REVIEW

Childhood pneumococcal vaccination in Europe

P.L. LOPALCO
University of Bari, Italy; European Centre for Disease Prevention and Control, Stockholm, Sweden

Key words

Pneumococcal infection • Pneumococcal vaccines • Childhood vaccination • European Union

Introduction

Invasive diseases caused by *Streptococcus pneumoniae* (pneumococcus) are a major public health issue in Europe as well as worldwide. Severe diseases caused by pneumococci are pneumonia, meningitis and febrile bacteraemia; otitis media is a more common, but less serious manifestation of pneumococcal infection.
Pneumococcus can affect all age groups but the bigger burden of disease is among children, elderly and other vulnerable people, like those with conditions associated with immune deficiency.
The World Health Organisation (WHO) estimated in 2005 that 0.7-1 million children below 5 years of age died of pneumococcal disease. Most of those deaths are in the developing countries [1]. In the industrialised world pneumococcal meningitis still shows fatality rates of 5-10% (much higher in those with underlying serious conditions); fatality rates of pneumococcal pneumonia are generally age-related and can range between 10 and 30% [2].
S. pneumoniae is showing a growing resistance to commonly used antibiotics. This highlights the urgent need for effective vaccines against pneumococcal infection.
Specific protection against capsular polysaccharide antigens is needed to prevent pneumococcal infections and invasive disease. Pneumococcal vaccines have been developed to cover the serotypes that are most frequently cause of invasive disease in different age groups.
Currently a 7-valent protein-conjugated (PCV7) and an unconjugated 23-valent vaccine are available worldwide. The 23-valent is licensed for use after 2 years of age and is designed for use in older children and adults. PCV7 is licensed for use under 5 years of age and can be easily integrated in most of the childhood vaccination schedules.
PCV7 has been licensed in the US in February 2000. In October 2000 the Advisory Committee for Immunisation Practice (ACIP) recommended the use of PCV7 for all American children aged 2-23 months and for those aged 24-59 months that are at higher risk of pneumococcal invasive disease [3]. The first evaluation carried out during the following years indicated substantial declines in invasive pneumococcal disease (IPD) in children and adults compared with pre-vaccine years; surprisingly the vaccine prevented more than twice as many IPD cases in 2003 through indirect effects on pneumococcal transmission (i.e., herd immunity) than through its direct effect of protecting vaccinated children [4].

Epidemiology of S. pneumoniae in Europe: what we do, what we don't and what we should know

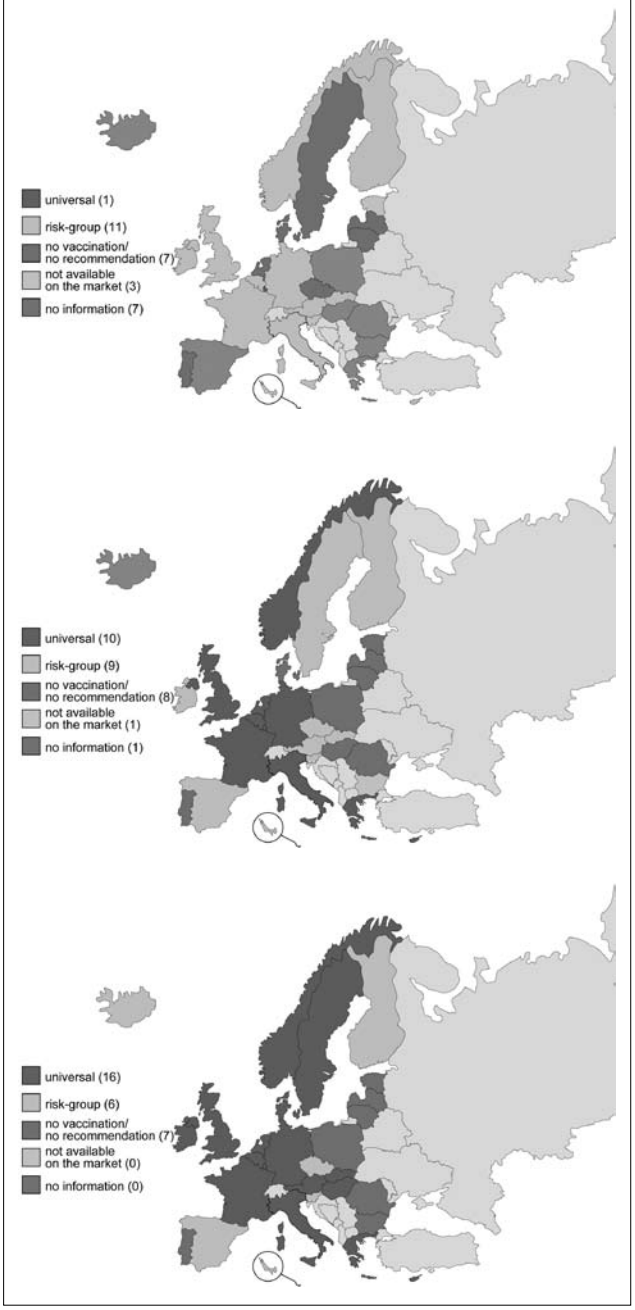
Taking an informed decision on introduction of a new vaccine is always a challenge. In the case of *S. pneumoniae* this issue is even more complex because the driver of the decision are – in addition to the cost of the vaccine – some epidemiological considerations that are not trivial. First of all, assessment of the burden of disease is complex: 1) *S. pneumoniae* causes a large spectrum of diseases from otitis media to septicaemia; 2) invasive diseases like meningitis and septicaemia can be caused by many different bacteria other than pneumococcus and only microbiological issues can define the etiological diagnosis; 3) in many medical settings it is not routinely identified the serotype and then often it is not possible to ascertain if it is a vaccine serotype (VT) or not; 4) the incidence of specific pneumococcal bacteraemia is strongly dependant by the attitude at routinely performing haemoculture. In addition, there are still many unknowns regarding the possible role of the vaccination in inducing changes in the ecology of *S. pneumoniae*. Some of these expected changes can be positive, like the reduction of antimicrobial resistant strains, but the most feared one is the strain replacement with non-VT. Last but not least, the herd immunity effect – well described in the US experience – is difficult to assess and, in particular, to measure.
Without any doubt surveillance of IPD in the European Union (EU) is a critical point in the decision making process for defining vaccination policies. There is still no EU-wide surveillance system for IPD. According to a recent survey coordinated by the ECDC, surveillance systems for IPD are very heterogeneous in the EU. On the other hand there are also some strengths that may represent a basis for EU-wide surveillance. One of those is the presence of pneumococcal meningitis surveillance

in all countries; the other one is the wide availability of serotyping that could provide important information for assessing the impact of vaccination programmes.
Nevertheless, even in absence of routine surveillance systems, many observational studies provided a lot of information on the burden of IPD in Europe. Of course, lack of coordination and standard methodology leads to difficult comparability and makes impossible any benchmarking.
A systematic review performed in 2006 highlighted a huge variability of incidence levels between different European countries [5]. Eighteen studies conducted in 10 different European countries were considered for the systematic review. Incidence values of IPD in children below 2 years of age ranged from 11.30 to 37.80 per 100,000; incidence rates were much higher (up to 90 per 100,000) when included occult bacteraemia. Combining the studies altogether the incidence resulted 27.03 per 100,000. No clear geographical pattern was shown, being the differences mostly attributable to different case definitions and diagnostic issues. When the Authors have included in the calculation only the incidence of pneumococcal meningitis, differences between countries were less evident ranging from 3.78 to 14.64; the combined value was 8.71 (95% CI 7.06 – 10.76 per 100,000). Those data are showing a picture substantially different from the US situation, where the incidence of IPD in the pre-vaccine era was estimated to be close to 80 cases per 100,000 in children below 5 years of age [4]. It is hard to say either pneumococcal disease burden is really that different in the US in comparison with Europe, or it is more the result of surveillance artefacts, nevertheless such discrepancies have had an important impact on the decision making process in the EU.
One of the most debated issues in Europe has been the impact of PCV7 vaccination on the ecology of *S. pneumoniae,* fearing that the strain replacement by non-VT could reduce the effectiveness of the vaccination programme.
The initial estimate, done by US CDC, was that serotypes included in PCV7 accounted for 86% of bacteraemia and 83% of meningitis in children les than 5 years of age. Serotype coverage of PCV7 in Europe has been estimated – in the pre-vaccine era – around 75% [5], sensitively lower than what expected in the American epidemiological setting. Unfortunately – also in this case – we cannot rely on a unique source of information and the variation between countries is pretty high: according to the registration file, PCV7 should cover between 54% and 84% of isolates from IPD in European children less than 2 years of age and between 62% to 83% in children 2 to 5 years of age [6].
According to the UK surveillance system, since PCV7 introduction in 2006 the number of reports of IPD due to non-VT almost doubled in children below 5 years of age; nevertheless the overall impact on IPD in children has to be considered still high because the huge reduction of cases due to VT [7]. Moreover, it is not possible to rule out the possibility that the increased number of reports might be due to surveillance artefacts linked to increased sensitivity of the system after the vaccine introduction.
In countries where the vaccine is widely used but not universally administered, such as Italy, Spain and Portugal, the situation is even more complex, results are difficult to interpret and forecast of trends are unfeasible. In a study conducted in Navarra (Spain) in 2006 the approach to the problem was different than surveillance data analysis [8]. The Authors conducted a case-control study to assess the vaccination status of children diagnosed with IPD. This way they assessed the effect of replacement at the individual level in the vaccinated children. The estimated effectiveness of vaccination with PCV7 in preventing IPD, regardless of serotype, was only 31%, because the vaccinated children had a 6 times greater risk of IPD due to non-VT than did those who were not vaccinated. These findings are difficult to compare with other observations done in Spain in low-coverage situation [9] and with other studies conducted in Portugal in a very similar situation [10] and any conclusive interpretation is not possible at the present. For this reason the issues of serotype replacement and vaccine effectiveness deserve further investigation in order to better understand some local dynamics related to different levels of vaccination coverage.

Introduction of PCV7 into European childhood vaccination schedules

The European Commission granted a marketing authorisation valid throughout the European Union for PCV7 (Prevenar) to Wyeth Lederle Vaccines on 2 February 2001. The marketing authorisation was renewed on 2 February 2006.
Even though the availability of PCV7 on the European market followed by only few months the introduction of Prevenar in the US routine childhood immunisation schedule, nevertheless the decision on starting PCV7 universal vaccination has been slow and patchy in the EU countries (Fig. 1).
In 2004 a European wide survey was conducted as part of a EU funded project on pneumococcal disease (Pnc-EURO). Information on pneumococcal vaccination policies – including both adult and children immunisation – were collected by the means of a standardised questionnaire that was completed by 23 countries [11]. According to the results from that survey, in 2004 vaccine was available on the market in all but 3 (Estonia, Slovenia and Malta) of those countries participating in the survey; at that time only 12 EU countries had developed national recommendations. Most of the countries recommended PCV7 to be used in high risk groups. Universal childhood vaccination was started only in Luxembourg.
Findings from this survey clearly illustrated how in Europe there was already an important delay in introducing PCV7 vaccination in comparison with the US. In 2004 only Luxembourg had started PCV7 universal vaccination programme. On the other hand the definition of "risk groups" was very different, then the number of

Fig. 1. Introduction of PCV7 in EU + EEA/EFTA Member States. Situation update in 2004, 2006 and 2008. Source of information and more details in the text.



recommended risk groups varied a lot from country to country from very limited to very extensive indications including children attending day-care, such as in France. On the other hand, at that time important evidence on the impact of pneumococcal childhood vaccination was already coming from the other side of the Ocean [4], raising the issue of equity and access to healthcare for those countries – like the majority of the EU – where the vaccine was available on the private sector but not reimbursed by the health insurance scheme.

In 2006 a EU-roundup was conducted by the Eurosurveillance journal in 25 EU countries plus Norway, Romania and Bulgaria, that at that time had not joined yet the EU [12]. Results from that survey showed a slowly moving situation, as 9 countries – after Luxembourg that was the first – had started a universal vaccination programme: Belgium, Cyprus, Greece, France, Germany, the Netherlands, Norway, UK together with some regions in Italy, where the national authorities recommended the PCV7 but delegated the decision on its introduction to the regions. In addition, 9 countries recommended the PCV7 vaccination for selected risk groups. At that time none of the Central-Eastern European countries had introduced yet universal vaccination.

More recently, a new EU wide survey has been conducted by the European Centre for Disease Prevention and Control (ECDC) in collaboration with the EUVAC network [13]. Updated information up to the end of 2008 have been collected in all EU countries plus Norway and Iceland [14]. In comparison with the situation in 2006, 6 more countries had started a universal vaccination programme (or delivered recommendation for universal childhood vaccination) with PCV7: Austria, Denmark, Hungary, Ireland, Slovakia and Sweden. Some findings from this survey are remarkable:

- the situation at the end of 2008 was really improved in comparison with the previous years;
- PCV7 is universally utilised in most of the Western European countries, but also some Central-Eastern countries started a universal vaccination programme;
- analysis of data on vaccine sales demonstrates that countries like Portugal and Spain – that did not start a universal vaccination programme – indeed largely utilise PCV7 vaccination, mostly through the private market [14].

Finally, it is important to underline that all the three surveys showed an extreme variability in terms of vaccination schedule: both number of doses and recommended intervals present a huge variation due to the need of adapting them to the basic childhood immunisation schedule. For this reason, the same vaccine product – Prevenar, that is centrally authorised through the EMEA – is actually used in several different ways in different EU countries (three or four doses schedule with an endless list of different time intervals).

Final considerations

Pneumococcal vaccination in children is a clear example of how vaccination programmes are dealt in a different way in the US than in Europe.

In the US, recognising IPD in children as a public health priority has led to the development of a multivalent vaccine designed on the basis of the national epidemiological situation, followed by the rapid decision on integrating it in the basic immunisation schedule. Immediately after vaccine introduction national authorities were able to assess the impact of the vaccination programme and to highlight the main challenges for further improvements.

Only one year after the introduction in the US, PCV7 was available for the use on the EU market. Nevertheless decision on PCV7 introduction has been very slow, patchy and – after introduction – few countries put in place effective systems for monitoring the impact of vaccination programme.
One explanation can be linked to the cost of PCV7 that actually has been the first expensive one in the vaccines panorama. In some countries just adding PCV7 would have meant to double the overall expenses for infant vaccination. In addition, lack of reliable epidemiological data prevented any assessment of cost-effectiveness at national or regional level. The fact that the seven serotypes included into the vaccine had been picked up according to the US epidemiology did not help the decision.
The availability of PCV7 on the private market only – in those countries without a national programme covered by health insurances – raises also some inequality issues.
Unfortunately, the role of EU institutions have been very weak in this field, due to several legislative constrains that make human vaccination a matter of almost exclusive national competence. The presence of the European Centre for Disease Prevention and Control (ECDC) [15] is trying to fill a gap by the means of establishing EU-wide surveillance systems, setting up steady discussion forums [16] and facilitating experience and best-practice sharing.
Nevertheless, there is a long way to go before establishing a good platform for common vaccination policies in the EU. In the meanwhile new vaccine products effective against IPD are coming on the market. Maybe this will be an opportunity for re-discussing pneumococcal vaccination policies and hopefully to agree upon a more harmonised European approach.

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■ Correspondence: P.L. Lopalco, European Centre for Disease Prevention and Control, Tomtebodavagen 11b, Stockholm, Sweden - Tel. +46 8 58601212 - E-mail: pierluigi.lopalco@ecdc.europa.eu