**Heptavalent Pneumococcal Conjugate Vaccine: growing knowledge and its implications for Italy**


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**Key words**

Pneumococcal conjugate vaccine • Universal immunization strategy • Direct and indirect effects

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**Introductive note**

A wide literature on *Streptococcus Pneumoniae* (Pn) infections is available, largely published in the recent years, after the introduction of the heptavalent conjugate vaccine in US and in Europe. This review is based on the most up-to-date scientific articles about this pathogen.

**Epidemiology of Streptococcus Pneumoniae: general features and current situation in Italy**

Diseases sustained by *Streptococcus Pneumoniae* account each year for a heavy burden all over the world, especially in the undeveloped Countries, being estimated by World Health Organization (WHO) that 1.6 million deaths, of which nearly 0.7-1 million in children less than 5 year of age, are attributable to this aetiologic agent [1].

Pn is a gram-positive capsulated diplococcal bacteria, widespread in the population, responsible for various pathological conditions of significant clinical importance: Invasive Pneumococcal Diseases (IPD), such as meningitis and sepsis, Community Acquired Pneumonia (CAP) and other less important clinical conditions widespread in the population, being the pathogen responsible of 1/3 of all cases of Acute Otitis Media (AOM) and sinusitis in paediatric age and, rarely, of infections in bones, joints or soft tissues [2, 3]. The experience gained in some European countries has revealed that besides meningitis, cases of sepsis and bacteraemic pneumonia, in paediatric age, account for the most consistent number of cases presenting manifestations of pneumococcal infection (reaching 70% of all cases of IPD) [4].

The natural and obligate reservoir responsible for the infection is man himself who naturally harbours the micro-organism in the naso-pharynx, according to a dynamic process dependent upon various factors and conditions; the state of carrier is, in fact, influenced not only by age (with a peak in prevalence in children aged < 2 years, thereafter decreasing progressively) [5, 6], but also by other factors such as frequenting a group of infants, breast feeding, belonging to a large family, use of antibiotics, the season, passive smoking and certain morbid conditions, such as pathological conditions that lead to a deficit in immuno-competence or respiratory viral infections [5]. Data in the literature concerning the role of risk factors, whether of a major or minor nature, in determining IPD have been widely discussed: according to some reports, the major conditions, such as neoplasias, chronic respiratory and circulatory diseases, recognized also for other vaccine-preventable diseases (e.g. influenza), have been demonstrated to play an important role in the occurrence of IPD. In this regard, in one study, approximately 80% of the hospitalized cases presented at least one clinical condition of associated co-morbidity [7], whilst in another report, more than 40% of the cases occurring in children aged > 5 years presented at least one of the following clinical conditions: HIV infection, congenital immunodeficiency, sickle cell anaemia or malignant tumours [8]. At the same time, other findings indicate that IPD can occur also in healthy subjects, as observed in a study performed on cases occurring in paediatric subjects and other age groups, none of whom were found to be carriers of any of the above-mentioned risk conditions [9, 10]. Age, therefore, in the experience of these authors would, in itself, represent a risk factor [11]. More detailed studies need to be focused on this latter aspect, in order to optimize vaccine prevention programmes and strategies against Pn in Europe, where, up until 2003, almost all member Countries had decided to adopt selective strategies targeted to subjects belonging to risk categories [12].

In Europe, the incidence of IPD, varies between approximately 8-25 cases per 100,000 inhabitants (on average in US 23.3/100,000) with wide differences between geographical areas. Nevertheless, the rarely used practice of confirmation by means of haemoculture, the frequent empirical use of antibiotics, as well as the suboptimal sensitivity of the most used laboratory test could lead to an under-estimation of the phenomenon.

In Italy, the most complete data available concern meningitis, collected by means of a special surveillance network (passive type), which was commenced in 1994 and performed in collaboration with the Ministry of Health, Regional Epidemiological Observatories, and the Italian National Health Institute (NIH). Between 1994-2006, overall approximately 3,000 IPD cases were reported in...
these records, notifications ranging from a minimum of 108 cases in 1994 to a maximum of 308 in 2003. The most frequently identified pathogen, within those preventable using current available paediatric vaccines, in the overall period 1994-2006, was Pn (45.2%), followed by Neisseria Meningitidis (42.4%) and Haemophilus Influenzae type b (Hib) (12.4%): in particular, Pn was found to be responsible for approximatively 30% of the forms in 1994, with percentages reaching 45% in 2004 and 55.7% in 2006 (relative increase due, in part, also to the simultaneous reduction in the number of cases caused by Hib) [13].

Recent active epidemiological surveillance studies enable a better estimation of the burden caused by the IPD in Italy. In 2002, the NHI launched a Pilot Programme of surveillance in two Regions, Piemonte and Puglia. The results showed that, with a reasonable and methodical use of diagnostic updating by blood culture, the incidence of the invasive forms reached values of 11.3/100,000 infants up to 2 years of age, results which were much higher than those previously estimated [14]. Other studies performed in Italy revealed an IPD incidence of 59.2 cases/100,000 infants < 3 years old [15], and of 47.4/100,000 children < 5 years old [16]. Continuation of the two latter investigations resulted in an even greater incidence, namely 63.8/100,000 (< 3 years) and 62.0/100,000 (< 5 years). Other data collected during 2005 from the active lab-surveillance on IPD in Piemonte revealed incidence rates of 16 and 12/100,000 in infants and in children aged 0-4 years, respectively [17].

Another national investigation, performed as part of an active hospital surveillance network, showed that the proportion of bacteraemia due to Pn reached 1.2% of all the blood cultures performed in children with a temperature > 38°C [18]: this value would appear to be very significant, particularly if compared with the data emerging from the case series in US, where the prevalence was approximately 1.6%. Findings reported in Italy reveal a similar incidence to those reported by other European Countries.

Matching between circulating and vaccine serotypes

The seven serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) contained in Pneumococcal Conjugate Vaccine (PCV), currently available on the market, are those most commonly widespread in the Western world, therefore it is possible to estimate that the hypothetical protection of the preparation is 88.7% in North America and Australia and 77.6% in Europe (where there is a significant circulation of the 1 and 8 Non-Vaccine sero-Types - NVT). It is tempting to suggest that in Africa, Latin America and Asia, where the 1 and 5 serotypes are more prevalent, coverage would be 67.3%, 63.4% and 43.1%, respectively [1].

The most recent data available in Italy reveal a good matching between circulating serotypes responsible for IPD and those contained in PCV, particularly under 2 years of age, where up to 81% of the cases of sepsis appear to be due to Vaccine sero-Types (VT). This would be in keeping with the results from the case series elaborated by the NHI surveillance system, for the period 1997-1999 [19].

In a more recent Italian study, performed during the period 1997-2000, typing more than 500 isolates from cases of IPD collected by a group of 65 laboratories, it was demonstrated that among children, 72% of the isolates belonged to serotypes included in the PCV [20], whereas analogous results have been observed in a 1-year population-based surveillance study, undertaken in two Italian regions (Piemonte and Puglia) where this percentage was approximately 79% in patients under 5 years of age [21].

Other studies in Italy focusing on the carrier condition in paediatric age have shown that the colonizing serotypes, thus potentially responsible for the pathological conditions, corresponded to vaccine ones with values ranging from 63% to 78%, thus showing that similar differences exist in the various studies as far as concerns age of the subjects examined, with the percentage of carriers being greater in the early years of life [22, 23]. Likewise, as far as concerns CAP, with the national experience in a group of children aged between 2 and 5 years, it was possible to estimate the theoretical coverage of PCV as 58% [24].

Safety and tolerability of PCV

With regard to the safety, a wide experience of broad offer of PCV has been carried out, primarily in US, confirming its excellent profile both when administered individually or in association with the other vaccines routinely used in infancy [25]. Polivalent conjugate vaccines have been tested in a number of clinical trials performed in different areas of the world, showing good safety and tolerability profiles, even among children infected with Human Immunodeficiency Virus (HIV). No significant adverse events have been identified in post-marketing surveillance in the US, where more than 20 million children have been immunized [1]. Our investigations performed in Liguria, the first Region in Italy where an universal infant free-immunization programme was started since 2003, confirm data regarding the safety of the vaccine, when given in coadministration with the hexavalent vaccine (DTaP-IPV-Hib -HepB): no serious adverse events have so far been reported, more than 80,000 doses being administered in infants (3-5-11 months schedule), with vaccination coverages reaching nearly 90% in 2005 [26].

Some Authors found a higher reactogenicity, both at a local and at a systemic level, after concomitant administration of PCV with DTaP-IPV-Hib-HepB or similar formulations in comparison to immunisation with these vaccines given alone [27-38]. All things considered, PCV displays acceptable side-effects: local reactions would, in fact, occur in like manner as found for DTaP vaccination (13-18% local reactions) and systemic effects are similar to those induced by conjugated vaccine for Hib meningitis (temperature > 38°C: 15-23%).
**Immunogenicity of PCV and currently available schedules**

Several studies have investigated the immunogenicity of PCV, also with the aim of identifying an antibody response value correlated with protection towards *N. meningitidis* associated disease. Some Authors have identified cut-off values which differed in relation to each vaccine serotype, but the way in which these thresholds have been calculated would appear somewhat arbitrary. At last, using the same model based on the results from the Northern California Kaiser Permanente (NCKP) study in US, the WHO decided to use a single antibody titre concentration value of 0.35 µg/ml, to be considered as protective against IPD by all the serotypes contained in the heptavalent vaccine [27, 39].

A number of trials have also been recently carried out both to evaluate the best vaccine schedule and to investigate the possible immunological interference in the response to PCV when administered together with other preparations foreseen in infant age. Nowadays, a general consensus exists with the fact that PCV is highly immunogenic, even when co-administered with other routine infant vaccines, following different immunisation schedules providing 3 priming doses in the first year of life and a booster in the second year. Immunogenicity of PCV has been investigated using both a 2-4-6 months + 12-15 months schedule, the US schedule [33, 35, 38, 40], and a 2-3-4 months + 12-23 months challenge, as used in UK, France and Germany [29-31, 34, 41].

A serum titre above the selected cut-off for all Vt was reached in 82-100% of the participants, after the administration of the third priming dose [29-33, 38]. Furthermore, a strong anamnestic response was evident following the administration of PCV as the booster dose given in the second year of life. Three studies have been conducted in infants in which Polysaccharide Pneumococcal Vaccine (PPV) was given as a booster (fourth dose) after a priming series of three doses with PCV-7 or PncOMPc (PCV-7 with a protein of *N. meningitidis* as a carrier): PPV as booster gave higher antibody concentrations than PCV-7 and PncOMPc, but not necessarily a higher efficacy (only studied for otitis media sustained by *N. meningitidis*). Studies, also using 3 doses in the primary cycle [27, 34-36].

More research has been performed in older children on this item, but little data on resulting immunogenicity have been published as using cut-off levels [41, 44-47].

Studies performed in the Scandinavian countries and in Italy have demonstrated a good immunogenicity of PCV, when administered simultaneously with DTaP-IPV-Hib or DTaP-IPV-HBV-Hib vaccines, using a 3-5-11/12 months (2 + 1) regimen [27, 36]. After the booster dose, results for all Vt are substantially superimposable to those obtained with vaccination schedules following a 3 + 1 regimen. Particularly, it was found that the percentage of infants achieving serum titres above the minimum cut-off value of 0.35 µg/ml, one month after the second dose, was 76-100% for all serotypes contained in the vaccine, with the exception of certain serotypes, as 6B and 23F, with values ranging from nearly 40% to 50%, respectively [27, 36]. Indeed, a certain number of polysaccharide antigens, namely 6B, 23F and 9V, used for the preparation of PCV, have demonstrated to be less immunogenic after the priming series in different studies, also using 3 doses in the primary cycle [27, 34-36]. Nevertheless, for serotypes 6B and 23F, even if initially displaying low immunogenicity, it has been found that the concentration of antibodies tends to increase considerably after the administration of a booster dose, given at 11-12 months. PCV is, thus, able to well stimulate immune response also using a two priming vaccination series, establishing an adequate immunological memory, as demonstrated by the elicited anamnestic response. This was found not only in healthy children but also within pre-term infants, a well known category at risk for developing IPD [36].

A spontaneous clinical trial is currently underway at our Research Centre at the University of Genoa, aimed at evaluation of the immunogenicity of the hexavalent vaccine DTaP-HBV-IPV-Hib when administered together with PCV, the schedule being 3 doses (3-5-11 months) during the first year of life: preliminary results, available in more than 100 subjects, confirm the absence of any immunological interference in terms of antibody response vs. all the antigens contained both in the hexavalent and in the conjugate pneumococcal vaccine (data under publishing) [26].

In conclusion, currently available data on immunogenicity of PCV suggest that the use of a vaccine schedule with three doses (2 + 1), delaying the booster dose at least 6 months after the priming series, may represent a valid and practical option for the primary prevention of the disease sustained by *Pn*: this strategy offers benefit in terms of protection and compliance to vaccination, but also under an economic point of view, as well as considering organizational aspects within the healthcare services [36].

Intriguingly, post-marketing surveillance data performed in US suggest that even when only two doses of vaccine were given in the primary schedule (2-4 months), children resulted protected against pneumococcal disease, albeit further information need to be obtained concerning the duration of this protection [48].

**Direct and indirect effects of PCV**

Data related to the effects of PCV in the prevention of IPD refer primarily to the US experience, where a strategy of universal immunisation has been ongoing since 2000.

A large number of papers have been published in the literature during the last years demonstrating both efficacy (randomised clinical trials) and effectiveness (population-based surveillance studies) of PCV against IPD, CAP and AOM. The first large randomized, double blind, trial was performed in US at 23 medical centers within Northern California Kaiser Permanente (NCKP) [33]. Nearly
38,000 healthy children were randomized 1:1 to receive either the PCV and the meningococcal conjugate type C vaccine, at 2-4-6 and 12-15 months of age. Per-protocol and intention-to-treat analysis revealed a PCV efficacy against invasive disease of 97.4% and 93.9%, respectively. Subsequent evaluation on the impact of the universal vaccination programme with PCV was performed in a postlicensure surveillance within the Kaiser Permanente population, in children aged < 5 years, monitoring the incidence of IPD in a period ranging from 1996 to 2001: in this large field study it was immediately shown a reduction of Pn-disease of 87% and 58% in infants and in 0-2-year-old subjects, respectively, with incidence rate caused by VT falling from 51.5-98.2 to 9.4 cases/100,000 in < 1 year-old children and from 81.7-113.8 to 38 cases/100,000 in children < 2 years [49].

As shown in Table I, numerous population-based surveys have confirmed the high effectiveness of the vaccine in preventing Pn-invasive disease [8, 9, 49, 50-54]. The last up date on the effectiveness of the PCV, used in US under a universal children immunisation strategy, has been recently reported by Centre for Disease Control and Prevention (CDC) [55]: data indicate that overall IPD rates among children aged < 5 years in 2005 were 77% lower compared with the years preceding vaccine introduction (1998-1999). At the same time, incidence of invasive diseases sustained by VT has decreased by 98%. Globally, an estimated 13,000 cases of IPD were prevented in US children < 5 years during 2005. Additional positive effects of the universal vaccination programme, not expected at the time when it was launched, have gradually emerged: in fact, since 2003, as many as 30% of the IPD in adults > 65 years of age continued to be caused to the VT and fewer than 20% in children < 5 years old in US [60]. Furthermore, individuals with certain co-morbid conditions might benefit less than healthier subjects from the indirect effects of the conjugate vaccine: this has been observed in older adults and in subjects with associated co-morbid conditions, whether primitively immuno-compromised (i.e. HIV infection) or not (i.e. renal failure, heart failure, lung disease) [60, 66]. This would appear to indicate that the direct protection of adults with

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<th>Tab. I. Reduction rate (%) of IPD, overall and by bacterial serotypes, by age-class, in children after the introduction of PCV.</th>
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VT = Vaccine Types
PCV could be very useful in determining an even greater protection as far as concerns these morbid forms [60]. It is plausible to believe that, in the next future, PCV will gradually take the place of the PPV, which could be used for a single re-immunization in certain risk-groups, this also due both to the gradual hypo-stimulation of the humoral response elicited by non-conjugated vaccine in subjects to whom repeated doses are administered and to the increase in side effect rate after repeated immunisations with PPV [66].

Also with regard to CAP, recent evidences have demonstrated the positive effect of the PCV when used under a universal immunisation strategy. Some of the most interesting results on these item are summarised in Table III.

Since the measurement of vaccine efficacy against confirmed pneumococcal pneumonia is constrained by the lack of a sensitive and specific method for establishing aetiology in cases of non-bacteraemic pneumonia, most studies have focused on measuring the overall effectiveness of the vaccine in preventing radiologically defined pneumonia irrespective of aetiology, following guidelines introduced by the WHO in 2001 for the radiological diagnosis [67-71]. Initially, the Kaiser Permanente Study demonstrated a 20.5% (95% CI = 4.4-34.0) effectiveness against clinical pneumonia with “positive film” (infiltrates beyond the peri-hilar area, consolidation or empyema). However, in that investigation, the effectiveness against all types of clinical pneumonia resulted not statistically significant (4.3%; 95% CI = 3.5-11.5). In that experience, the radiological diagnosis was performed according to routine practice by the radiologists, on duty at the hospital in which the child was seen for clinically diagnosed pneumonia: the protective efficacy against radiologically confirmed all-cause pneumonia was 17.7% [68]. In a more recent investigation, Grijalva et al., by means on analysis and comparison of the discharge charts collected from approximately 20% of

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<th>Age group (years)</th>
<th>Overall IPD (%)</th>
<th>IPD by VT (%)</th>
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IPD = Invasive Pneumococcal Diseases; VT = Vaccine Types

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<th>Radiologically confirmed CAP (%)</th>
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<tr>
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<td>Grijalva et al. [72]</td>
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the US hospitals, observed a considerable drop in the number of hospitalisations for pneumonia in the period from 1997 to 2004: at the end of the study period, all-cause pneumonia admission rates showed a significant reduction by 39% (95% CI = 22-52) in children aged < 2 years, with an annual decline of 506 per 100,000, representing about 41,000 prevented cases in 2004. In particular, during the 8 study years, the reduction in the rate of pneumonia, coded as having Pn-disease, resulted of 65% (95% CI = 47-77) [72]. Two large clinical trials, recently performed in South Africa and Gambia among young children, with a 9-valent PCV, demonstrated a vaccine efficacy against pneumonia of 25% and 37%, respectively, using the WHO criteria for the radiological diagnosis [67, 69]. Furthermore, in a recent US post-marketing surveillance study, a significant reduction in CAP rates was also seen in 0-2 year-olds, in 2003-2004, compared with earlier periods [73]. Preliminary data on the effects of the PCV in Liguria, Italy, a Region where a universal immunisation strategy for all infants was started since 2003, emerged from a research, under publishing, financed by the Italian Ministry of Research and the University and coordinated by our Center: as derived from the analysis of the Hospital Discharge Charts in this Region, a significant reduction in the hospitalisation rates for pneumonia, both pneumococcal and overall, and for AOM was registered in children aged 0-24 months, comparing pre (2000-2002) vs. post-vaccination (2003-2005) periods (data under publishing) [26]. As far as concerns AOM, PCV has demonstrated to confer a “modest” protection. This is what resulted in one of the first controlled randomized trials (FinOM) investigating this item, in which PCV-7 was given to infants, following a 2-4-6 and 12-month schedule [32]. This study was carried out testing biological specimens obtained from children in whom tympanocentesis had been performed: the per-protocol efficacy of PCV-7 for clinically diagnosed AOM, caused by VT, was found to be 57% (95% CI = 44-67%), but due to observed partial replacement of VT, the overall efficacy of the vaccine in this study was finally estimated to be 34% (95% CI = 21-45%), yet. This study was too small to demonstrate overall efficacy considering all-cause AOM as outcome (VE = 6% with 95% CI = 4-16). These results confirm those previously published by Black et al. in the original NCKP study, where a PCV efficacy of 66.7% (p = 0.035) and of 7% (95% CI = 4.1-9.7) was found against episodes of clinically diagnosed AOM, due to VT and by all pathogens, respectively [33]. In the NCKP study, protection against the placement of tympanostomy tubes resulted 20.1% (95% CI = 1.5-35.2) and 20.3% (95% CI = 3.6-34.1) in the per-protocol and in the intention-to-treat analysis, results much higher than that observed in the FinOM study. A number of papers, both randomized clinical trials and field epidemiological investigations, have studied efficacy and effectiveness of PCV against AOM within the pediatric population (Tab. IV) [2, 39, 40, 42, 55, 74-80]. In particular, Grijalva et al. compared rates of outpatients visits, using the National Ambulatory and Hospital Medical Care Survey in US, before (1994-1999) and after (2002-2003) the introduction of PCV: AOM visit rates showed a 20% decline in children aged < 2 years [76]. This rate is in keeping with findings emerging from clinical trials in which a 9-valent Pn-conjugate vaccine was investigated, showing a vaccine efficacy of 17% against all-cause AOM, in Israeli children aged 1-3 years: furthermore, a good coverage from this vaccine just against the antibiotic-resistant strains, responsible for AOM, was supposed [81]. Otitis media, indeed, represents one of the principal indications for antibiotic treatment, thus contributing to a large extent to the onset of antibiotic-resistance [76]: also considering this, since otitis media is a considerable cause of morbidity among the paediatric population, as stated by WHO, the cited “modest” effect of PCV finally results in a significant global benefit [1].

Other effects of PCV on replacement and pattern of antibiotic-resistance

Attention has been focused, over the last few years, on some reported negative effects associated with the extended use of PCV, likely, paradoxically, to nullify, in the very near future, all that has been achieved to date: which means the risk of new serotypes, also cause

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HEPTAVENT PNEUMOCOCCAL CONJUGATE VACCINE
of IPD, replacing those currently contained in the vaccine and the selection, thus the increase, of antibiotic-resistant strains. Replacement is a phenomenon mainly dependent on secular trends, within the natural ecology of Pn: even if it was previously reported also in areas where PCV was not part of the immunisation schedule, recently, after the introduction of the vaccine within the universal immunisation programmes, it has been suggested it might be caused by the reduction in the prevalence of people colonized with VT and by the possible substitution of these latter with other NVT [82].

A number of clinical trials have investigated this item, with discordant results: in the FinOM trial, an increase in AOM sustained by NVT had been described in children vaccinated with PCV: this event occurred 27% more in the immunised than in the control group [32, 42]. The NCKP study and another research by Prymula et al. failed to confirm this evidence for both PCV and PCV-11, yet [33, 39]. At the same time, another clinical trial in children aged 1-7 years, vaccinated with PCV, found no substitution of VT by other pathogens in middle ear fluid collected during the first episodes of AOM [45].

During the last years, the incidence of IPD cases, sustained by serotypes present and not in the PCV, has been largely monitored within well structured lab-based surveillance systems in different countries. Like this, in some populations, as subjects < 5 years and adults > 40 years, it has been shown that the reduction in IPD caused by VT was associated with a parallel increase in cases by NVT strains [60]. In a study carried out in US, within a surveillance network in eight paediatric hospitals, the isolates of NVT 15 and 33 were found to be increased in the post-vaccination phase [50]. Likewise, surveillance data in US from 1994 to 2004 confirmed this behaviour, comparing NVT 15 and 33 with serotypes 1 and 3, used in this comparison because they represented, in the pre-vaccination era, the principal serotypes causing IPD amongst those not included in the PCV [83]. Another reported NVT causing IPD, important as far as concerns the phenomenon of replacement, is 19A, as revealed from the microbiological surveillance data of the Active Bacterial Core System in US, in the period 1996-2004, when incidence rates by this type increased from 2 to 8.3/100,000, in children under 2 years of age [61, 48].

The most recent data by the CDC show that, although IPD caused by VT declined through 2005, overall IPD rates leveled off beginning in 2002, primarily because of increases in the incidence of IPD caused by NVT 19A: among children aged < 5 years, the incidence of IPD by this serotype increased from 2.6 cases in 1998-1999 to 9.3 cases per 100,000 in 2005, the largest reported increase for any one serotype. In 2005, 40% of the 1,200 additional cases of NVT-IPD among children aged < 5 years was caused just by serotype 19A [55].

Even if it is, obviously, advisable to continue to monitor this event, the most recent data, emerging from the mentioned population-based surveys, show that the overall magnitude of the phenomenon is small compared with the reduction in disease sustained by VT, as already fully discussed [8, 60]. On the other hand, there can be no doubt that more widespread protection than that available with PCV-7 would be welcome: several clinical trials are currently underway, aimed at evaluation of new pneumococcal vaccines, even conjugated with different proteic carriers, with a larger spectrum of action than PCV-7, containing up to 9, 10, 11 and 13 antigens of the micro-organism (Tab. V) [62, 67, 84-88].

As far as concerns the effect of universal vaccination on antibiotic resistance pattern, it has been shown that, following the introduction of PCV universal programme, an overall reduction in the resistance to the most frequently used antibiotics occurred: this is what appeared in 2002, within a surveillance network, activated in 1993-1994, in eight US hospital, monitoring IPD in the paediatric age [50]: the proportion of isolates resistant to penicillin has decreased by almost 50%, the first time such a decrease in resistance has been noted since surveillance began. This is not surprising considering that the resistance of Pn to antibiotics is a phenomenon more frequently observed for the serotypes that cause IPD and, therefore, identifiable particularly with those included in the vaccine. Likewise, the same surveillance activity reported the proportion of NVT isolates not susceptible to penicillin as increased during the study period: only a slight trend towards an increase in the years 2001 and 2002 compared to 2000 was registered, yet, the phenomenon resulting, on the whole, an event of little clinical importance [50]. Results confirming the significant positive effect of the wide use of PCV on the pattern of antibiotic resistance clearly emerged from another lab-based survey by the Active Bacterial Core System in US: in infants < 2 years, the incidence of resistance to penicillin, as far as concerns the micro-organism causing IPD, showed a dramatic 81% drop, from 70.3/100,000 in 1999 to 13.1/100,000 in 2004. At the same time, this phenomenon was observed also in adults, a non-immunised population, who thus, in this respect, benefited also from the above mentioned herd immunity effect [61].

To summarize, in the period immediately following the introduction of routine immunisation with PCV in US, it became immediately evident that IPD occurring in children < 2 years, the target of the programme, were always less frequently sustained by Pn-strains resistant to penicillin, cefotaxime or erythromycin. Nevertheless, as from 2002, this phenomenon involved also children aged > 2 years, later also involving a group of more elderly subjects, with a reduction in the resistance to penicillin observed also in subjects > 65 years of age. It is tempting to suggest that this was due primarily to a reduced colonization by the Pn-serotypes included in the PCV, which, harbouring usually in the naso-pharynx of children, are also able to select resistant strains under the pressure exerted by eventual antibiotic treatment. Albeit, this theory was not found to be valid for the 6A and 19A serotypes, for which sensitivity to chemoantibiotics still remains substantially unchanged, thus confirming the limited impact of vaccination on the naso-pharyngeal colonization by these two strains [66].
Cross protection of PCV vs. non-vaccine serotypes

In respect with cross-protection, various studies have demonstrated a direct protective effect of PCV towards IPD sustained by the NVT 6A, a polymer of a tetrasaccharide repeating unit, which differs in a single linkage from the tetrasaccharide of 6B [68, 89]. This same phenomenon has not been demonstrated for other NVT, in particular 19A, even if the vaccine contains a serotype, namely 19F, which is substantially similar [50, 90]: this lack of cross-protection is indirectly confirmed by the increase in the IPD sustained by serotype 19A in children < 5 years and in the elderly. We believe this finding should be taken into due consideration, particularly bearing in mind the fact that currently this serotype is the most common cause of IPD in US [55, 91]. Furthermore, 19A has been demonstrated to be resistant to various antibiotics [48].

Moreover, even when cross-protection has been observed in clinical trials, as in the case of the 6A serotype, the post-marketing studies failed to reveal any reduction effect on naso-pharyngeal carriage [82, 92]. In parallel with these findings, the cases of IPD sustained by the 6A serotype revealed a significant reduction only in subjects < 5 years, but not in the rest of the population, thus suggesting that a cross-protection alone is unable to generate an indirect protective effect [89].

In the light of the results obtained, the Authors suggest that, since cross-protection is lacking against some NVT, despite being characterized by an important clinical impact, future vaccine formulations should include also the latter and, in particular, 19A [48].

Economic analysis of the universal infant immunisation programmes with PCV: implications for Italy

Despite the scientific solidity demonstrating the broad effectiveness of the universal infant vaccination programmes with PCV, documented worldwide and especially in US, the introduction in Europe of the vaccine, licensed since 2001, into the national immunisation schedules has been delayed in several countries (Fig. 1), mainly due to financial considerations, strictly linked to the cost per dose, higher, on average, than that of the other routine used vaccines. A number of papers from US, Canada, Australia and Europe has been published in the last years focusing the economic evaluation of the PCV used under a universal immunisation strategy [93-103].

A very interesting systematic review on this item, considering the main researches published between 2002 and 2005, has been recently done by Beutels et al [104]: despite evaluated studies on Cost-Efficacy Analysis (CEA) and Cost-Utility Analysis (CUA) had used a similar methodology of analysis, on a Markov model, the calculated Incremental Cost-Effectiveness Ratios (ICER) differed greatly between experiences, being sometimes favourable sometimes the opposite. This ethereogeneous scenario could, at least in part, depend by the different basic assumptions inserted in the used model of analysis, namely (i) the incidence and the burden of the Pn-associated diseases, with consequent direct and indirect costs, (ii) the price of the vaccine itself and of the whole immunisation programme (logistic and organisational aspects) and (iii) the estimated vaccine efficacy. Moreover, most of these researches considered immunisation programmes structured on a 4-dose schedule (3 + 1), with the only exception of two studies, in which a regimen of 3-doses (2 + 1), administered to children during the first year of life, had been evaluated: this last strategy is currently adopted in the Scandinavian countries and in some Italian Regions. But the main bias of nearly all the studies published in the mentioned period was that only direct effects, those obtained among vaccinated children, had been considered in the economic analysis of the immunisation campaign: the positive indirect effects among not immunised population, deriving from the herd immunity and the reduction in antibiotic resistance, as largely discussed before, had not been taken into right account, thus neglecting a significant part of the overall benefit of the immunisation programme. Introducing the herd immunity effect in the epidemiological model of analysis of any economic study evaluating programmes of universal immunisa-
tion with PCV need to be considered as mandatory: only using such an approach it is possible to give policy makers a real picture of the overall financial benefits of the preventive strategy, thus orienting interventions in the area of Public Health under a rational approach, balancing available resources and health priorities. This has also been clearly demonstrated by the most recent publications on this item from Canada, UK, US and the Netherlands [60, 102, 105-109]: these experiences have concluded that if both the herd immunity effect and the reduction in the strains resistant to penicillin are considered, the ICER of universal immunisation programmes is seen to be highly favourable and even cost-saving. This is what results also in a study performed in Norway, where a financial cut-off of Euro 54,000 per Life Year Gained (LYG) was set by the Government for the implementation of any health-care intervention. In fact, assuming that three vaccine doses could provide the same protection as four, considering the effect of herd immunity and both direct and indirect costs in the economic analysis of the universal immunisation strategy of all new borns, Authors found that the programme would have resulted cost-saving: just in consideration of these results, the PCV was officially recommended starting in 2005 into national schedule in this country [109].

On the basis of the above described experiences in European countries where a universal strategy with PCV has been adopted and considering that the epidemiological scenario of the diseases sustained by Pn in these geographical areas is nearly superimposable to that existing in Italy, we support an active, free-of-charge, 3 dose-schedule (2 + 1) programme for the immunisation of all Italian children during the first year of life, as the best strategy both under the health care and the financial point of view.

Conclusive remarks

Recent evidences reported in our paper, showing the direct and indirect protection afforded by PCV-7 when used under a universal children immunisation strategy, clearly suggest the need to adopt this preventive tool in both developed and under developing countries, as recently stated in a position paper by the WHO. In US especially IPD and CAP showed a significant decrease since 2000, when the vaccine was first introduced on the market. Analogue results have been registered in respect with antibiotic non-susceptible pneumococcal infections. A positive effect, even if less evident, was also observed with respect to AOM. Currently, nor the replacement and the increase in antibiotic non-susceptible strains not included in the vaccine seemed to be able to alter the cited overall benefits: the possible availability of new conjugated vaccines, with an extended serotype coverage, is welcome yet, particularly in the

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*Fig. 1. European recommendations for use of PCV in children and mode of payment: up-date to February 2008 (data kindly provided by Weyth Vaccines Italy).*
view of the lack of cross-protection by currently available vaccine against type 19A and 6A, with its implication on herd immunity. In any case, continue monitoring the mid-term potential negative impact of the routine extended use of the PCV among children need to be considered a public health priority in the next years for all countries which decide to adopt universal immunisation programmes.

To date, the introduction of the PCV in Italy for routine national vaccination of all newborns seem to be fully justified by both the epidemiological scenario and the estimated predicted efficacy of the vaccine vs. the local circulating serotypes: co-administering the PCV with the currently recommended hexavalent vaccine (DTPa-PV-HBV-Hib), using a 3-dose schedule in the first year of life, has to be considered the most efficient strategy, balancing the need of protection against the Pn-associated diseases and both the economic and organizational aspects of the programme, thus its mid-term sustainability.

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