive Pneumococcal Disease due to any of the seven serotypes in Prevenar™: Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2003- To Date)

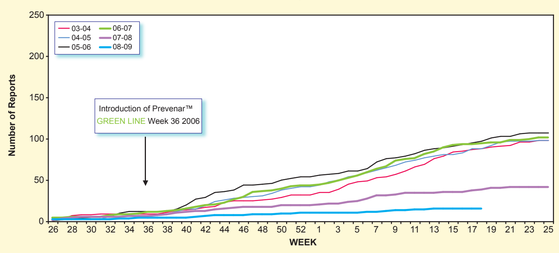


Cumulative weekly number of reports of Invasive Pneumococcal Disease due to any of the serotypes NOT IN Prevenar™: Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2003- To Date)

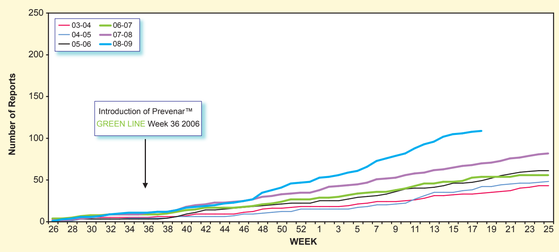


2-4 years

Cumulative weekly number of reports of Invasive Pneumococcal Disease due to any of the seven serotypes in Prevenar™: Children aged 2 to 4 years in England and Wales by Epidemiological Year: July-June (2003- To Date)

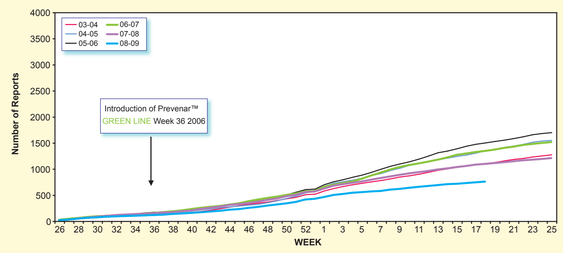


Cumulative weekly number of reports of Invasive Pneumococcal Disease due to any of the serotypes NOT IN Prevenar™: Children aged 2 to 4 years in England and Wales by Epidemiological Year: July-June (2003- To Date)

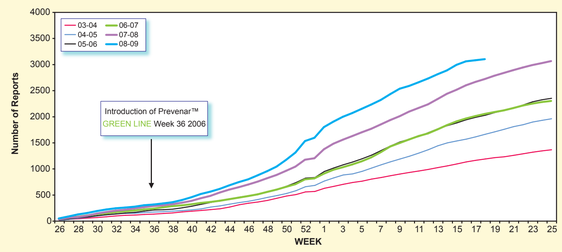


≥5 years

Cumulative weekly number of reports of Invasive Pneumococcal Disease due to any of the seven serotypes in Prevenar™: Persons aged >5 Years in England and Wales by Epidemiological Year: July-June (2003- To Date)



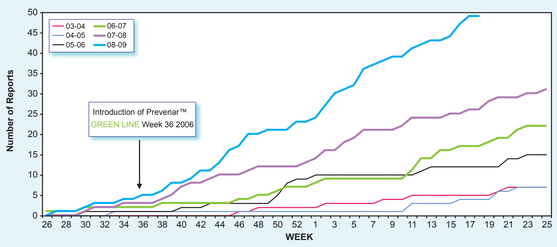
Cumulative weekly number of reports of Invasive Pneumococcal Disease due to any of the serotypes NOT IN Prevenar™: Persons aged >5 Years in England and Wales by Epidemiological Year: July-June (2003- To Date)



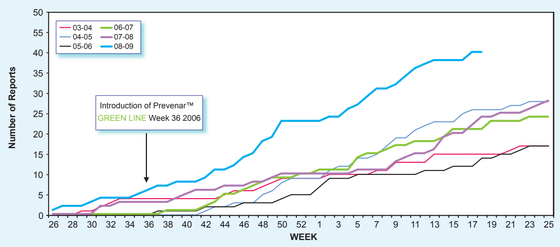
Serotype replacement

The incidence of disease however due to non-vaccine serotypes has been increasing and serotype replacement remains a concern highlighted here by graphs showing the cumulative incidence of serotypes 7F, 19A and 22 F.

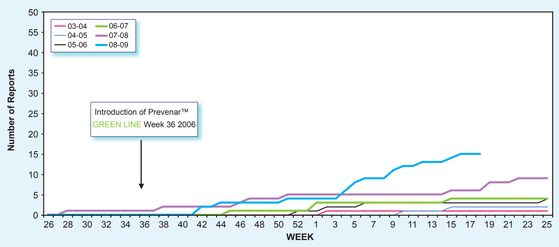
Cumulative weekly number of reports of Invasive Pneumococcal Disease due to serotype 7F Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2003- To Date)



Cumulative weekly number of reports of Invasive Pneumococcal Disease due to serotype 19A Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2003- To Date)



Cumulative weekly number of reports of Invasive Pneumococcal Disease due to serotype 22F Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2003- To Date)



Introduction of new conjugate pneumococcal vaccines

Two new pneumococcal conjugate vaccines – a 10-serotype vaccine produced by GSK, and a 13-serotype vaccine produced by Wyeth – have been recently developed with the former licensed and the latter imminent.

PCV10 includes all the serotypes in PCV7 plus serotypes **1, 5 and 7F**. Eight of the ten serotypes are conjugated to protein-D; derived from non-capsular *Haemophilus influenzae* (ncHI). An earlier version of this vaccine (with 11 serotypes) was shown to be moderately effective against acute otitis media caused by ncHI.

PCV13, like PCV7, is conjugated to CRM197. This vaccine contains all the serotypes in PCV10, plus serotypes **3, 6A, 19A**.

Potential Coverage of PCV 7, PCV10 and PCV13

From July 2005 to June 2006, 797 cases of IPD in children under 5 years of age were reported to the Health Protection Agency Centre for Infections. By the end of epidemiological year 2007/2008 this number had dropped by 41% to 470 cases. There was no significant reduction in cases in ≥ 5 years olds

Percentages of all IPD caused by serotypes covered by PCV7, PCV10 and PCV13 are shown below

Age group	Year	Number	PCV7	PCV10	PCV13
< 5 years	2005/2006	797	70%	81%	92%
	2007/2008	470	24%	53%	74%
≥ 5 years	2005/2006	5514	42%	62%	75%
	2007/2008	5496	28%	49%	67%

Comparing the potential benefits of PCV10 and PCV13

To compare the potential benefits (in terms of costs saved and QALYs gained) of PCV10 and PCV13 over and above PCV7 in England and Wales a simple cohort model was constructed.

Methods

- A cohort model was developed to estimate the number of cases, deaths and QALYs lost that were potentially preventable by PCV10 or PCV13
- The latest epidemiological data from the HPA was used to estimate disease incidence attributable to each pneumococcal serotype.
- Costs of hospital care were obtained from standard sources. Other costs and quality of life weights for pneumococcal-related outcomes were obtained from the literature
- Sensitivity analyses were performed

Assumptions & limitations

- All costs/ benefits were compared relative to PCV7
- Herd immunity was not considered
- Non-invasive disease endpoints were excluded
  - Invasive ncHI included in sensitivity analysis
- Replacement of PCV10 / PCV13 types not included
- Stable epidemiology in base case
  - Dynamic situation re. serotype distribution not accounted for
- Effectiveness of additional types assumed to be the same as overall PCV7 effectiveness

Results

Scenario	PCV10		PCV10 inc ncHI		PCV13	
	Costs saved/£	QALYs gained	Costs saved/£	QALYs gained	Costs saved/£	QALYs gained
Base case	**884,000**	**717**	**1,056,000**	**1039**	**1,319,000**	**1115**
Low case fatality	884,000	486	1,056,000	807	1,319,000	740
Low vaccine efficacy	732,000	593	842,000	804	1,067,000	903
3.5% discount rate	535,000	225	641,000	334	810,000	359
3.5%/1.5% discount rate	535,000	405	641,000	593	810,000	636
3 year time horizon	338,000	326	435,000	553	667,000	646
5 year time horizon	503,000	454	631,000	733	884,000	815
10 year time horizon	697,000	574	855,000	892	1,105,000	952

Conclusions

- There has been a marked reduction in the rate of cumulative increase of IPD cases caused by the 7 serotypes in PCV7 since vaccine introduction
- Of the IPD remaining in England and Wales an extra 29% is potentially preventable in children by switching to PCV10 and an extra 50% by switching to PCV13.
- Higher valency vaccines appear to offer modest benefits in terms of costs saved and QALYs gained compared to PCV7
- PCV13 is estimated to prevent more cases and save more QALYs than PCV10, but the inclusion of ncHI narrows this margin
- Estimating the potential benefits is complex because of the dynamic epidemiology of pneumococcal disease. This was a simple model which does not account for herd immunity or serotype replacement
- Evidence of replacement disease caused by serotypes not in either of the two new conjugate vaccines (e.g. 22F) is occurring

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