

Impact of the universal pneumococcal immunisation programme for 80+ year olds in England and Wales using the 23-valent plain pneumococcal polysaccharide vaccine (PPV): January 2005

Report from the Health Protection Agency, Centre for Infections (CfI) by
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SUMMARY

1. In England and Wales, universal pneumococcal immunisation in the elderly (80+ year olds) began in August 2003. The estimated coverage by end April 2004 achieved as a result of this universal programme in England was 26%. This compares with a cumulative coverage of 36% in this age group in the 10 years prior to August 2003 achieved through the former selective PPV programme for those at increased risk of invasive pneumococcal disease (IPD).
2. The incidence of IPD in 80+ year olds in England and Wales in the epidemiological year July 2003 to June 2004 was 9% lower than the annual average based on the previous 7 epidemiological years. The change in this age group compares with an overall increase across all age groups of 4% in 2003/4 compared with the annual average in the previous 7 years.
3. Serotype was determined for 736 (62%) of the 1184 IPD cases in 80+ year olds identified by the CfI between 4/11/2003 and 4/11/2004; of these, PPV vaccination status has to date been determined for 499 of these 736 individuals (68%).
4. Among vaccinated cases, the proportion with a vaccine-preventable serotype increased with time since vaccination from 79% in those vaccinated in the previous 2 years, to 91% and 95% in those vaccinated 2-4 and 5-10 years ago respectively.
5. Using data on the proportion of vaccinated cases with a vaccine serotype, the effectiveness of PPV vaccine in the 80+ year age group was estimated to be 71% (95% CI 34-78) for those vaccinated within the previous 2 years and 23% for those vaccinated 2-4 years ago, with no evidence of protection for those vaccinated 5-10 years ago.
6. Based on estimated vaccine coverage in the 80+ age group, effectiveness of PPV vaccine against IPD using the screening method was conservatively estimated to be 73% (63-81) for those vaccinated in the previous 2 years, falling to 41% (20-58) and 13% (-13 – 33) for those vaccinated 2-4 and 5-10 years ago respectively.
7. The observed 9% reduction in IPD incidence in 80+ year olds in England and Wales in the 2003/4 epidemiological year is compatible with an estimated 70% effectiveness against vaccine serotype IPD in this age group, 93% of IPD cases in

unvaccinated being due to vaccine serotypes and an estimated average coverage during the epidemiological year April 2003 to March 2004 of around 15-20%, the actual coverage between August 2003 and March April 2004 being 26%.

8. Based on laboratory confirmed cases, there is no discernable effect of PPV on the case fatality rate from IPD in the 80+ age group.

Background

Since August 2003, the 23-valent plain pneumococcal vaccine (PPV) has been offered to all individuals aged 80 years and over. In April 2004 PPV was offered to all 75+ year olds, and will be offered to all 65+ year olds from April 2005. This paper provides an update on the impact of the programme on invasive pneumococcal disease (IPD) in the 80+ age group and reports vaccine effectiveness estimates for this age group based on laboratory-confirmed cases in England and Wales between 4/11/2003 and 4/11/2004. Age-specific vaccine coverage achieved as a result of the new elderly PPV programme is being measured annually by the HPA Centre for Infections (CfI) by requesting information from each PCT on the eligible population and the numbers vaccinated prior to and in response to the programme in the relevant age groups.

Monitoring the impact on IPD

A joint dataset of all IPD cases reported in England and Wales has been created at the CfI since 1996 by reconciling computerised reports received from laboratories with data from isolates referred to the Respiratory and Systemic Infection Laboratory (RSIL) for serotyping. Approximately 4900 annual cases of IPD are identified through the joint data set, of which an average of 47% of pneumococcal isolates were referred for serotyping. In order to more accurately monitor the impact of PPV on IPD in those ages targeted for vaccination and to increase serotyping rates, laboratories that had not already done so were asked to submit a strain to RSIL for serotyping.

Enhanced surveillance in the 80+ year olds was established by the CfI from November 2003. From that date, all serotyped cases of IPD in this age group have been followed up with the reporting/referring laboratory to obtain the name and address of the patient's general practitioner who was then contacted for information on vaccination history, outcome of infection and underlying risk factors (for which pneumococcal immunisation was recommended prior to the introduction of the universal programme for the elderly). Enhanced surveillance of the 75-79 year olds commenced in April 2004 when the vaccination programme was rolled out to this age group.

The results of the follow up of cases of IPD in 80+ year olds identified by the joint CfI database between 4th November 2003 to 4th November 2004 are reported here.

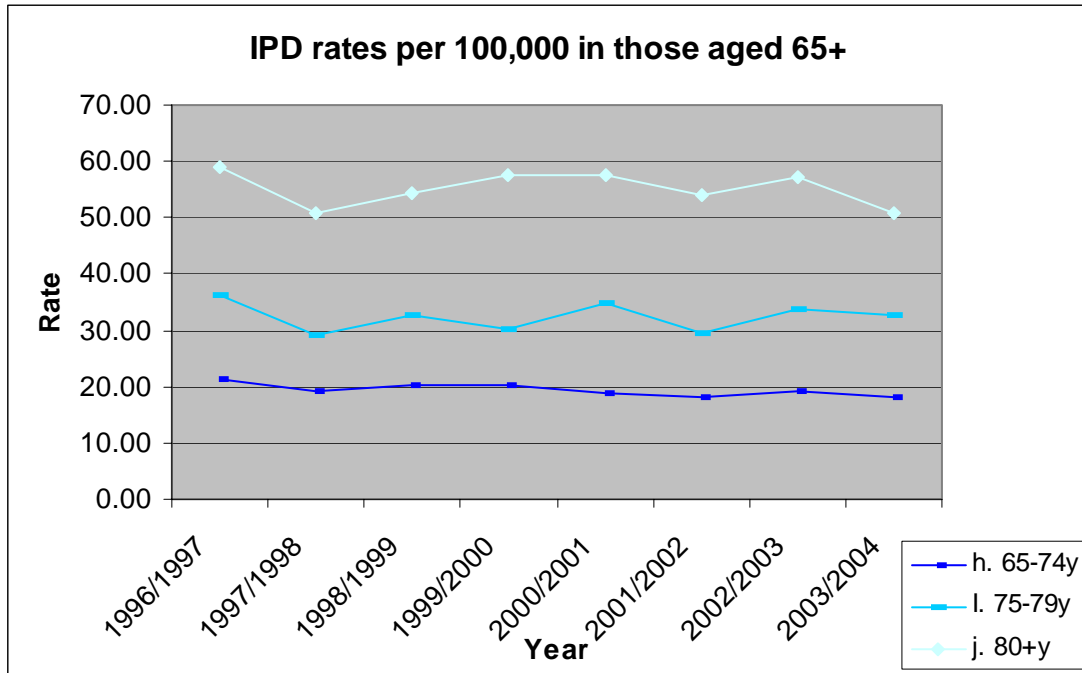
Incidence pre and post programme

The rates of IPD per 100,000 population in the 80+ age group have remained fairly stable since 1996/1997 with an annual average over the period of 55.8 per 100,000 (Table 1). In 2003/4 there was a 9% reduction in IPD reports in this age group; in contrast incidence rates in all other age groups were higher in 2003/4 than the average annual over the previous 7 years with the exception of the 65-74 year olds who showed a reduction of 8% in 2003/4 to 18.0 from an average of 19.6 per 100,000 (Table 1, figure).

Table 1: Age-specific rate per 100,000 population by epidemiological year. July to June in England and Wales*.

Age Group	1996/97- 2002/03		2003/04	
	Total Reports	Average annual rate per 100,000	Reports	Annual rate per 100,000
<1y	2074	47.8	354	58.5
1-4y	2327	12.9	364	15.1
5-9y	507	2.1	77	2.4
10-14y	244	1.0	34	1.0
15-44y	4932	3.2	809	3.7
45-64y	6467	7.6	1035	8.1
65-74y	6045	19.6	795	18.0
75-79y	3938	32.2	562	32.7
80+y	8423	55.8	1175	50.8
Total	34958	9.5	5206	9.9

* Based on reconciled joint IPD dataset held at CfI



Interpretation of the change post programme

In the 80+ age group the standard deviation of the annual rate from 1996/97 to 2002/03 was 2.8 with no trend over time. Therefore a 95% confidence interval for the average rate is 50.2 to 61.4, which would give an approximate 95% confidence interval for the change in 2003/04 from a 1% increase to a 17% decrease, the observed change of -9% being within this range. If efficacy against all IPD for vaccination in the programme versus not vaccinated or vaccinated before the programme began is 64% (see later) and with a coverage 26%, then a reduction of 16.6% would be expected in the 2003/4 epidemiological year in the 80+ age group. In practice, individuals were only recommended for vaccination from August 2003 onwards so a coverage estimate of 26% is too high and the actual coverage of the at-risk population during this year was likely to be only 15-20%. Thus a smaller reduction than 16.6% would be expected - around 9% to 13%, and assuming no protection afforded to individuals vaccinated prior to the 2003/4 epidemiological year. The observed change in IPD incidence in the 80+ age group, though small, is therefore consistent with that expected.

Enhanced surveillance of IPD in the elderly.

During 04/11/2003 to 04/11/2004 a total of 1,184 reports of IPD were received by the CfI in 80+ year olds, 62% of which (739/1184) had a strain submitted to RSIL for serotyping; of these, 242 had been referred as a result of the active request for submission of an isolate for serotyping. Serotype was successfully determined for 736/739 of referred strains.

GP details were obtained for 650 patients with isolates that were serotyped by RSIL. To date over 90% (603/650) of GPs contacted have completed the follow-up questionnaire. A response rate of 81.9% (603/736) of all serotyped reports has been achieved to date in the 80+ years age group.

Vaccination History

Over one half of patients for whom there was a GP response were unvaccinated (302/603), approximately one third (197/603) were vaccinated prior to infection, and vaccine status was not known in 17.2% (104/603) of reports.

Of those individuals who were vaccinated prior to infection, 56/197 were vaccinated as part of the elderly vaccination programme (ie since August 2003), the remainder being vaccinated prior to the programme. The majority of those vaccinated prior to the programme were in a clinical risk group for which vaccination was recommended under the former selective programme (83%, 117/141) compared with 52% (29/56) among those vaccinated since August 2003.

Serotype Distribution

92% (555/603) of serotyped isolates from patients with a GP response were included in the 23-valent plain polysaccharide vaccine, based on exact serotype without assumption of cross protection within serogroups. The proportion of reports that were potentially vaccine-preventable varied according to PPV history (Table 2), with recently vaccinated cases having a lower proportion of vaccine-preventable serotypes.

Table 2: PPV-preventable serotypes in 80+ year olds with IPD by vaccine history

Time since PPV	Vaccine-preventable			%Vaccine preventable
	Yes	No	Total	
<2years	48	13	61	78.7
2-4 years	49	5	54	90.7
5-10 years	73	4	77	94.8
>10 years	5		5	100.0
Not vaccinated	280	22	302	92.7
Vaccine history NK	100	4	104	96.2
Total	555	48	603	92.0

Demographics and mortality

Sex distribution did not vary according to vaccination status (p 0.404); overall, 58.6% (353/602 reports) with gender information were female (1 report gender NK).

Outcome data were available for 518/603 reports; the overall cases fatality rate was 56%. (Table 3) There was no evidence of a lower case-fatality rate in vaccinated individuals.

Table 3: Outcome by vaccine history

Vaccine Status	No	Yes	Died		Total
			Fatality	Not Known	
Vaccinated in programme	21	28	57.1%	7	56
Vaccinated prior to programme	61	71	53.8%	9	141
Unvaccinated	133	142	51.6%	27	302
Vaccination status NK	14	48	77.4%*	42	104
Grand Total	229	289	55.8%	85	603

**Excludes NK. Many GP practices have returned the questionnaires stating that the patient has died, but omitted vaccine history or clinical information. The immunisation department is actively following-up cases with an unknown vaccine history and/or outcome in order to minimise bias, this process is ongoing.*

At this stage of the surveillance PPV has had no effect on the mortality rate of IPD in the 80+ year old group.

Vaccine Coverage

Vaccine uptake in the 80+ age group has been estimated as 26.1% since August 2003 and 36.2% in the 10 years prior to the start of the programme (August 1993 to August 2003). These estimates are based on returns to the CfI from 237 of the 303 (78.2%) PCTs in England.

Vaccine Effectiveness ¹

Vaccine effectiveness was calculated using the screening method [1] (which requires information on the proportion of cases vaccinated compared with the proportion of the population in that age group vaccinated) and the Broome method [2] (which only requires information on the proportion of vaccinated cases infected with a vaccine-preventable serotype compared with the proportion in unvaccinated cases). With both measures, the effect of time since vaccination has been explored.

Screening method:

The proportion of cases vaccinated by time since vaccination was calculated from the data given in Table 2. Corresponding coverage estimates were made for two scenarios. The conservative scenario (ie likely to underestimate coverage and therefore vaccine effectiveness) assumed 26% vaccination within 2 years of disease onset, 17% from 2-4 years, 17% from 5-10 years and 40% unvaccinated. A non-conservative scenario assumed 36% vaccinated with 2 years, 12% from 2-4 years and 12% from 5 to 10 years and again 40% unvaccinated. Note that when calculating effectiveness, coverage is corrected to only include those vaccinated within the period of interest or unvaccinated (e.g corrected cover = $0.26/(0.26+0.4) = 0.39$) with those vaccinated outside the period of interest excluded from the analysis.

¹ The term effectiveness is used to note the direct protection afforded to vaccinees as measured in a non randomised post-marketing observational study. Efficacy is reserved for protection as measured in a randomised controlled trial.

Finally a conservative effectiveness estimate was calculated by comparing those vaccinated within the programme to those vaccinated outside the programme or unvaccinated.

Effectiveness estimates are for protection against the serotypes in the vaccine unless otherwise stated.

Broome method:

This method compares the vaccination status of persons with vaccine and non-vaccine serotypes. This method assumes that vaccinated individuals are at the same risk of non-vaccine type infections as unvaccinated persons

$$VE = 1 - OR$$

(where OR is the odds ratio of a person with a vaccine serotype being vaccinated compared to that of a person with non-vaccine serotype)

Table 4: Vaccine effectiveness estimates by the screening and Broome methods

Method	Definition of vaccinated	Comparison group	VE (95% CI)
Screening	In the Programme (26% cover)	Not vaccinated in the programme or unvaccinated	70% (59-79)*
Screening	Within 2 years (with 26% cover)	Unvaccinated	73% (63-81)
Screening	Within 2 years (with 36% cover)	Unvaccinated	81% (74-86)
Broome	In the programme	Not vaccinated in the programme or unvaccinated	75% (46-89)
Broome	Within 2 years	Unvaccinated	71% (34-78)

*If efficacy is calculated against **any IPD** then the estimate is 64% with 95% CI 52%-73%.

Efficacy by time since vaccination

Efficacy was also calculated by the screening and Broome methods for those vaccinated 2-4 years and 5-10 years previously.

Table 5: Efficacy by time since vaccination

Method	Definition of vaccinated	Comparison group	VE (95% CI)
Screening	2 - 4 years (cover = 17%)	Unvaccinated	41% (20-58)
Screening	5 – 10 years (cover = 17%)	Unvaccinated	13% (-13-33)
Broome	2-4 years	Unvaccinated	23% (-144-74)
Broome	5 – 10 years	Unvaccinated	-43% (-408 – 55)

Efficacy is much lower than the estimates within 2 years of vaccination.

Comment

Enhanced surveillance of IPD has shown evidence of around 70% protection against vaccine-type IPD in 80+ year olds vaccinated within the 2 years prior to infection using two independent epidemiological methods. This is in a patient group in whom over half have identified risk factors for IPD. Meta-analysis of PPV efficacy estimates from RCTs and effectiveness estimates from observational studies in the 65+ age group have suggested that there is only moderate protection in high risk patients - around 20% [3]. However, the high risk populations included in the meta-analysis were generally patients with more clinically severe conditions such as hospitalised with COPD or bronchogenic carcinoma.

Although PPV coverage in the 80+ year age group may not yet be sufficiently high to observe a major effect at a population level, the observed reduction of 9% in the incidence of IPD in 80+ age group in England and Wales in the period July 2003 to June 2004, is encouraging. This reduction in IPD incidence in 80+ year olds in 2003/4 is compatible with a 70% effectiveness against vaccine serotype IPD in this age group, 93% of IPD cases in unvaccinated being due to vaccine serotypes and an estimated average coverage during the epidemiological year 2003/4 of around 15-20%, the actual coverage between August 2003 and March April 2004 being 26%. No effect of vaccination on case fatality rate was apparent but mortality data are currently incomplete; moreover attribution of causality is often difficult to determine, even when risk factor data are available. Plans are in progress to link IPD cases with

ONS deaths in order to obtain more complete vital status data and information on underlying conditions predisposing to a fatal outcome.

The scheme of enhanced laboratory surveillance is now well established. The response rate to our requests for strains and information has been encouraging with laboratories responding to 89% of the requests and GPs responding to 93% of our letters. The CfI continues to follow up outstanding requests for information in this age group through reminder letters and telephone follow-up where appropriate. From 01/01/2004, the enhanced surveillance was extended to include all cases of IPD known to the CfI in the 75+ year group. To date we have received 380 reports in this age group, 225 have been serotyped, and we have received 103 responses from GPs. It is anticipated that sufficient data will be available from mid 2005 in order to assess the impact and in this group. From April 2005, the enhanced surveillance scheme will be extended to include the 65+ year group.

References

[1] Farrington C.P. Estimation of vaccine effectiveness using the screening method. *International Journal of Epidemiology*, 1993; 22: 742-746.

[2] Broome CV, Facklam RR, Fraser DW. Pneumococcal disease after pneumococcal vaccination: an alternative method to estimate efficacy of pneumococcal vaccination. *N Engl J Med* 1980; 303 (10):549-52.

[3] Melegaro A and Edmunds J. The 23 valent pneumococcal polysaccharide vaccine. Part 1. Efficacy of PPV in the elderly: a comparison of meta-analyses. *Euro J Epidem* 2004; 19: 253-364.