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Effectiveness of the 13-valent pneumococcal conjugate vaccine: Emerging data from invasive pneumococcal disease, pneumonia, acute otitis media and nasopharyngeal carriage

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A new WHO position paper has been published recently stressing the high priority of the inclusion of PCVs in childhood immunization programs worldwide. Planning for national use of pneumococcal vaccines should take besides other factors the distribution of pneumococcal serotypes in different age groups into consideration. In addition to the serotypes included in PCV7, PCV13 contains serotypes 1, 3, 5, 6A, 7F and 19A and this vaccine provides the broadest serotype coverage of PCVs globally. In Europe and the US, the vaccine was approved in late 2009 and early 2010, respectively. Only two years after introduction of PCV13 introduction into many NIPs globally, vaccine effectiveness for the PCV13 serotypes has been documented for several clinical outcomes (invasive pneumococcal disease (IPD), including sepsis/bacteremia and acute meningitis, community-acquired pneumonia, and acute otitis media) and nasopharyngeal carriage from several countries (USA, England and Wales, Germany, Spain, Uruguay, Israel). Moreover, serotype-specific effectiveness has been

demonstrated for serotypes 1, 6A, 7F and 19A, which were the most prevalent and emerging serotypes pre-PCV13 immunization.
***Key words**: pneumococcal disease, pneumococcal serotypes, prevention, pneumococcal conjugate vaccine, children.*

Streptococcus pneumoniae is a major source of morbidity and mortality worldwide. It is estimated by the WHO that approximately one million children die of pneumococcal disease every year, mostly in developing countries [1]. Pneumococcal infections are among the leading causes of death from a vaccine-preventable illness in children younger than 5 years of age [2]. Invasive diseases caused by pneumococci include meningitis, bacteremia, and pneumonia with bacteremia and/or empyema [3].

Only recently, a WHO position paper has been published (4) which replaces the 2007 position paper on 7-valent pneumococcal conjugate vaccine (PCV7) [1]. Incorporating the most recent developments in the field of pneumococcal vaccines this position paper focuses on PCVs and their introduction and use in national immunization programs. Of note, WHO recommends the inclusion of PCVs in childhood immunization programs world-wide. In particular, countries with high childhood mortality (i.e. under 5 mortality rate of >50 deaths/1000 births) should make the introduction of PCVs a high priority. Planning for national use of pneumococcal vaccines should take besides other factors the distribution of pneumococcal serotypes in different age groups into consideration.

The 13-valent pneumococcal conjugate (PCV13, Prevenar 13®, Pfizer Inc., NY, USA) was developed as a successor of the 7-valent pneumococcal conjugate vaccine (PCV7, which contains serotypes 4, 6B, 9V, 14, 18C, 19F and 23F; Prevnar®/Prevenar®, Pfizer Inc.), for use in infants and young children to prevent

disease such as invasive pneumococcal disease (IPD), non bacteremic pneumonia and acute otitis media (AOM), caused by the 13 pneumococcal serotypes contained in the vaccine. In addition to the serotypes in PCV7, PCV13 contains serotypes 1, 3, 5, 6A, 7F and 19A [5] and this vaccines offers the broadest serotype coverage [5, 6].

For PCV13, the global pediatric filings were initiated in late 2008 and, to date, regulatory applications for PCV13 have been approved in 98 countries (Pfizer, data on file, as of May 2012) spanning six continents. In Europe, the vaccine received positive feedback from the Committee for Medicinal Products for Human Use (CHMP) on 24th September 2009 and received market authorization on 11th December 2009. In the US, FDA approved Prevnar 13 on the 24th February (7). In Europe and the US, wide use of PCV13 started in early 2010 as part of mass vaccination programs, so that in many countries we now oversee up to two years of surveillance data of the post PCV13 era.

Given the proven efficacy and effectiveness of PCV7, it was widely accepted that clinical trials to assess the efficacy of a conjugate vaccine with expanded serotype coverage, using an unvaccinated control group, were not ethically feasible. Relative efficacy assessments using rare clinical end points such as IPD would have required very large study populations, as controls would have to be vaccinated with the available conjugate vaccine. Consequently, the immune response induced by the new 13-valent pneumococcal conjugate vaccine was used to provide an assessment of the protective efficacy of the vaccine. IgG-binding antibodies directed to the capsular polysaccharide, and the associated functional activity of these antibodies assessed by opsonophagocytosis assays (OPAs), are immunological correlates of protection. Accordingly, the recommendations of the

WHO issued in the technical report series [8] and the update of this technical report [9] were used for licensing of PCV13.

Global disease burden and serotype distribution: still limited data only for the Asian region

The wide use of PCV7 nearly eliminated the IPD burden by the 7 serotypes [10, 11]. Consequently, serotype epidemiology of IPD caused by non-PCV7 serotypes following the introduction of PCV7 was of particular interest and comprehensives global summaries of the prevailing and emerging serotypes causing IPD in children have shown that serotypes 1, 3, 5, 6A, 7F and 19A were emerging. Among those serotypes the emergence of serotype 19A has raised the greatest concern [12]. The serotypes included in PCV13 account for most of the invasive pneumococcal disease burdens, and the estimated serotype coverage in most regions globally was ranging between 80–90% [13].

While the burden of pneumococcal diseases is well described in developed regions such as Europe, and North America, data from many Asian countries are rather incomplete [13]. A recent review summarized the available literature for pneumococcal serotype data from the SE Asia region, and clearly highlighted the need for increased surveillance in this region of the world. The major concern in this region was the increasing prevalence of highly-resistant pneumococci due to routine antibiotic usage as documented by the Asian Network for Surveillance of Resistant Pathogens (ANSORP), an international organization dedicated to surveying antimicrobial resistance in bacteria in the Asian region. Based on the limited data available the authors described serotypes 19F, 23F, 14, 6B, 1 and 3 to be the most prevalent in the region and calculate a serotype coverage of 46% and 65% for PCV7 and PCV13, respectively [14]. These findings are in agreement

with the systematic review on pneumococcal serotypes causing IPD in children aged less than 5 years globally by Johnson et al. [15].

Effectiveness of PCV7 and PCV13

Over nearly a decade, PCV7 has demonstrated high efficacy against invasive pneumococcal diseases caused by vaccine serotypes in children younger than 2 years of age. Its effectiveness has been confirmed under routine use in the USA [11] and many other countries [16]. As PCV7 has shown dramatic reduction in disease and mortality rates in the countries in which it has been introduced, the newly introduced 13-valent pneumococcal vaccine was also expected to have substantial additional disease impact. Monitoring of vaccine effectiveness was, therefore, essential to determine the true impact, in particular for the six additional serotypes included in PCV13 and not included in PCV7.

While pre licensure clinical trials provide essential information on the efficacy of a vaccine in carefully monitored circumstances and trial procedures tend to maximize follow-up and assure complete immunization in as high a proportion of subjects as possible, post licensure surveillance also provides valuable information on vaccine performance that complements data from pre licensure studies. A primary question regarding post licensure is whether the vaccine's effectiveness is similar, worse or better than that predicted from the clinical trials (efficacy). For pneumococcal disease, a carful interpretation of these results needs to be done, as among other factors access to vaccination and natural fluctuation of serotypes (e.g. serotype 1) has to be taken into consideration [17].

Population-based data on the incidence of IPD in England and Wales (2+1 schedule)

A recent publication on the population-based incidence of IPD in England and Wales reported on a total of 264 children born since April 2008 and aged <24 months. Vaccine effectiveness by dose and serotype was estimated for the 6 additional serotypes in PCV13 using the indirect cohort method, in which cases with non-vaccine serotype IPD acted as controls. Vaccine effectiveness was calculated as 1 minus the odds of vaccination in those with IPD due to a PCV13 serotype/odds of vaccination in those with IPD due to a non-PCV13 serotype. Cases were categorized into those eligible to receive one or more priming doses of PCV13 at age 2 or 4 months (and aged between 2.5 and 13 months at time of infection) and those eligible for the 13-month booster dose who had received doses of either PCV7 and/or PCV13 at age 2 and 4 months (and were aged between 13 and 23.9 months at time of infection). Among 166 IPD cases reported by July 2011 in PCV13 eligible children with known serotype and vaccination status, PCV13 effectiveness was 78% (95% confidence interval[CI] -18% to 96%) for 2 doses in children 1 year of age and younger and 77% (95% CI 38% to 91%) for 1 dose in children over 1 year of age. There were sufficient cases to estimate serotype-specific vaccine effectiveness for at least 1 dose given in the first or second year of life for serotypes 1, 3, 7F, and 19A. Significant protection was demonstrated for serotypes 7F and 19A with an effectiveness of 76% (95% CI 21% to 93%) and 70% (95% CI 10% to 90%) for ≥1 dose, respectively. This study also reported vaccine effectiveness of 62% and 66% for serotypes 1 and 3, respectively, although the CIs spanned zero [18]. At a recent scientific meeting (International Symposium on Pneumococci and Pneumococcal Diseases-8 [ISPPD-8], 2012), an update on the IPD effectiveness from England and Wales (18) was provided based on a total of 466 IPD cases. Vaccine effectiveness for the additional six PCV13 serotypes and serotype 6C after two primary doses (≤12 months of age) was 79% (95% CI, 38 to 93) and after one dose (>12 months of age) 66% (95% CI, 26 to

85). Interestingly, vaccine effectiveness after 2 primary doses was particularly good (statistically significant, over 80%) for serotype 1 [19]. In addition, up to date IPD surveillance data is available online and shows a significant reduction of reported IPD cases by the 6 additional serotypes after introduction of PCV13 (Figure 1).

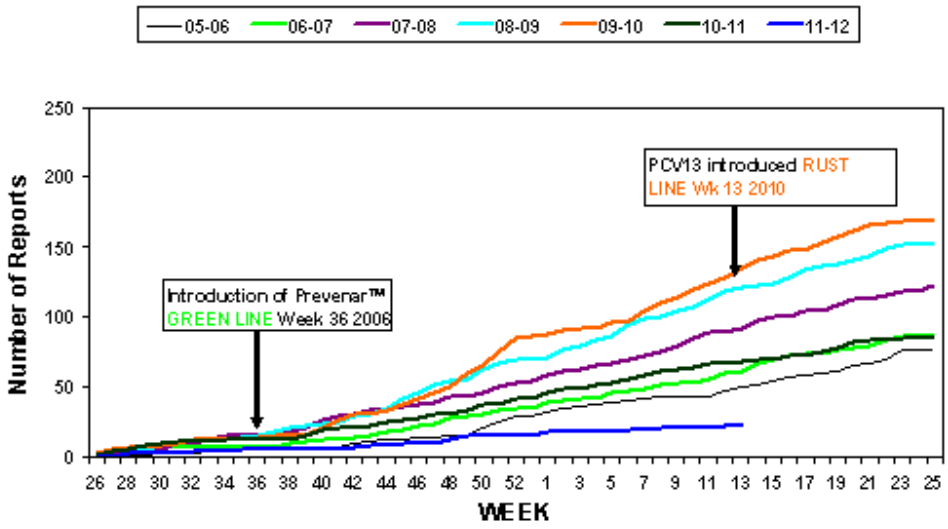

Figure 1; Cumulative weekly number of reports of IPD due to any of the six serotypes in PCV13 but not in PCV7 in children aged < 2 Years in England and Wales by epidemiological year (July-June), 2007- 2012.

Source: Health Protection Agency, Centre for Infections Homepage: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Pneumococcal/EpidemiologicalDataPneumococcal/CurrentEpidemiologyPneumococcal/InPrevenar13NotInPrevenarPCV7/pneumo07Cummulativeweeklyunder2IN13NOTIN7vacc/ accessed May 9th 2012.

Population-based data on the incidence of IPD from the United States (3+1 schedule)

In the United States, IPD is monitored through Active Bacterial Core surveillance (ABCs), an active population and laboratory-based system [11]. The analyses include cases reported in 8 continuously participating ABCs sites: selected counties in California, Georgia, Maryland, Minnesota, New York, Oregon, and Tennessee, and the state of Connecticut. The total population under surveillance was 19,060,270, according to 2007 post-census population estimates. Data from this surveillance system were presented as an oral presentation at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in September 2011 (20) and updated at the ISPPD meeting in 2012 [21]. IPD incidence during the baseline period 2006 through 2008 was used for comparison. IPD rates for PCV13 serotypes were significantly lower ($p<0.0025$, compared with rates for respective quarters during the baseline period) in the fourth quarter of 2010 (8.5 cases per 100,000 vs. 24.1 cases per 100,000) and the first quarter of 2011 (7.2 cases per 100,000 vs. 27 cases per 100,000) after the initiation of wide use of PCV13 in the first quarter of 2010. Statistically significant reductions in IPD rates due to PCV13 serotypes 7F (-86%) and 19A (-87%) were also reported. At a recent online conference at the Centers for Disease Control and Prevention, CDC, C.M. Cox presented data on cumulative cases of the 6 additional serotypes in PCV13 in children <2 years old, showing a significant reduction of incidence (Figure 2) [22].

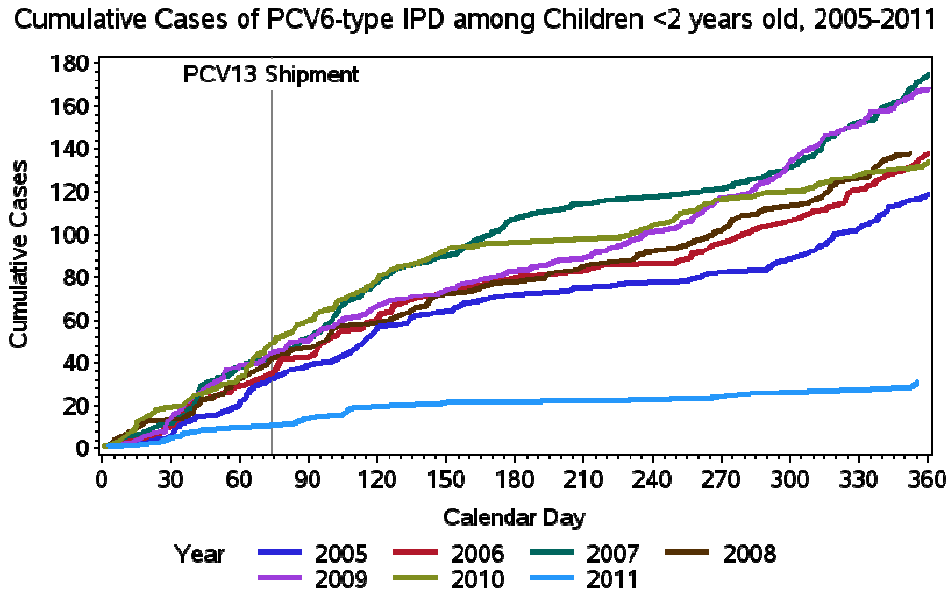

Figure 2: Cumulative cases of the 6 additional serotypes included in PCV13 and not included in PCV7 in children < 2 Years in the United States, 2005-2011, figure derived from C.M. Cox (22).

Reported cases of IPD from the German National Reference Center for Streptococci

In Germany, nationwide IPD surveillance is performed by the capture-recapture method using a clinical and a laboratory data source. Preliminary data on laboratory reports are available at the German National Reference Center for Streptococci. These data should be interpreted in the context that both conjugate vaccines (3+1 schedule), 10-valent pneumococcal conjugate vaccine (GlaxoSmithKline) and PCV13, have been available in Germany since 2009. The Market share of PCV13 is (by 2011) however >85% in a country, where the

pediatrician has the free choice for vaccines with full reimbursement for both vaccines [23].

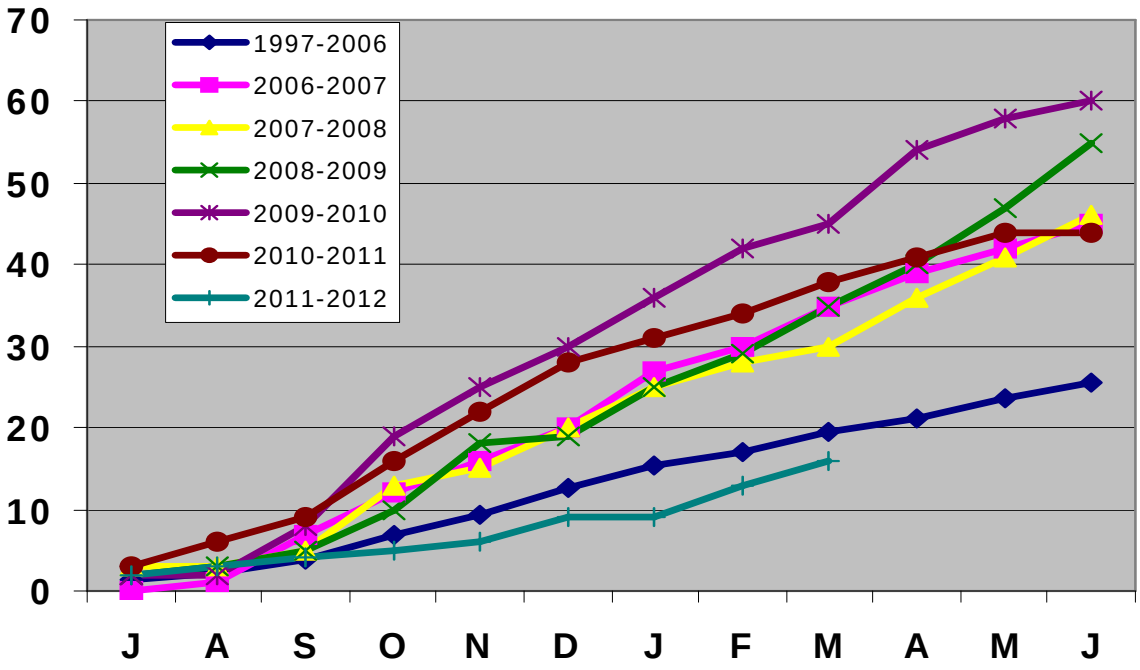

Figure 3: Cumulative Cases of the 6 Additional Serotypes included in PCV13 and not included in PCV7 in children < 2 Years old in Germany, 1997-2012 [23].

Impact data of PCV13 on IPD in children in Madrid, Spain

Systematic use of PCV13 for children aged <2 years began in Madrid (approximately 6 million inhabitants) in June 2010 using a 2+1 schedule, following transition from PCV7, which was introduced as part of an immunization program in November 2006 (3+1 schedule). The HERACLES study aimed to assess

changes in the incidence rate of invasive pneumococcal disease (IPD) in hospitalized children (<15 years) before and after PCV13 implementation. Briefly, a prospective, laboratory-confirmed (culture and/or PCR) IPD surveillance study was performed from May 2007 to April 2011, in all hospitals with a pediatric department (27 centers). A total of 115 IPD cases were identified from May 2010 to April 2011 compared with 499 cases in the pre-PCV13 period (163 cases: May 2007 to April 2008; 167 cases: May 2008 to April 2009; 169 cases: May 2009 to April 2010). In children aged <2 years a reduction of IPD cases caused by serotype 1 (54 cases 2009/2010 vs. 37 cases 2010/2011) and serotype 19A (48 vs. 28 cases, respectively) was observed [24, 25].

Emerging data on community-acquired pneumonia and acute otitis media post PCV13 introduction

Following the introduction of PCV7 in Uruguay in 2008 significant reductions in hospitalizations for community-acquired pneumonia (CAP) were demonstrated [26] and this trend continued after the transition to PCV13 in 2010. Decreases in hospitalizations for CAP have been seen with a 75.9% reduction in hospitalized chest radiograph-confirmed pneumonia (presumed to be bacterial) in children < 2 years of age. Importantly, a significant reduction of 69.2% has also been documented for hospitalizations for empyema and complicated pneumonia. Population-based surveillance following vaccination with PCV7 and PCV13 in several regions of Uruguay has demonstrated a 44.9% reduction in pneumonia (inpatient and outpatient) for children < 2 years of age [27, 28]. Moreover, in England there was a significant decrease in empyema in children <15 years of age after the introduction of PCV13 into the national immunization schedule [29].

In addition, in a prospective study conducted between October 2010 and September 2011 in Rochester, USA, 60 children vaccinated with PCV13 were enrolled and followed for AOM. Historic comparison was made to 58 children prospectively enrolled in a separate, similarly designed study from October 2007 to September 2009 in which PCV7 was administered [30]. There was a significant lower rate of pneumococcal AOM episodes in the PCV13 period compared to the PCV7 period. Among episodes of pneumococcal AOM there were no episodes caused by serotypes included in PCV13 during the PCV13 period, compared with 7 of 15 episodes during the PCV7 period.

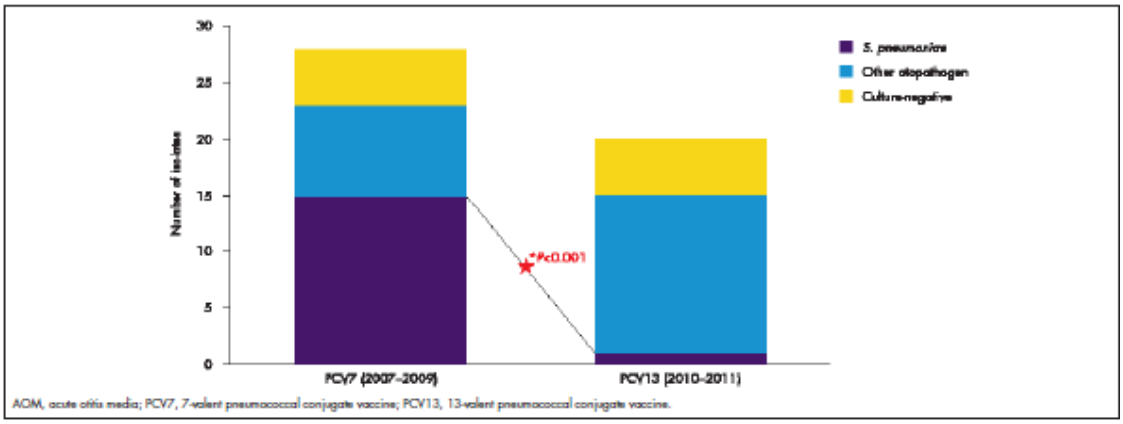

Figure 4: Reduction in pneumococcal AOM in the PCV13 period (2010-2011) in the United States vs. a historic control (PCV period, 2007-2009).

Early results from NP carriage studies

There is increasing evidence that reduction in nasopharyngeal (NP) carriage in pneumococcal conjugate vaccine-vaccinated subjects may serve as an indirect marker for the vaccine effectiveness protection (http://www.ktl.fi/roko/pneumocarr/publications.html) against invasive and non-

invasive disease. Therefore, the current review also includes data from two carriage studies.

Study on new acquisition of nasopharyngeal carriage in Israel (6096A1-3006)

A randomized double-blind multicenter study compared the impact of PCV13 and PCV7 on NP carriage, immunogenicity, and safety in healthy infants. A total of 1866 infants were enrolled at 11 sites in Israel; 930 infants received PCV13 and 933 received PCV7 in a 2, 4, 6-month (infant series) and 12-month (toddler dose) regimen together with other pediatric vaccines as recommended by national vaccination schedule. NP swabs were collected at ages 2, 4, 6 months (baseline) and at 7, 12, 13, 18 and 24 months when subjects were considered fully vaccinated. Rates of newly identified NP acquisition from ages 7 to 24 months (PCV13:PCV7 rate ratio), and prevalence after the infant series, i.e., proportion of cultures testing positive at ages 7, 12, 13, 18 and 24 months (PCV13:PCV7 prevalence odds ratio) were evaluated. NP carriage was statistically lower in the PCV13 group for the 6 additional serotypes combined and for individual serotypes 1, 6A, 6C, 7F, and 19A [31].

ACTIV study on carriage in children with acute otitis media in France

With the approval of PCV7 in France in 2001, an ongoing national surveillance study (Association Clinique et Thérapeutique Infantile du Val de Marne [ACTIV]) was initiated to evaluate the effect of PCV7 on pneumococcal carriage in children presenting with AOM to private pediatricians nationwide. With the introduction of PCV13 in 2010, the French authorities recommended a transition from PCV7 to PCV13 for routine immunization of infants and toddlers at any time of the schedule at 2, 4, and 12 months of age. The transition from PCV7 to PCV13

offered a unique opportunity to evaluate the impact of the PCV13 on carriage. From October 2010 to May 2011, 943 infants and toddlers, 6 to 24 months of age, with AOM were enrolled in the study; 651 subjects received at least 1 dose of PCV13, 285 received PCV7 only, and 7 were not vaccinated. Overall pneumococcal carriage, that of the additional serotypes in PCV13 (in particular serotypes 19A and 7F) and that of Prevenar 13-related serotype 6C was significantly reduced among Prevenar 13-vaccinated children as compared to children exclusively vaccinated with PCV7 [32].

In summary, only two years after introduction of PCV13 introduction into many NIPs globally, vaccine effectiveness for the PCV13 serotypes has been documented for several clinical outcomes (invasive pneumococcal disease (IPD), including sepsis/bacteremia and acute meningitis, community-acquired pneumonia, and acute otitis media) and nasopharyngeal carriage from several countries (USA, England and Wales, Germany, Spain, Uruguay, Israel). Moreover, serotype-specific effectiveness has been demonstrated for serotypes 1, 6A, 7F and 19A, which were the most prevalent and emerging serotypes pre-PCV13 immunization. There is increasing evidence supported by IPD and nasopharyngeal carriage data of cross-protection for the PCV13-related serotype 6C.

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