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Challenges in estimating the impact of pneumococcal conjugate vaccines through surveillance

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Introduction

Despite improved care, *Streptococcus pneumoniae* is still among the most common cause of bacterial meningitis (together with *Neisseria meningitidis*) in developed countries with almost a third of children left with life-long auditory and/or neurological sequelae and a case fatality rate around 10% (1, 2). An estimated 3 million new cases of pneumonia occur annually in Europe leading to around 31,000 deaths and although the exact burden of pneumococcal pneumonia is not known, it is assumed that *S. pneumoniae* is by far the leading bacterial pathogen causing pneumonia in industrialized countries (3). Among invasive pneumococcal diseases (IPD), bacteremia without a focus is undoubtedly the most common clinical presentation (4, 5). If untreated, it may evolve into focal invasive disease in 0-6% of children (6, 7).

Based on capsule polysaccharide composition, *S. pneumoniae* is classified in 92 different serotypes forming 46 serogroups. In 2000 a conjugate vaccine has been licensed for use in children below 5 years of age in the USA. This first pneumococcal conjugate vaccine (PCV) contained capsular polysaccharide antigens of seven serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), each of them conjugated to a modified Diphteria toxin carrier protein. Very soon after the heptavalent conjugate vaccine (PCV7) was introduced a dramatic impact was seen on IPD in the USA (8). The 7 vaccine serotypes have been virtually eradicated from carriage in vaccinated children (9) and as a consequence transmission of these serotypes to unvaccinated population has been reduced with a subsequent reduction of disease due to these serotypes (10). In Europe, PCV7 was licensed in 2001. However, in the majority of EU countries, PCV7 was not introduced into the universal vaccination schedule before 2006; vaccination policies in the period between PCV7 marketing and its universal use widely differed across countries. In December 2010, 16 countries had introduced PCV7 into the universal schedule at national level (11).

As some clinically important serotypes were not covered by the PCV7, extended valence vaccines have been developed. In 2009, two new conjugate vaccines have been licensed in Europe and thereafter marketed in many countries. One is a 10-valent vaccine (PCV10) containing antigens from the same seven serotypes than PCV7 together with capsular polysaccharide antigens from serotypes 1, 5 and 7F. They are conjugated for 8 of them to a surface protein D from *H. influenzae* and for 2 of them to modified Diphteria toxin and Tetanus toxoid, respectively. The other one is a 13-valent (PCV13), which contains capsular polysaccharide antigens from serotypes 1, 3, 5, 6A, 7F, 19A, all conjugated to the modified Diphteria toxin (http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&mid=).

This review describes the factors that may have influenced PCV7 vaccine impact and IPD burden across different settings in Western European countries and discusses why in Europe, overall vaccine impact seems more limited than in the USA (12-16).

Impact of PCV7 vaccine in Europe: Incidence before and after PCV7 implementation

Table 1 compares the change in overall IPD incidence in children <2 years before and after PCV7 use in 9 European countries (only studies providing national data are included). Incidence declined in every study, but the percent reduction varied widely across countries, related – but not solely - to the vaccine uptake. All 3 countries (France, England & Wales and Germany) that used PCV7 universally for at least two years, with a vaccine uptake ≥75%, showed a significant decline in incidence, ranging from 30% to 65%. Three countries showed a high and significant reduction (ranging 45-57%) after only a year of PCV7 universal use (Germany, Norway and Denmark). The reduction in EU countries was however systematically lower than in the US, where IPD incidence in children <2 years declined by 69% after only one year of PCV7 universal

use (8). Interestingly, most EU countries showed a high reduction in PCV7 serotype incidence, ranging 67-96% in children <2 years of age (12, 15, 17-19), similar to the 78% reduction in the US (8), suggesting a high PCV7 effectiveness on vaccine serotypes.

Assessing IPD burden and vaccine impact

A classical method for determining and monitoring the IPD burden is the epidemiological surveillance, involving collection of data on IPD cases and on pneumococcal isolates.

Many factors may influence the estimated burden of pneumococcal invasive disease. Some of them may increase (hence overestimate) the measured disease incidence or decrease (hence underestimate) it.

Population or pneumococcal factors affecting the real disease burden

Firstly, major variations are observed between developing industrialized countries in terms of living conditions, crowding and hygiene, which clearly influence nasopharyngeal carriage of *S. pneumoniae*,, a prerequisite to infection (20, 21). Secondly population transmission of *S. pneumoniae* in European countries may vary according to intensity of social contacts, attendance to day-care, which starts as early as 2 months of age in some countries (22). Thirdly, some populations seem to have genetic predisposing factors (which have not been elucidated yet) to developing IPD, such as American Indians (rates 10 times higher than those of non-native American children) or Australian aborigenes (23, 24). However, these populations also live in lower socio-economic conditions and higher promiscuity. Moreover there are some known immune deficiencies, which predispose to IPD such as HIV/AIDS, sickle cell anemia, leukaemia, transplant patients and these populations may account for a substantial proportion of IPD cases. In an US study for example, half of the adults less than 65 years of age with IPD were suffering

from HIV/AIDS (25). Fourth, pneumococcal factors may also play an important role in IPD burden as serotypes and/or genotypes have differing propensity to cause invasive disease (26-28), or even death (29, 30). Moreover, some serotypes, like serotype 2, which was causing 12 to 27% of lobar pneumonia at the beginning of the 20th century in Europe has 'disappeared' (31), although it is still present in some countries like Bangladesh (32). Others serotypes have yet unexplained cyclical patterns like serotype 1 in Northern Europe (33) and some serotypes cause large population outbreaks (serotype 1 and 5) (34). The distribution of pneumococcal serotypes prior to vaccine introduction also most likely influenced the dynamic of replacement colonization and disease caused by non-PCV7 types. Indeed, in the first 1-2 years after universal use, non vaccine types (NVT) incidence did not increase in the US where PCV7 types were responsible for 80-90% of IPD in children less than 5 years of age (35). By contrast, it rose by 43-140% in the <2 years in the Netherlands, France, Belgium and England &Wales (12, 17, 19, 36), where PCV7 coverage was 50-60% prior to PCV7 introduction (35).

Fifth, interventions such as antibiotic or vaccine use may influence the burden of disease. Antibiotics will reduce nasopharyngeal carriage and transmission of susceptible *S. pneumoniae*, among which will be some clinically important serotypes (serotypes 1, 5, 7F). In contrast, antibiotics will select for antibiotic resistant clones, many of which are included in PCV7. However antibiotic resistant NVT clones have emerged, such as 19A in the USA and many European countries (16, 37, 38).

Factors biasing burden estimates

IPD case identification

Blood sampling for culture vary among countries, regions and medical practices. Some countries such as the USA had recommendations of systematic blood culturing in every young child with

fever without a focus in both in- and outpatients settings (39). A few studies have demonstrated that the IPD incidence increased parallel to the number of blood culture samples in a population (40, 41).

S. pneumoniae detection in the laboratory

Optimal recovery of *S. pneumoniae* in the laboratory can be impaired at several steps in the process. First, previous antibiotic use before sample collection will affect the sensitivity of the diagnosis. In case of IPD, both CSF and blood will yield culture negative results rapidly after the beginning of treatment (42, 43). Second, the pre-analytical phase is essential: samples need to be collected, transported and handled appropriately, as *S. pneumoniae* will not survive over a few hours if not incubated on appropriate medium. In children, collecting the weight-appropriate amount of blood to maximize the detection of circulating bacteria and using the adequate culture bottle was only performed in 35% of the cases in a recent study. Most often, insufficient quantity of blood was used (44). Third identification of *S. pneumoniae* by the laboratory requires minimal infrastructures and training. Two classic phenotypic tests are used to identify *S. pneumoniae*, bile solubility and optochin susceptibility, both of which have been shown to occasionally fail to provide correct identifications (45).

Alternative laboratory techniques for S. pneumoniae detection

To overcome these hurdles in identifying the causative pathogen of invasive bacterial diseases in children, alternative techniques have been tested based on antigen or nucleic acid detection. In one pediatric study in the USA, soluble pneumococcal polysaccharide antigens were detected by use of a rapid immunochromatographic test on urine of almost 100% children with *S. pneumoniae* bacteraemia, 75% with lobar pneumonia, but also in 8% of afebrile children (46). In other studies the role of *S. pneumoniae* carriage in the nasopharynx was underlined as a cause of

false positive results, rendering the use for diagnosis of suspected pneumococcal infections in children limited (47, 48). However, antigen detection has been used on pleural fluid with promising results (49).

Molecular methods may allow for rapid and enhanced detection of *S. pneumoniae* in blood or any sterile fluid especially in the cases of culture negativation by previous antibiotic use (50). PCR detection may be based on different target genes. Classically *ply* and *lytA* genes (2 virulence genes) have been used, but false positive results may be seen with *S. oralis* or *S. pseudopneumoniae* and in more recent studies, *cpsA*, a gene which belongs to the capsular locus has been added as a target (45, 50). However, PCR detection of *S. pneumoniae* DNA in blood may also lack specificity in young children who commonly carry *S. pneumoniae* in the nasopharynx, with 17% false positive in healthy children (33% in less than 2 year-old) in one study (51). In another study on children 3-36 months of age presenting at emergency room with fever without a focus, 206/459 (45%) children had a positive PCR with a negative culture, whereas only 16% had a false positive PCR in the control group (52). PCR detection is thus certainly relevant on CSF or pleural fluid, but interpretation of a blood positive result must be cautious and linked to clinical presentation. The most recent studies using real time PCR and quantification of bacterial load (50, 53), offer promises of future development of these diagnostic tools. Several studies have attempted to use serology for pneumonia diagnosis. Protective levels however vary from one serotype to another, are depending upon age and carriage acquisition and require comparison of antibody level in an early and a convalescent sample. Serological testing has been performed for epidemiological studies which usually demonstrate good sensitivity for bacteremic pneumonia diagnosis, but limited use in blood culture negative pneumococcal pneumonia, mainly due to the lack of a gold standard (54).

Comprehensiveness of surveillance system

Although nearly all EU countries have a national IPD surveillance system and a national reference laboratory for *S. pneumoniae* (11), surveillance methods, case definitions and population under surveillance are very heterogeneous across countries. In the era of conjugate pneumococcal vaccines, most EU countries reinforced their IPD surveillance systems to inform decisions on vaccine policies (11). Reporting rates have thus increased in many countries after PCV7 use, not only due to surveillance enhancement, but also to increased awareness. However, many studies do not adjust incidence rates to the level of under-reporting, though the magnitude of incidence changes before and after PCV7 use is also influenced by whether data are adjusted for under-reporting. For instance, in Belgium, incidence reduction in the <2 years was estimated at 23% without any adjustment, at 37% when incidence are adjusted for under-reporting (19); in Germany, incidence reduction was 45% and 56% respectively with and without adjustment for under-reporting (14). Moreover, EU national surveillance systems mostly report hospitalised cases, as blood cultures are generally limited to inpatient. Historically, the focus of surveillance in Europe has been meningitis (thus the most severe cases). Although nearly all EU countries started to report other invasive diseases after PCV7 introduction, most European countries still report a higher proportion of meningitis compared to US surveillance studies: the proportion of IPD cases in children <2 years that were meningitis (defined as *S. pneumoniae* isolation from CSF) in the pre-PCV7 period was 50%, 27%, 24% and 15% in Italy (55), France (13), Denmark (56), and Belgium (16) respectively, compared to 5% in the US ABC sentinel surveillance (57). As EU countries cover more severe IPD cases compared to the US, comparison of epidemiological changes across these two areas is difficult to interpret.

Conclusions

PCV7 has had a significant impact on IPD in Europe, but the observed reduction in the incidence was overall lower than in the USA. A first contributing factor is the lower proportion of PCV7 serotypes causing IPD prior to vaccine introduction in the EU compared to the US, with a higher rise of NVT. However, other factors are related to methods of estimating the vaccine impact: all EU surveillance systems include more severe cases and most have improved the reporting of IPD cases post-vaccine introduction, thus underestimating vaccine impact when the analysis does not adjust for changes in reporting. Impact studies that compare incidence before and after PCV7 introduction are thus difficult to interpret and compare. It is of utmost importance that vaccine impact studies are designed controlling for the many biases and analyzed carefully. Progresses have been made to harmonize and improve IPD surveillance in European countries. Nevertheless, there is still a need to harmonize data analysis among countries and stay aware of the limitations of such studies and cautious in interpreting their results. There is also a need for high quality effectiveness studies to evaluate the extended valency PCV vaccines that have been recently introduced.

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Table 1 Reported incidences of IPD in children < 2 years in European countries before and after PCV7 introduction

Country	Pre PCV7 IPD Incidence/10^5	Year PCV7 marketed	Year PCV7 universal	PCV7 uptake[2]	Post PCV7 IPD incidence/10^5	% reduction in incidence (significance)
Belgium[1] (19)	129.7 (2002-03)	2004	2007	79% (2008)	82.4 (2008)	37 (SS)
France (13)	30 (2001-2002)	2001	2006	44% (2006)	24 (2006)	21 (SS)
France (17)	32.7 (1998-02)	2001	2006	85% (2008)	22.1 (2007-08)	33 (SS)
Netherlands (12)	34.5 (2004-06)	2001	2006	94% (2008)	22.5 (2006-09)	35 (SS)
England & Wales[1] (36)	54.2 (adjusted)	2002	2006	85-92% (2009)	23.6 (2009-10, adjusted)	56 (SS)
Norway (18)	67.7 (2004-05)	2001	2006	80% (2006)	32.6 (2007)	52 (SS)
Ireland (58)	40.0 (2008)	2002	2008	88% (2010)[3]	26.3 (2009)	37 (NA)
Switzerland (59)	29.6 (2001-05)	2001	2005**	50%* (2009)	14.5 (2009)	51 (NA)
Denmark (15)	54.8 (2000-07)	2001	2007	69% (2007)	23.8 (2008)	57 (SS)
Germany[1] (14)	20.0 (1997-03)	2001	2006	80% (2007)	11.0 (2007-08)	45 (SS)
Germany (60)	20.0 (1997-2003)	2001	2006	80% (2007)	14.1 (2008-09)	30 (NA)

1: incidence has been adjusted for the under-coverage and under-reporting of the surveillance system

2: for full schedule (2+1 or 3+1)

3: for 2 doses only as vaccine was introduced at the end of the study year (Sept 2008)

* for 2 doses

** free of charge in 2006

SS: statistically significant

NA: non available

Opmerking [IL1]: Where is 1