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Product name: **Prevenar**
Procedure No. EMEA/H/C/000323/II/0080

SCIENTIFIC DISCUSSION

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I. SCIENTIFIC DISCUSSION

1.1. Introduction

Prevenar is a pneumococcal conjugate vaccine developed by Wyeth Lederle Vaccines. The vaccine contains capsular polysaccharide of 7 serotypes conjugated to a carrier protein. The European Marketing Authorisation was granted in February 2001 for use in infants and young children from 2 months through 2 years of age for the prevention of invasive pneumococcal disease (IPD). Following a type II variation (EMEA/H/C/323/II/18) in August 2004, the indication was extended to children aged 24 months to 5 years. The indication was further extended in January 2007 to include protection against otitis media caused by the serotypes against which Prevenar protects (EMEA/H/C/323/II/76).

Prevenar is a sterile solution of saccharides of the capsular antigen of Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F individually conjugated to the non-toxic mutant of diphtheria toxin (CRM197 protein). The vaccine is presented in single dose (0.5 ml) vials and pre-filled syringes.
The infant primary vaccination schedule consists of three doses beginning at 2 months of age and given with an interval of at least one month between doses. A booster dose is recommended in the second year of life. Previously unvaccinated infants from 7-11 months are recommended to receive three doses, children from 12-23 months of age are recommended to receive two doses and children aged 24 months - 5 years one single dose. The route of administration is deep intramuscular injection.

The pre-licensure pivotal efficacy trial in US infants (Northern California Kaiser Permanente (NCKP) trial) demonstrated vaccine efficacy (VE: 87% (95% CI: 7, 99)) against bacteraemic pneumonia, which was included in the indication of Prevenar. However, overall reduction of clinical pneumonia was only 10% (95% CI: 0.1; 19.8). At the time of the granting of the initial Marketing Authorisation, protection against pneumonia could not be sufficiently demonstrated. Therefore the data on clinical pneumonia was only included in section 5.1 of the SPC.

The MAH submitted this application to include pneumonia caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F other than those associated to with bacteraemia in infants and children from 2 months of age to 5 years of age.
During the Vaccine Working Party (VWP) meeting in January 2007, the overall wording of the indication was discussed in view of the addition of otitis media to the indication (variation II-76, which received a positive opinion in January 2007).

No new clinical study reports supporting the proposed extension of indication to include prevention of pneumonia were submitted. However, additional data from the NCKP trial, data from two trials conducted post-licensure with an investigational 9-valent pneumococcal CRM197 conjugate vaccine (PCV9) and data from a US post-marketing surveillance study were provided. All new documentation was provided in the form of published articles in scientific journals.

1.2 Clinical aspects

1.2.1 Rationale for the proposed change

The efficacy of Prevenar against IPD is well established and has been documented in several studies. Population-based post-marketing analysis of the impact of Prevenar in the US has reported a 69% decline (~1.3 fewer episodes per 1000 children) in culture-confirmed invasive pneumococcal disease in children <2 years by 2001 *(Whitney et al. 2003)* Apart from the observed reduction in vaccine type disease among children below 5 years after the introduction of Prevenar in the child immunisation program in the US, indirect effects (herd immunity) have been observed in older children, adults and in the elderly >65 years.

IPD is the most severe clinical manifestation of the pneumococcal disease spectrum, but represents a small fraction of the pneumococcal disease burden. In Europe today, the reported incidence of IPD among children less than 2 years of age is about 40 cases per 100,000 children per year. By contrast, it

is estimated that, each year, about one percent of young children would have an episode of pneumococcal pneumonia.

Bacterial pneumonia is a significant cause of paediatric morbidity and mortality, particularly in less developed countries where most of the yearly 2 million deaths due to pneumonia are reported. The microbiologic aetiology of pneumonia remains problematic in the absence of standardised, non-invasive, diagnostic tools that are both sensitive and specific.

Efficacy against bacteraemic pneumonia cannot be projected to that against non-bacteraemic pneumonia, which represents the overwhelming fraction of pneumonia cases. Whereas vaccine induced antibodies are effective against pneumococcal bacteraemia, they may not have a similar effect on pneumococcus at the mucosal level where higher antibody concentrations are required for protection. It is further possible that an increase in non-bacteraemic infections, caused by non-vaccine serotypes, may have partly offset the reduction due to vaccine serotypes (although this phenomenon has had little impact on the overall effect against invasive diseases).

Paediatric community acquired pneumonia (CAP) is a medical condition that is not clearly delineated. Although clinical features have not been evaluated thoroughly, tachypnoea, as suggested by the World Health Organisation (WHO), appears to be the main predictive clinical sign. In practice, the best available method for diagnosis of pneumonia is chest radiography. Within this background of diagnostic imprecision, a few studies have evaluated the incidence rates of pneumonia. In developed countries, rates in children less than 5 years of age range from 30 to 40 per 1,000 child-years. In developing countries, incidence rates are, on the average, five to ten times greater, and pneumonia causes 20% of the deaths in children less than 5 years.

Establishing the aetiological diagnosis of paediatric CAP is a complicated problem in clinical practice. Many viruses, and bacteria that include S. pneumoniae, can cause pneumonia, and mixed infections or bacterial supra-infections are common. Taken together, studies show that 25 to 40% of radiologically proven pneumonia can presumably be considered as pneumococcal. These projections were concurrent with the estimates of vaccine preventable fraction of pneumonia from the recent double-blind, controlled trials of pneumococcal conjugate vaccines (trials in the Republic of South Africa, The Gambia, and at NCKP, see below). Since vaccine efficacy cannot be 100%, the vaccine-preventable fraction that ranged from 20 to 37% likely underestimates the pneumococcal contribution to pneumonia.

Serotype distribution in complicated pneumonia has been described in one multi-centre, retrospective, US study that involved 368 children hospitalised for pneumococcal pneumonia. Of these 368 cases, 133 children were considered to suffer from a complicated form of pneumonia (essentially, pleural effusion or empyema). Whereas 86.5% of strains from uncomplicated pneumonia were Prevenar serotypes, only 58.3% of isolates were Prevenar types in complicated presentations *(Tan TQ et al. 2002).*

As the published studies indicated protection against pneumococcal pneumonia, the MAH presented the available data to support the extension of the indication to include protection against pneumonia caused by Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.

1.2.2 Clinical Data

NCKP efficacy trial *(Black S. et al.)*

Between October 1995 and August 1998, 37,868 healthy, 2-month-old infants were enrolled in this study, and they received either Prevenar or a control vaccine at 2, 4, 6 and 12-15 months of age, concomitantly with other recommended infant vaccines. Cases of pneumonia (seen in the outpatient clinic, emergency room, or hospital) were identified through the computerised databases of diagnosis made by the treating physician at NCKP, which included bronchopneumonia, viral pneumonia, pneumonia with consolidation, and pleural empyema. A positive radiograph, defined as any area of

consolidation, empyema, or a parenchyma infiltrate, was considered to correspond more likely to a bacterial infection. At the end of blinded follow-up in April 1999, the study population included children up to the age of 3.5 years.

Of 11 cases of bacteraemic pneumococcal pneumonia that occurred during follow-up in this trial, pneumococcal isolates from 9 cases were vaccine serotypes in the intent-to-treat analysis; 8 were from control patients. The effectiveness estimate was 87.5% (p = 0.04). Including the two additional nonvaccine serotype cases in controls for an analysis of all serotypes, the effectiveness was 90.0% (p = 0.01). One case was observed among vaccinees.

To measure the vaccine-induced reduction in incidence of clinical pneumonia that cannot be microbiologically proven to be of pneumococcal aetiology, multiple outcomes were analysed:

- The first episodes of any clinical diagnosis of pneumonia, the outcome of highest sensitivity but lacking specificity, were decreased by 4.3% (p=0.27).

- Among children who completed their immunisation series per protocol, the rate of clinical pneumonia with a positive radiograph, the outcome of higher specificity but less sensitive, was reduced by 20.5% (95% CI, 4.4 to 34.0%). Vaccine efficacy was greatest for children younger than 2 years: 32.2% (95% CI, 3.3 to 52.5%) in less than one year of age and 23.4% (95% CI, 5.2 to 38.1%) in less than two years of age. Vaccine efficacy estimate was lower in those older than 2 years, 9.1% (p=0.61). Based on the intent-to-treat analysis with an incidence rate of 10.6 cases per 1,000 child-years, it was estimated that there would be approximately 5 cases of clinical pneumonia with a positive radiograph, as defined by the authors, prevented per 1,000 infants immunised, before they reach the age of 2 years.

Table 1: Efficacy for first episode of pneumonia in children receiving Prevenar versus controls.

Outcome	Intent-to-Treat			Per-Protocol		
	Cases/1000 person-years		VE % (95% CI)	Cases/1000 person-years		VE % (95% CI)
	Prevenar	Control		Prevenar	Control	
All clinical pneumonia	43.5	45.8	6.0 (-1.5-11.0); P=0.13	53.4	55.9	4.3 (-3.5-11.5); P=0.27
Clinical pneumonia, radiograph obtained	26.3	28.9	8.9 (0.9-16.3); P=0.03	30.9	34.2	9.8 (0.1-18.5); P=0.05
Clinical pneumonia, positive radiograph	8.3	10.1	17.7 (4.8-28.9); P=0.01	8.7	11.0	20.5 (4.4-34.0); P=0.02

The data from the NCKP trial were extrapolated to the population of children aged less than 2 years living in the 25 Member States of the EU (birth cohort statistics, preliminary estimates for 2005, Eurostat 01-2006). Applied to a birth cohort of 4,816,400 infants, the number of radiologically defined pneumonia would be 102,100 per year in children less than 2 years. The projected number of vaccine-prevented episodes of radiologically confirmed pneumonia in this age group would be about 24,000 in any one year, considering that 5 episodes would be prevented in the first two years of life per 1,000 vaccinated children.

It was acknowledged that the effectiveness of Prevenar against pneumonia was demonstrated in the NCKP trial. The overall reduction (4.3%) (p=0.27) of the primary outcome measure was, however, low. Efficacy was more promising in the group with positive radiographs (20.5%), however the calculated vaccine efficacy value for this group was lower in children older than 2 years, 9.1% (p=0.61).

For those with potentially more serious pneumonia (consolidation), the efficacy was 73%. These data suggest that pneumococcal infections play a more important role in severe disease, which is clinically relevant. However, at the time of the initial Marketing Authorisation the CHMP considered that the pneumonia part of the NCKP trial suffered from important deficiencies, since there were no pre-specified criteria for the diagnosis and no bacteriologic confirmation. Taking this into consideration, the CHMP did not approve a pneumonia indication at the time of the granting of the initial Marketing Authorisation, but the effectiveness data on pneumonia were included in section 5.1 of the SPC.

The CHMP noted that the NCKP data suggested a waning protection against radiologically confirmed pneumonia in children >2 years. The reasons for the apparent lack of benefit of Prevenar in older children were considered unclear. Similar decreases in effectiveness against invasive pneumococcal disease (or acute otitis media (AOM)) with age have not been demonstrated, so it was not considered likely that this finding represents waning immunity in this age group. The CHMP therefore requested that the apparent age differences in effectiveness of Prevenar should be further discussed by the MAH.

The MAH indicated in his response that the expected value for vaccine effectiveness was based on the assumption that the onset and the duration of a vaccine-induced protective immune response match the peak incidence of the vaccine-targeted infection.

Black S, et al. have re-evaluated the effectiveness of Prevenar against pneumonia using WHO-criteria for reading chest radiographs (issued in 2001). Overall, vaccine efficacy against a first episode of clinical pneumonia with a positive radiograph was 30.3% (95% CI: 14.7- 45.7) in the per protocol analysis (*Hansen J, et al.*). However, this analysis did not include stratification by age.

Several factors including waning immunity and lower contribution of pneumococcal vaccine serotypes to pneumonia, could explain this observed waning protection in older children as mentioned in the initial publication (Black S, et al.). Waning immunity has not been observed for invasive diseases. Vaccine efficacy against IPD caused by vaccine serotypes (VST) has remained high, 97.4%, through the same follow up period of the NCKP trial in the per protocol analysis of April 1999 (*Black S, et al.).*

In the Finnish Otitis Media (FinOM) follow up study, which was included in the previously submitted variation to extend the indication to include AOM (EMEA/H/C/000323/II/0076) and followed the study children up to the age of 5 years, nasopharyngeal carriage of vaccine serotypes was reduced in the Prevenar group, 8.5% versus 13.0% (relative risk of 0.62, 95% CI: 0.41- 0.95) (*Palmu A, et al.*). This global trend for lower carriage of vaccine serotype pneumococci among vaccinated children in the FinOM follow up study was considered not supportive of a hypothesis of "waning immunity" in older children.

The MAH further responded that altogether, it was unlikely that waning immunity was a predominant factor for the lower protection against pneumonia that has been observed in children older than 2 years of age. By contrast, it was considered that the contribution of vaccine serotypes to the total burden of pneumonia might change as a function of age. In older children, vaccine serotypes may represent a decreasing proportion of pneumococcal pneumonia. Epidemiological studies on IPD in European children have shown a natural trend for the seven vaccine serotypes to have a lower contribution to disease in older children (*Miller E et al., Perez Mendez C et al., McIntosh E et al., Vergison A et al.).*

Replacement of vaccine serotypes by non-vaccine serotypes has been reported in AOM during the FinOM trial during the study follow-up period up to the age of 24 months (*Palmu A, et al.*). Because the large majority of pneumonia cases were mucosal, non-invasive infections, such a phenomenon could not be ruled out. It was also considered possible that pneumococcal pneumonia represents a smaller percentage of pneumonia in children older than 2 years because other bacterial pathogens (Mycoplasma pneumoniae or Chlamydia pneumoniae) cause a larger fraction in the older age group.

In general, the CHMP agreed that most often paediatric pneumonia is not bacteraemic, however the aetiology of childhood pneumonia cannot be identified in the vast majority of cases as no reliable non-invasive diagnostic procedures are available that could be used routinely. Therefore, the CHMP agreed

that it was not possible to investigate what could be the contribution of these microbiological factors to the observed waning protection against clinical pneumonia in children above 2 years of age.

In conclusion, the CHMP agreed that according to the NCKP trial the fraction of disease burden preventable by Prevenar, in the EU each year, for children in the first two years of life would represent approximately 24,000 episodes of radiologically defined pneumonia.

Placebo-controlled trials with an investigational PCV9 in South-Africa and Gambia

The investigational PCV9 vaccine used in these studies contained the seven pneumococcal CRM197-conjugated antigens in Prevenar, plus serotype 1 and 5 CRM197 glycoconjugates. Both studies included CAP endpoints. Children in the study populations were poor and represented a population characteristic for developing countries. In addition, a substantial proportion of children in the South African study, about 25%, were born to HIV-infected mothers.
In these two trials, microbiological diagnoses could not be made for the CAP-related endpoints. Assuming that the serotype distribution in these clinical entities was similar to that in IPD in the same population, the likely impact of the seven Prevenar components could then be calculated.

South African trial (Klugman Ket al.)

In this South African study (n=39836), 19,922 children received the 9-valent pneumococcal polysaccharide vaccine conjugated to CRM197, and 19,914 received placebo (both at 6, 10, and 14 weeks of age). All children received Haemophilus influenzae type b conjugate vaccine. Efficacy and safety were analysed according to the intention- to-treat principle.

Clinical pneumonia was defined as radiologically confirmed pneumonia or a clinical diagnosis of lower respiratory tract infections (LRTI), without wheeze on auscultation, but with crackles and/or bronchial breathing. Severe pneumonia was defined as cough of less than 14 days with lower chest wall indrawing and/or feeding difficulties, convulsions, central cyanosis or encephalopathy.

In the per-protocol analysis, there were 113 first episodes of pneumonia among HIV-negative children receiving PCV9 and 158 among HIV-negative controls, for a vaccine efficacy estimate of 25% (95% CI: 4-41%).

Mortality was not significantly reduced: 5% among all children and 6% among HIV-infected subjects. Pneumonia and bronchiolitis were associated with 66% of deaths among study subjects. There were 153 deaths attributable to pneumonia in the PCV9 group and 160 in the control group, for a 4% reduction in mortality attributable to pneumonia (p=NS). The results from the Intention-to Treat (ITT)-analysis can be found in table 2.

Table 2: Efficacy of PCV9 against first episodes of radiographically confirmed pneumonia; intent-to-treat analysis. South-Africa (VE= Vaccine efficacy)

	PCV9	Control	VE (95% CI)	p
HIV-negative	169	212	20 (2, 35)	0.03
HIV-positive	182	209	13 (-7, 29)	0.19
All children	336	428	17 (4, 28)	0.01

Efficacy against virus-associated pneumonia in the South African study (for which a pneumococcal aetiology could not be confirmed by blood culture) was 31% (95% CI, 15 to 43%). This effect was significant for HIV-infected children but did not reach statistical significance for HIV-uninfected

children. These observations provide evidence of the role of pneumococcal superinfection in virus-associated pneumonia in this study in children whose conditions required admission. In particular, there was significant efficacy against influenza A-associated pneumonia, both overall and in HIV-infected children

In the South African study, the efficacy against IPD caused by any of the seven Prevenar types was 72%, an estimate that is very similar to that against IPD caused by any of the nine types in PCV9. Immune responses to Prevenar were similar to the overall response to the serotypes in the PCV9 vaccine; therefore, it was considered that efficacy against Prevenar type pneumonia would be similar to that against PCV9 type pneumonia, but that the overall efficacy against pneumococcal pneumonia might be about 10 to 15% lower because of reduced serotype coverage. This would signify an efficacy for Prevenar against radiologically confirmed pneumonia of 20 to 30% and against all clinical pneumonia of 5 to 6%. These projections were congruent with the results from the NCKP study.

With respect to pneumonia, efficacy was only presented for radiologically confirmed pneumonia (VE: 17% in the total cohort). As argued by the authors, the use of a radiological endpoint probably underestimated the true vaccine efficacy, since the specificity of alveolar consolidation, as a diagnostic test of pneumococcal pneumonia is suboptimal. Among HIV-negative children, there were 169 first episodes among PCV9 recipients and 212 among controls, for a VE of 20% (per-protocol 25%). These findings were similar to those of the Kaiser trial for radiological pneumonia . For the HIV infected children in South Africa, the study failed to show statistically significant efficacy against radiologically confirmed pneumonia (13%, 95% CI, -7 to 29%). However, the burden of vaccine preventable pneumonia was 909 cases per 100,000 child-years in this infected population, whereas it was 100/100,000 child-years in the HIV-uninfected population.

However, the burden of vaccine preventable pneumonia was 909 cases per 100,000 child-years in this infected population, whereas it was 100/100,000 child-years in the HIV-uninfected population. The lower efficacy estimate might be influenced by other pathogens such as Pneumocystis carinii infecting the HIV-infected population.

An important finding was the observed efficacy of the vaccine against antibiotic resistant strains. Overall, the vaccine reduced the incidence of penicillin-resistant pneumococci by 67%. Antibiotic resistant strains were more commonly reported in HIV-infected children, with penicillin-resistant strains found in one third of IPD cases. Currently, almost all drug-resistant clones belong to the 7 vaccine serotypes.

The 9-valent vaccine differed from Prevenar as it contained 2 additional serotypes (1 and 5). These two serotypes, however, occurred in few IPD cases: serotype 1 was identified in 1 of a total of 11 cases in the vaccine group vs. 4 of 43 cases in the placebo group.

The corresponding figures for serotype 5 were 0 vs. 2. The most common vaccine serotypes in the placebo group were 6B and 14 as well as the related serotype 6A. A non-significant increase of non-vaccine serotype IPD was seen among vaccinated subjects, but the limited number of cases (13 vs. 9 placebo cases) allows no conclusion to be drawn.

Overall, this controlled study showed significant efficacy of the PCV9 vaccine against IPD and pneumonia. Efficacy against vaccine serotype IPD was 72% and, thus, somewhat lower than that seen in the NCKP trial (VE: 93%). These results might be partly explained by the inclusion of HIV-positive children in the African trial, for whom vaccine efficacy was lower (65% vs. 83% for HIV-negative children). This was the first efficacy study in HIV-infected children and showed that the pneumococcal conjugate vaccine is also useful in this high risk group. The level of protection obtained in this study was observed over a mean follow-up of 2.3 years without a booster dose.

Vaccine efficacy against bacteraemic pneumococcal CAP caused by a vaccine serotype was 61% (95% CI, 16 to 82%) in the ITT analysis, whereas the VE estimate was not statistically significant in the PP analysis.

The CHMP considered that this large controlled trial in South Africa using a pneumococcal conjugate vaccine similar to Prevenar provided supporting data with respect to efficacy against radiologically confirmed pneumonia.

Gambian trial (Cutts F et al.)

In this study carried out in The Gambia (n=17437), clinical pneumonia was defined as history of cough or breathing difficulty of less than 14 days' duration, with a raised respiratory rate for age or with indrawing of the lower chest wall. If a doctor diagnosed indrawing, the pneumonia was classified as severe. About 10% of cases were classified as severe.

The primary endpoint of this independent study was a pneumonia outcome measure and thus, this study confirmed and defined more precisely vaccine efficacy against pneumonia with consolidation. The study demonstrated that the 9-valent vaccine had high efficacy against radiological pneumonia (VE: 36% ITT-analysis, 37% per-protocol analysis) and substantially reduced admissions and improved child survival. No decrease of vaccine efficacy with age was noted in this study by contrast to observation in the Kaiser trial. However, a malaria diagnosis seemed to reduce vaccine efficacy.

Vaccine efficacy against radiological pneumonia attributed to the vaccine serotypes was 70% (95% CI: 31-88) (see also table 3 below).

The extent of vaccine efficacy against vaccine serotype invasive disease (VE: 71% ITT) was similar to that noted in the South African trial (VE: 72%). Test for HIV infection was not performed in this study.
Overall 65% of IPD episodes were of serotypes contained in the 9-valent vaccine and 48% were of serotypes in Prevenar. Thus, a greater effect on IPD was noted for the 9PCV vaccine. The most common serotypes causing IPD were 14, 5 and 23F. A non-significant increase in non-vaccine serotypes was observed, but the full potential of replacement diseases could not be assessed since children were randomised individually. Indirect protection was not evaluated, which needs to be monitored also in a developing country setting.

The preventable burden of pneumococcal-related pneumonia was at least 7 times greater than that of invasive pneumococcal disease (absolute rate 15 vs. 2 episodes per 1000 child years). The finding of a 16% reduction in mortality suggested that CAP is a more common cause of childhood mortality than previously recognised.

Table 3: Efficacy of PCV9 against first episodes of radiographically confirmed pneumonia, per-protocol analysis (Gambia).

	Vaccine (n=8189)		Placebo (n=8151)		VE % (95% CI)
	Number	Rate/1000 child-years(95% CI)	Number	Rate/1000 child-years (95% CI)	
Overall	333	26 (23.3, 28.9)	513	40.9 (37.5, 44.6)	37 (27, 45)
Age (months)					
3-11	124	34.4 (28.8, 41.0)	188	53.0 (45.9, 61.1)	35 (19, 48)
12-23	181	25.8 (22.3, 29.9)	285	41.7 (37.1, 46.8)	38 (25, 49)
24-29	28	12.7 (8.8, 18.4)	40	18.7 (13.7, 25.4)	32 (-10, 58)
Admission Status					

	Vaccine (n=8189)		Placebo (n=8151)		VE % (95% CI)
	Number	Rate/1000 child-years(95% CI)	Number	Rate/1000 child-years (95% CI)	
Outpatient	180	14.0 (12.1, 16.2)	253	20.2 (17.8, 22.8)	30 (15, 43)
Inpatient	153	11.9 (10.2, 14.0)	260	20.7 (18.4, 23.4)	42 (30, 53)
Vaccine Serotypes					
X-ray positive	8	0.6 (0.3, 1.2)	26	2.0 (1.4, 3.0)	70 (31, 88)
Lung aspirate	3	0.2 0.07, 0.7)	11	0.8 (0.5, 1.5)	73 (-2, 95)
All Serotypes					
X-ray positive	19	1.5 (0.9, 2.3)	45	3.5 (2.6, 4.7)	58 (27, 77)
Lung aspirate	6	0.5 (0.2, 1.0)	20	1.5 (1.0, 2.4)	68 (18, 89)

The efficacy against clinical pneumonia was low; overall 7% in the per-protocol analysis and 6% in the ITT analysis. This might be due to the low specificity of the clinical diagnosis with misclassification of clinical pneumonia.

However, efficacy was significant against all pneumonia, as well as radiologically confirmed pneumonia, in both trials. Amongst HIV-negative children (over 90% of children in South Africa), efficacy estimates were higher for radiologically confirmed pneumonia: 37% (95% CI, 25 to 48%), in the South African trial.

1.2.3 Post-marketing experience

Prevenar in clinical pneumonia in the US and indirect effects of vaccination (herd immunity)

In the US, the impact that routine infant immunisation with Prevenar had on invasive pneumococcal diseases including bacteraemic pneumonia is well documented. Its impact on CAP has been evaluated in a US population-based surveillance program for CAP among enrolees of Group Health Cooperative, a commercial insurance program in the State of Washington *(Nelson JC et al. 2005*). Pneumonia cases were identified as ICD9 codes for diagnosis made at inpatients or outpatients visits, and chest radiographs reports and hospitalisations records were reviewed. Among children less than 2 years, age-specific rates of CAP were lower in 2003-2004, 19.3 per 1,000 child-years, compared to time periods before Prevenar (1998-2000) or during its introduction phase (2001-2002), when rates were estimated to be 21.3 and 25.4/1,000 child-years, respectively. Furthermore, the authors reported that a more pronounced reduction was noted on hospitalised cases in this age group, with an incidence rate ratio of 0.56 (95% CI, 0.40 to 0.79) for the years 2003-2004 versus 1998-2000. A consistent reduction in CAP rates in older children and adults after PCV 7 introduction was not detected. In this report, a comparison was made between the incidence rate during pre- and post-Prevenar time periods. Differences in case ascertainment, in intercurrent viral infections and changes in the degree of surveillance consequent to the introduction of pneumococcal vaccination were potential biases that may affect such comparison. Nonetheless, such a reduction was consistent with the expected direct effect of Prevenar on CAP in this age group.

The CHMP considered that this population-based surveillance program for CAP provided evidence that the introduction of Prevenar has resulted in reduction of CAP rates in the age group 0-2 years. However, no indirect effects in older children and adults were detected and no consistent reduction in CAP rates was noted in these age groups.

The CHMP therefore considered that this observation needed to be addressed by the MAH, especially in the light of the substantial decrease in the incidence of invasive pneumococcal disease reported among older adults after the introduction of US-wide childhood immunisation with Prevenar.

The MAH responded that in this study, consistent variations in age-specific rates of community-acquired pneumonia (CAP) for all age groups, except young children less than 2 years of age were described. Compared to the pre-vaccine era, rates increased in the study years 2001 - 2002, and then slightly decreased in 2003 - 2004. Overall, these findings do not provide any evidence of an indirect effect (herd immunity) for pneumonia in older children or in adults

As there was no aetiological diagnosis of pneumonia, it was considered impossible to investigate whether a reduction in pneumococcal pneumonia due to vaccine serotypes would have been overshadowed, either by an increase in cases due to non-vaccine serotypes, or by other pathogens including influenza that could contribute to the burden of pneumonia in adults. In young children, pneumococcal pneumonia may result from the mucosal spread of pneumococcus to the lower respiratory tract related to the nasopharyngeal carriage of this pathogen. Despite the absence of diagnostic methods to identify the causative agent in pneumonia, the observed reduction in rates of CAP in children less than 2 years of age indicates that replacement by non vaccine serotypes did not blunt the beneficial reduction in cases caused by vaccine serotypes. This age group is the most susceptible to pneumococcal infections because protective immunity would not have been established without vaccination. Therefore, one may speculate that these non-vaccine serotypes are associated with a lower likelihood of pneumonia in older children and adults. Nonetheless, the possible role of host factors specific to the elderly, that leave this age group more susceptible, cannot be ruled out.

Additionally, several factors in the adult population might have led to an increase in reported cases of CAP that would obscure a true decrease in pneumococcal pneumonia caused by vaccine serotypes. These include possible changes over time in the diagnosis and treatment practices for pneumonia, as well inconsistencies in diagnosis codes.

Pneumonia in adults and the elderly is also associated with influenza infection, and variations in the severity of influenza seasons are known. Such variations were considered likely to influence the reported rates of pneumonia in any given season.

The absence of a microbiological diagnosis for pneumonia, together with the fact that it was not possible to explore possible factors that would influence the rates of reported pneumonia, were limitations to this study.

The CHMP acknowledged the limitations of the study.

Population-based impact of pneumococcal conjugate vaccine in young children (Poehling KA et al.)

The primary objective of this observational study was to evaluate the reduction in pneumococcal diseases on a population basis after the introduction of Prevenar in the US, and it was the first to document declines in all pneumococcal-related diseases since the introduction of Prevenar in children aged < 2 years.

Using reviews of medical insurance databases in two geographically and demographically distinct US regions (Tennessee and Rochester, New York), the authors measured annual rates of medical visits for pneumococcal-related diseases (otitis media, pneumococcal and non-specific pneumonia, and invasive disease) for children aged less than 2 years and children aged 3-5 years in the years prior to (1995-2000 for Tennessee; 1998-2000 for New York) and the two years after (2000-2002) Prevenar introduction. Expected disease rates were calculated for children aged less than 2 years in each post-vaccine year, and the difference between the expected and observed rates was defined as the estimated vaccine effect. Additionally, ratios of disease rates between children aged less than 2 years and those aged 3-5 years were calculated (because vaccine-related outcomes should preferentially decline in vaccinated children, and because year-to-year variability in pneumococcal diseases should affect both

age groups equally on an absolute incidence basis). Potentially important differences between these populations include overall lower socioeconomic status and higher proportion of racial/ethnic minorities in the Tennessee population, with a two-fold greater proportion of children under 2 years who were considered "high-risk" than the New York population.

The Tennessee population included 442,281 child-years of observation for children <2 years and 586,027 child-years of observation for children aged 3-5 years; child-years of observation for the same age groups in the New York population were 44,233 and 77,540, respectively. These observation times were further broken down into three time periods: 1) baseline (1995-2000 for Tennessee; 1998-2000 for New York), 2) a transition period during which practitioners began to use Prevenar (2000-2001), and 3) a post-Prevenar period (2001-2002). For the post-Prevenar year, there were 67,380 child-years of observation for children <2 years in Tennessee, and 9,485 child-years of observation for the same age group in New York. The rate of visits for pneumonia and invasive disease for children <2 years was higher in Tennessee (110-135/1000 child-years) than in New York (87/1000 child-years), whereas the rate of visits for otitis media was higher in New York (2125-2247/1000 child-years for children <2 years and 795-903/1000 child-years for children aged 3-5 years) than in Tennessee (1175-2019 and 471-562 visits/1000 child-years for each age group, respectively). Rates of visits for pneumonia and invasive disease were similar in each area for children aged 3-5 years (44-53/1000 child-years).

To control for yearly variability in disease rates, rate ratios (children aged <2 years vs. 3-5 years) were calculated for each disease for each year and population (Tennessee and New York).
Finally, the authors calculated the estimated vaccine effects on medical visits for pneumococcal-related diagnoses, based on the product of 1) the average ratios for the 2 pre-vaccine years (1998-2000) and 2) observed rates in children aged 3-5 years. Compared with the pre-vaccine baseline, it was estimated that the significant declines in pneumonia and invasive disease represented a decrease of 8 emergency department (ED) visits and 12 outpatient (clinic) visits per 1000 Tennessee children, and 33 fewer outpatient visits per 1000 New York children. A higher decrease was noted for otitis media. Per 1000 Tennessee children, significant declines in otitis media represented 56 fewer ED visits and 62 fewer outpatient visits. Declines in ED visits were similar for New York children, an estimated 34 fewer visits per 1000 children; outpatient visits for otitis media were most drastically reduced in this group, with 396 fewer outpatient visits for otitis media per 1000 children.

The overall impact of routine Prevenar vaccination on pneumonia and otitis media in this study was 10-fold and 100-fold greater, respectively, than the reported decrease of 1.3 culture-confirmed invasive pneumococcal disease cases per 1000 children in 2001, as reported by the US Centers for Disease Control and Prevention (*Whitney C et al*) and were also considerably greater than estimated by the pre-licensure experience at NCKP (*Black S et al. 2001)*.
The CHMP considered that this study had several limitations, i.e. a) the vaccination status of the children in the post vaccine years was not known (the results with a greater decrease in culture-confirmed pneumococcal disease in New York (92%) than Tennessee (69%) suggests that New York had a higher uptake), b) the study population was selected including only those who qualified for commercial insurance in the two states, c) potential errors in the administrative database (e.g. possible inconsistency in diagnostic codes; multiple visits for a single episode of illness may be indistinguishable; and only billed visits would be included) and d) lack of confirmation of pneumococcal disease as the causative study outcomes.

Additionally, vaccine shortages in 2001-2002 may have decreased the vaccination rate overall, and so the findings of this study may in fact be an underestimation of the impact of Prevenar vaccination on pneumococcal and pneumococcal related diseases.
diseases. However, the results of this population-based study were considered important. With regard to invasive disease and pneumonia, there was a 16% decline in hospitalisations and a 17% decline in outpatient visits in Tennessee. A larger decline was noted in New York, with outpatient visits being reduced by 35% compared to the pre-vaccination period.

In conclusion, this population-based study provided data on the impact of routine vaccination with Prevenar on pneumonia (and invasive disease) in children <2 years. Rates of hospitalisations, emergency visits and outpatients visits for pneumonia fell by 16 to 18% as compared to pre-

vaccination rates. Due to high prevalence of pneumonia, the impact of Prevenar in this study was 10-fold greater than the reported declines in invasive disease in children aged <2 years. Based on the data from the NCKP trial, it was estimated that for every episode of invasive disease prevented, Prevenar would prevent on average 4.4 episodes of pneumonia.

Continued Surveillance of pneumococcal disease - serotype replacement and antibiotic resistance

The CHMP considered that there is a need for further continued surveillance of prevalence of invasive pneumococcal disease in order to study serotype replacement with potential virulent organisms, emergence of antibiotic resistance in non- vaccine pneumococcal serotypes and any modification in the clinical manifestations of the disease.

A small increase in the frequency of disease caused by non-vaccine serotypes has been observed; while in general these newly emerging serotypes are susceptible to penicillin (with the exception of serotype 19A in the United States (US) *(Kyaw M, et al)*, the ability of organisms to acquire resistance determinants is well known. Additionally, considerable declines have also been observed in bacteraemic pneumonia incidence during the same time period. Recent reports demonstrate a shift in pneumococcal disease states such that pneumonia now makes up a greater proportion of the total documented number of all IPD in US children less than 5 years of age than in the pre-vaccine era. The reasons for this observation were unclear: but could be in part related to outbreaks caused by serotypes not included in the vaccine independent of any vaccine selection pressure *(Byington C, et al.)*.

The MAH presented surveillance programmes in the EU; some of these at least in part supported by Wyeth. The MAH also presented a discussion of the surveillance programs of several European countries, including type and scope of surveillance, funding sources, and outcomes of such surveillance programs.

The CHMP considered that surveillance studies should also include a close monitoring of pneumonia and nasopharyngeal carriage with respect to serotype replacement and bacteriological shifts as well as patterns of antibiotic resistance in the EU. Therefore the MAH was requested by the CHMP to present an overview on this issue.

The MAH pointed out in his response that less than 5% of paediatric pneumonia were bacteraemic or complicated by pleural effusion. Therefore, in the absence of sensitive and specific non-invasive diagnostic methods, laboratory confirmation of the aetiology will not be obtained for most paediatric pneumonia. Consequently, the assessment of the impact that Prevenar immunisation programs will have on pneumonia will be essentially based on monitoring clinically defined syndromes.

The MAH presented an overview from population-based surveillance programmes, based on computerised databases of hospital admissions and of general practitioners consultations in the UK, where Prevenar was introduced in September 2006 (Melegaro A, et al.) and the Netherlands, where Prevenar was introduced for all infants in June 2006.

Furthermore, a five-year surveillance of nasopharyngeal carriage among young French children aged 6 to 24 months presenting with AOM was set up in 2001, when Prevenar was introduced in France, to follow evolving patterns of S. pneumoniae microbiology and antibiotic resistance trends. In July 2006, routine immunisation with Prevenar was recommended for all infants less than 2 years of age.

In addition, a study of nasopharyngeal colonisation will be performed in 6-24 month olds from 2007 to 2011 as a follow up assessment to the above mentioned study EU-005 (“Evaluation of pneumococcal carriage in French children younger than 2 years of age”) in France.

The MAH has previously committed in the frame of the variation EMEA/H/C/323/II/76 to extend this surveillance program for another period of 5 years until 2011. During the 2006-07-study year, approximately 90 paediatricians and 30 general practitioners throughout France will collect nasopharyngeal swabs from two groups of children, 6 to 24 months of age, presenting at their clinics.

At the same practices, approximately 700 children who are presenting with AOM and 300 children who are otherwise healthy will be enrolled each year.

The CHMP considered the response acceptable and agreed with the MAH's commitments to monitor serotype replacement and antibiotic resistance.

Overall, the CHMP considered that the planned surveillance programmes would be sufficient to detect potential shifts in the serotype distribution.

Extrapolation of available data to the European setting

The MAH presented an overview concerning vaccine- attributable reduction in pneumococcal disease among European children less than 2 years or 2 to 5 years of age.

In the European Union, the published values for the serotype coverage for IPD in children < 2 years of age range from 54 to 85% (median value, 73%); for children 2 to 5 years of age, they range from 48 to 73% (median value, 61%).

Based on national reports from Europe, the serotype coverage rate for IPD in children 2 to 5 years of age was about 10 percentage points less than for children < 2 years of age. Furthermore, in these surveillance systems, which are mostly passive and laboratory based (essentially, by hospital, region or city), the reported incidence of invasive pneumococcal disease (cases per 100,000 population per year) in children less than 2 years of age varies widely from 5.9 to 174 (median value, 26). The burden of paediatric IPD in Europe is considerable, even though the reported incidences vary 100-fold from country to country. Nonetheless, it remains difficult to obtain the actual rates for some countries. Under-reporting, differences in reporting methods, antibiotic prescribing and disparities in blood-culturing practices may distort the true picture, although real differences do exist due to variability in pneumococcal carriage, transmission, exposure and susceptibility among different populations.

By contrast to IPD, there is less variability in the reported rates of pneumococcal meningitis (range, 3.0 to 16.1; median value, 9), which probably reflects the diligence with which any clinician faces of a suspected case of bacterial meningitis. Although few European countries have reported specifically the rates of invasive pneumococcal disease in the 2- to 5- year- old age group, incidence values range from 2.4 to 29.6 for IPD (median value, 8) and from 1.0 to 2.4 for pneumococcal meningitis (median value, 2).

From these national reports in Europe, a three- to four- fold greater rate of invasive pneumococcal disease was observed in children less than 2 years of age compared to children 2 to 5 years of age. Taken together, it could be estimated that impact of Prevenar against the reported invasive pneumococcal disease burden in European children would be as outlined in the Table 4.

Table 4: Anticipated Prevenar impact against the reported IPD burden in European children

		IPD incidence	Serotype coverage	Estimated decrease in IPD cases (per 100,000 children per year)
Low estimate	< 2 years old	5.9	54%	3.4
	2 to 5 years old	3.0	48%	1.4
High estimate	< 2 years old	174	85%	148
	2 to 5 years old	16.1	73%	12

The anticipated vaccine- attributable reduction in pneumococcal disease is from two (3.4/1.4) to twelve (148/12) times larger for children less than 2 years of age than for children 2 to 5 years of age. In the absence of wide variations in the degree of poverty, crowding or underlying chronic diseases across Europe, any disparity in the effectiveness of Prevenar could be therefore attributable to the age of the paediatric group under investigation. Consequently, Prevenar vaccination in Europe would reduce most of the disease burden because the vaccine serotypes target the paediatric population that has the greatest rates of pneumococcal disease, namely young children less than 2 years of age.

Impact of vaccination on the incidence of pneumonia in children < 2 years of age in the EU

As the CHMP considered that the current database on efficacy was comparably weak and primarily based on US data, the MAH was requested to submit a detailed programme on how the impact of incidence of pneumonia in children < 2 years of age will be studied in the EU.

The MAH responded that Prevenar showed to be effective against childhood pneumonia, both blood culture-positive episodes ("bacteraemic pneumonia") that were caused by the vaccine serotypes and radiograph-positive episodes that, in the absence of sensitive and specific detection methods, were assumed to have been caused by the vaccine serotypes. With respect to the impact of Prevenar immunisation on nasopharyngeal colonisation, a decrease in the proportion of vaccine serotypes was observed that was compensated for by an increase in the proportion of non-vaccine serotypes.

The result of Prevenar vaccination on another mucosal surface, in this case, infections of the middle ear, has also been studied, and the impact on vaccine and non-vaccine serotypes documented. In the FinOM trial, a shift upon Prevenar immunisation for the pneumococcal serotypes isolated from children presenting with a first episode of AOM could be observed.

For the Prevenar serotypes, this was equivalent to a vaccine efficacy value of 57%, and for serotype 6A, a vaccine efficacy value of 57% was also measured. There appeared to be a decrease for episodes caused by most of the other vaccine-related serotypes (for 19A, 9N, and 23A, but not 18B). On the other hand, for episodes caused by the non-vaccine serogroups, there was no change (serotype 3 and 22), a slight increase (serogroup 15, 16, 35 and 38), or a more substantial increase (serogroups 33 and 11) in the Hepatitis B group compared to the Prevenar group.

Although there were no comparable data for paediatric pneumonia because of the paucity of clinical isolates, one can speculate, based on the results for AOM, that pneumonia caused by non-vaccine serotypes is unlikely to overshadow the benefits of the reduction in vaccine serotype disease. Post-Prevenar surveillance establishes that a substantial fall in the incidence of vaccine serotype IPD has been tempered by a small increase in the incidence of non-vaccine serotype IPD, leading to an overall positive protective effectiveness of Prevenar against all IPD episodes. With respect to non- invasive pneumococcal disease, as exemplified by blood culture-negative/radiograph-positive episodes of pneumonia, the role of non-vaccine serotypes in eventual "serotype replacement" pneumococcal disease remains to be elucidated.

In preparation for the introduction of Prevenar into the National Immunisation Program in the United Kingdom, the Health Protection Agency (*Melegaro A, et al.*) has reassessed the burden of pneumococcal disease. Based on a statistical model that used national data sources and general practitioner sentinel surveillance systems, from 1995 to 2000, it was estimated that:

- S. pneumoniae is responsible for 26% of general practitioner consultations for community-acquired pneumonia.
- The incidence of outpatient pneumonia, children less than 2 years of age, is about 100 episodes/100,000 population/year.
- The incidence of hospitalisation for "lobar pneumonia (organism unspecified)", in children 1 to 11 months of age, is 260 / 100,000 population/year.

In a two-year prospective study of 13 UK hospitals between 2001 and 2002 (*Clark J, et al.*), the incidence among children less than 5 years of age with "severe" CAP was 194 cases/100,000/year, of lobar pneumonia "assessed in hospital" was 56 cases/100,000 population/year, and of hospitalisation for CAP was 320 admissions/100,000 population/year.

Taken together with previous surveillance results from Europe for the incidence of CAP in children less than 2 years of age (Clark J, et al.), the range of values for community-based surveillance is roughly 100 to 2000 cases/100,000 population/year, and for hospital-based surveillance about 300 to 2000 cases/100,000 population/year.

Consequently, as an order of magnitude, the annual incidence for CAP in children less than 2 years of age is about 1000 cases / 100,000 population.

Based on the assumption that the pneumococcus is responsible for about one-third of childhood CAP, the incidence of pneumococcal CAP in young European children is roughly 300 cases / 100,000 population / year, leading to an order of magnitude in Europe (birth cohort, 4.9 million) of about 29,000 annual pneumococcal CAP cases among children less than 2 years of age.

The efficacy of a pneumococcal conjugate vaccine against pneumococcal CAP should fall between the value for a mucosal infection (i.e., about 60% against pneumococcal AOM) and the value for an invasive infection (i.e., about 90% against IPD). Consequently, it can be anticipated in Europe that Prevenar could prevent each year between 18,000 and 26,000 cases of pneumococcal CAP in children less than 2 years of age.

Once Prevenar has been introduced into national immunisation programmes in Europe, ecological shifts in the circulation of pneumococcal serotypes within the population can be anticipated. Non-vaccine serotypes will predominate in colonisation of the nasopharynx of vaccinated children, which might lead to increased rates of disease.

Surveillance will continue in France for mucosal colonisation among young children suffering from AOM. This will provide an insight into potential non-vaccine serotype causes of pneumococcal CAP. Surveillance will continue throughout Europe for IPD, including bacteraemic pneumonia, which will provide documentation of any possible non-vaccine serotypes causing pneumococcal CAP. Finally, from the clinical perspective, large-scale surveillance of childhood pneumonia will be conducted in the United Kingdom and in the Netherlands to establish the short-term and long-term clinical effectiveness of Prevenar.

Current surveillance plans in Europe should establish the clinical effectiveness of Prevenar against CAP in both the short and long term perspectives. If long-term effectiveness of Prevenar against CAP cannot be established, "serotype replacement" might be an explanation. (The MAH is developing a 13-valent pneumococcal conjugate vaccine in Phase III trials that will additionally target clinical important "pediatric" and "outbreak" serotypes). Documentation of any important non-vaccine serotypes for mucosal disease is provided by the French study; whereas childhood IPD caused by non-vaccine serotypes is monitored in many European countries.

The CHMP agreed with the argumentation of the MAH and considered this point resolved.

Pre-Prevenar experience

The MAH also provided an overview of the clinical experience before the introduction of Prevenar in England and Wales (*Eastham et al. ,Taiwan (Hsieh Y et al.), Spain (Aristegui J et al.) and the US (Tan T et al.)*

It was concluded that in the period before introduction of Prevenar vaccination, complicated pneumonia cases fell into three categories, as described in table 5.

Table 5: Categories of complicated pneumonia cases before introduction of Prevenar, classified by the predominant serotypes / serogroups and their antibiotic sensitivity.
PenS = penicillin sensitive, PenR = penicillin resistant

Country	Predominant serotypes	Antibiotic susceptibility
England & Wales	Serogroups 1, 14 & 3	PenS
Taiwan	Serogroups 14, 6 & 23	PenR
USA	Serotypes 1, 3, 6B, 14 & 19F	Antibiotics "able to suppress partially the infection for a period of time"

The prevalence of antibiotic susceptibility among the clinical isolates may provide an explanation. England & Wales exemplified a setting where there is little antibiotic resistance, and complicated pneumonia cases tend to be associated with the 'outbreak' serotype 1, and the 'paediatric' serotypes, 14 and 3.

By contrast, in a country with a strong prevalence of antibiotic resistant pneumococcal strains in circulation, which is typical of Taiwan, the 'paediatric' serogroups 14, 6, and 23 cause all of the complicated pneumonia cases. Finally, the US seems to represent an epidemiology that falls somewhere between the previous extremes, which may be a dual result of moderate antibiotic usage and of the wide scale introduction of Prevenar into the National Immunisation Program. For the Prevenar serotypes, there has been a decrease in 6B, 14 & 23F isolates from cases of complicated pneumonia, but no change for 19F. For the non-vaccine serotypes, there is a continuing predominance of serotype 1 and an increase in serotypes 3 and 19A cases. In conclusion, to rely on coverage for a particular serotype (i.e. the proportion of clinical isolates belonging to a given serotype) without precisely defining the underlying, age-specific incidence of IPD may be misleading. Relying solely on "serotype coverage proportions" can propagate confusion about the pertinence of any set of epidemiological data, and it is important that serotype-specific and age group-specific, population-based surveillance is maintained and enhanced in Europe.

The CHMP considered that the MAH has given a fair overview of the literature on the clinical experience before the introduction of Prevenar.

Complicated pneumococcal pneumonia (i.e. empyema, complex parapneumonic effusion, or necrotising pneumonia) in children

Parapneumonic empyema (PPE) can be a complication of pneumonia in children, which has been reported from England & Wales, Taiwan and the US. Among the organisms that can be isolated from the pleural fluid Streptococcus pneumoniae is the pathogen most often identified in cases of paediatric PPE. Other bacterial pathogens include Staphylococcus aureus and Streptococcus pyogenes, but the prevalence of these contributory microorganisms varies across studies. In addition to uncomplicated pneumonia in young children and complicated pneumococcal pneumonia in older children, outbreaks of pneumococcal disease, especially pneumonia, that were due to epidemic serotypes (such as serogroups 1, 5, 8, or 12) were reported in the literature. These occur most characteristically among close-living collections of non-elderly adults (e.g., homeless shelters, jails and military settings) or in "crowded, often impoverished, communal settings." These outbreaks of pneumococcal disease, especially pneumonia, were due to epidemic serotypes among certain narrow age ranges, such as neonates and older children, as well as outbreaks in adults. Continuing surveillance will determine their importance among the target group for Prevenar vaccination in Europe. As will be addressed in the remainder of this response, complicated pneumococcal pneumonia (i.e., empyema, complex parapneumonic effusion, or necrotising pneumonia) tends to be caused by relatively few pneumococcal serogroups (i.e., serogroups 1, 3, 6, 19, and 23), occurring among older children at a rate of about 5 cases / 100,000 population/year.

1.2.4 Risk Management

Although no formal Risk Management Plan was submitted at the time of the initial Marketing Authorisation in 2001 or at the 5- year renewal earlier in 2006 the MAH has several clinical studies ongoing as follow up commitments to the Marketing Authorisation. The information obtained from these, together with the data from surveillance programs in place in a number of countries, will ensure that there is a continued review of the risk benefit ratio for Prevenar. Any change observed will be notified to the appropriate authorities. The CHMP also agreed that the addition of pneumonia to the indications for Prevenar would not fundamentally change the use of the vaccine; however, this indication should help to improve compliance with national recommendations to enhance vaccination uptake.

Listed below are the ongoing studies with Prevenar that Wyeth has undertaken to respond to the outstanding MAH commitments, which addressed questions raised at the time of granting of the Marketing Authorisation or which originate from other post-authorisation procedures.

- **EU-002:** Population based nationwide surveillance of invasive pneumococcal disease in France.
- **EU-003:** Population based study (100170) on systemic pneumococcal infections (SPI) among children in Germany (2000 – 2003).
- **EU- 005:** Evaluation of pneumococcal carriage in French children younger than 2 years of age.
- **6106A1- 500:** Study to assess the effect of prophylactic use of antipyretics. Report to be submitted 30 July 2007 6106A1- 800: PM surveillance study on fever related events and febrile seizures.
- **100681:** Comparison of early and late immunisations of 3 doses of conjugate vaccine in allogenic stem cell transplant subjects.

Surveillance for antimicrobial resistance trends was considered an important part of IPD surveillance. To that end, the European Antimicrobial Resistance Surveillance System (EARSS) has been implemented to conduct ongoing surveillance regarding antimicrobial susceptibility trends across Europe. EARSS is a European surveillance and information system that provides validated data on the prevalence and spread of major disease- causing bacteria with resistance to one or more antibiotics. EARSS performs ongoing surveillance of seven indicator bacteria commonly causing infections in humans including Streptococcus pneumoniae.

Finally, results of an EU wide survey funded by the European Union project on pneumococcal disease (PnC - EURPO) has recently summarised all publicly funded national surveillance programs across the EU and presents, in tabular form, the data elements being collected by each program (*Pebody RG, et al.).*

Several European countries have adopted routine vaccination with Prevenar (e. g., Germany, France, The Netherlands, Norway, and the UK). In a number of these European countries, such as France, Norway and the UK, the public health authorities have launched surveillance programs that will closely monitor the evolution of the serotype distribution in invasive disease and the antibiotic susceptibility of pneumococcal isolates. It should be noted that the individual public health authorities run these surveillance programs. In Germany, a population-based nationwide surveillance of IPD cases among children requiring hospitalisation (ESPED) is ongoing.

Since Germany introduced Prevenar into the national immunisation programme in the summer of 2006, the MAH has previously committed to fund this surveillance study for an additional two years (2007 - 2008). This surveillance was considered appropriate by the CHMP to detect and monitor the extent of serotype replacement for invasive disease and to provide information on antibiotic susceptibility of emerging strains.

Epidemiological studies based on nasopharyngeal culture may provide insights into the microbiology of non-invasive pneumococcal infections. In France, the MAH will conduct a continuing 10-year

study on the microbiology of the nasopharyngeal flora associated with AOM in children 6-24 months of age. Furthermore, the MAH has engaged in a number of surveillance studies to monitor pneumococcal disease.

1.2.5 Overall Discussion and conclusion

Following the assessment of the data from the NCKP trial, the CHMP considered that the potential risks with the use of the vaccine need to be addressed. Serotype replacement might reduce the benefit of the vaccine and change the epidemiology of pneumococcal disease, which may have adverse consequences for children over time. As demonstrated for otitis media in the US, widespread use of Prevenar has resulted in replacement of vaccine types by non-vaccine types in nasopharyngeal carriage.

In the FinOM trial a significant increase in AOM episodes due to non-vaccine serotype was observed, reducing VE against pneumococcal AOM from 57% to 34%. Several subsequent carriage studies have documented shifts towards non-vaccine pneumococcal serotypes. Corresponding data on pneumonia were considered more limited.

However, in both 9PCV trials an increase of non-vaccine serotype invasive disease in vaccinated children compared with placebo was noted, although at a non-significant level. The CHMP therefore considered that this phenomenon deserves close monitoring. For pneumonia, serotype replacement with potential virulent organisms, emergence of antibiotic resistance in non-vaccine pneumococcal serotypes and any modification in the clinical manifestations of the disease should be specifically addressed. Until now most surveillance studies have been performed in the US, but data should also be collected in the EU, since serotype epidemiology and resistance pattern differ substantially between continents and countries. The CHMP considered that the MAH presented satisfactory plans for surveillance in his response.

The CHMP also noted that invasive disease from non-vaccine serotypes has increased up to a 3-fold post Prevenar vaccine licensure, which may also be the case for pneumonia.

Additionally, an increased occurrence of empyema was reported from UK and other countries. Empyema or parapneumonic empyema (PPE) is most frequently associated with pneumococcal serotype 1, a serotype not contained in Prevenar. A US report from Texas stated that PPE in the post-PCV era is more common, representing up to one-third of the IPD in children. Serotype 1 remains the most common but it appears that serotypes 3 and 19A are emerging.

The CHMP was also concerned that more virulent serotypes will take over the place/space left by vaccine serotypes. Other authors do not confirm an increase in empyema and even report a decrease in number of patients with empyema. In other countries an increase in empyema is seen but this increase does not seem concordant with Prevenar usage. The surveillance systems put in place by the MAH were considered sufficient to address the issue of such serotype shifts.

The MAH stated in his submission that in view of the magnitude of the pneumonia burden, the vaccine efficacy shown in pre- and post-licensure experiences against acquired pneumonia (CAP) represents important population wide, long-term, public health benefits. Although the short-term balance looked favourable, the CHMP considered that the long-term evolution of pneumococcal invasive disease as well as empyema by non –vaccine serotypes is not yet clear.

The claim that Prevenar decreased the burden of ‘non-invasive pneumococcal’ pneumonia in young children seems correct, and the data have been published in a peer-reviewed journal. A post marketing surveillance study reports a decrease in pneumonia and two 9-valent vaccine trials also document a decrease in clinical pneumonia and radiologically defined pneumonia; which adds further support to the claim. Although the vaccine efficacy for pneumonia is lower than for invasive pneumococcal disease, the disease burden from pneumonia is larger and therefore the vaccine contribution to health is considerable.

The MAH provided an estimation of the extent of disease in the EU that could be prevented by the vaccine. The data from the NCKP trial were extrapolated to the EU population of children aged less than 2 years. The projected number of vaccine-prevented episodes of radiologically confirmed pneumonia in this age group would be about 24,000 in any one year, considering that 5 episodes would be prevented in the first two years of life per 1,000 vaccinated children. However, the CHMP pointed out that the next generation of pneumococcal conjugate vaccines including more serotypes could have an even greater effect.

The CHMP considered that the benefit-risk for Prevenar is positive for the extension of the indication from active immunisation against bacteraemic pneumonia to active immunisation against pneumonia. The target population was considered the same for both indications and the pneumonia indication will not result in any change in the use of the vaccine.