

INVASIVE PNEUMOCOCCAL DISEASES IN CHILDREN AGED 1-59 MONTHS IN SICILY, ITALY: IMPORTANCE OF ACTIVE FAMILY PAEDIATRICIAN SURVEILLANCE AND VACCINATION COVERAGE.

Emanuele Amodio¹, Claudio Costantino¹, Mario Giuffrè¹, Maria Piccione¹, Fabio Tramuto¹, Francesco Vitale¹ and Working group

Working Group

Dr. A. Bella, Dr. S. Stefani, Dr. C. Abate, Dr. M. Allù, Dr. M. Arena, Dr. F.R. Armenia, Dr. I. Barberi, Dr. G. Barraco, Dr. F. Belbruno, Dr. L. Bozzanca, Dr. G. Bruno, Dr. G. Canzoneri, Dr. C. Casà, Dr. N. Casuccio, Dr. L. Contrino, Dr. M. Cuccia, Dr. G. Cavaleri, Dr. R. D'Angelo, Dr. S. Di Naro, Dr. P. Di Stefano, Dr. P. Dones, Dr. F. Emma, Dr. R. Falsaperla, Dr. G. Ferrera, Dr. G. Geraci, Dr. E. Ghiraldi, Dr. G. Gramaglia, Dr. F. Iacono, Dr. Incorpora, Dr. A. Lizzio, Dr. S. Madonia, Dr. C. Malato, Dr. G. Marcantonio, Dr. S. Margani, Dr. F. Merlino, Dr. L. Nicastro, Dr. G. Nicoletti, Dr. L. Palillo, Dr. P. Pavone, Dr. A. Porto, Dr. G. Puglisi, Dr. A. Rotondo, Dr. V. Salvo, Dr. M. Santagati, Dr. C. Santangelo, Dr. I. Sferrazza, Dr. G. Stassi, Dr. F. Tumminelli, Dr. A. Varvaro, Dr. M. Vitale.

SUMMARY

Purpose: Aim of this study was to analyze pediatric invasive pneumococcal disease rates several years after the implementation of infant pneumococcal vaccination.

Methods: The study was carried out in Sicily and involved about 30,000 children, aged 1-59 months, actively monitored by 100 family pediatricians during 2010 and 2011. All children who met the inclusion criteria were considered eligible, recorded using a standardized case report form and investigated for the presence of *S. pneumoniae* in specimens from sterile sites.

Results: None of the 40 eligible children was confirmed as a case of invasive pneumococcal disease. The incidence rate of invasive pneumococcal disease cases was 0.0/100,000 in both years. Regional childhood pneumococcal vaccination coverage rates were 90.7% in 2010 and 92.0% in 2011.

Conclusions: Our results show that during the study period invasive pneumococcal disease cases were rare in Sicilian children, suggesting a very effective control of the disease in a region with very high vaccination coverage against *S. pneumoniae*.

Introduction

Streptococcus pneumoniae is considered a major health problem worldwide, being a cause of high morbidity and mortality, especially among infants and elderly subjects [1]. In Europe, during the pre-vaccination era, about 260,000 episodes of serious pneumococcal diseases were estimated to occur yearly among children aged 1-59 months [2]. Since 2007, the World Health Organization (WHO) has recommended the worldwide introduc-

Address of the authors

¹ Department of Sciences for Health Promotion and Mother-child care "G. D'Alessandro" of the University of Palermo.

Send correspondence to: Emanuele Amodio, emanuele.amodio@unipa.it

Received: December 13th, 2013 — Revised: December 28th, 2013 — Accepted: January 14th, 2014

tion of the conjugate pneumococcal vaccination into national immunization programs (NIPs), with the aim of reducing the burden of invasive pneumococcal diseases (IPD) [3]. Moreover, the WHO has also recommended appropriate surveillance of IPD, by estimating the vaccine coverage rate and monitoring the effect of vaccination continuously [3]. In Italy, pneumococcal vaccination in infants has been recommended since the 2005-2007 national immunization program [4]; however, in Sicily, universal infant vaccination with pneumococcal conjugate vaccine began in 2004, with 3 doses at 3, 5 and 11 months. Nevertheless, despite the gradual increase of vaccine uptake, there is a general lack of local data regarding the burden of pediatric IPD after the introduction of the universal vaccination program.

In order to contribute to the data supporting the effectiveness of pneumococcal vaccination in infants, in the present study, we analyzed IPD rates in a sample population of children aged less than 5 years in Sicily during two years of active surveillance.

Material and methods

Study design

Prospective, population-based surveillance study carried out in all 9 Sicilian districts (Agrigento, Caltanissetta, Catania, Enna, Messina, Palermo, Ragusa, Siracusa, and Trapani) among a pediatric population. An active surveillance program was conducted from 1st January 2010 to 31st December 2011 by 100 family pediatricians who were willing to participate to the surveillance network. Considering a mean of about 300 children aged 0-59 months for each family pediatrician [5], the surveillance was expected to cover a total of about 30,000 pediatric subjects, accounting for about 10% of the entire general population aged less than 5 years and living in Sicily in 2010 and 2011 (294,187 and 296,170 subjects, respectively). Moreover, data on regional pneumococcal vaccination coverage were obtained from the Health Department of the Sicilian government.

Eligible subjects and case definition

All family pediatricians were well-trained to actively assess all patients with clinical suspicion of IPD. As a consequence, children who met the following inclusion criteria

were considered eligible and further investigated for IPD:

- axillary temperature ≥ 39.0 °C and/or clinical suspicion of IPD (as any invasive *S. pneumoniae* syndrome);
- negative urine analysis for urinary tract infections based on fast urine test;
- C-reactive protein (CRP) > 15 mg/L.

The exclusion criterion was refusal of the parent or legal guardian to give written consent. The role of the family pediatrician was to enroll eligible patients and fill in a standardized case report form (e-CRF) including demographic information, baseline diagnosis, history of receipt of a conjugate or polysaccharide pneumococcal vaccine, and absence/presence of factors known to be associated with IPD. Finally, IPD cases were defined as eligible subjects with the isolation of *Streptococcus pneumoniae*, or a positive Polymerase Chain Reaction (PCR) test, from a normally sterile site [6, 7].

Laboratory analyses

Upon enrolment, a blood sample was collected. Specimens from other sterile sites (pleural, joint, and cerebrospinal fluids) were collected as per routine medical practice. All samples were cultured for bacteria. According to the study by protocol, if *S. pneumoniae* was detected in a participant, antimicrobial susceptibility was tested for and a subculture of the isolate was transferred to the laboratory of the Azienda Ospedaliero-Universitaria Policlinico "Gaspere Rodolico" in Catania in order to perform serotyping using a commercial kit for latex agglutination (Pneumotest latex kit, Statens Serum Institute, Copenhagen, Denmark). Finally, PCR testing was performed on sterile fluids of all subjects who met the inclusion criteria. Genomic DNA was extracted using the Pure Link RNA Mini Kit (Invitrogen) and PCR amplification of the *lytA* and *ply* genes was used to identify presumptive *S. pneumoniae*.

Statistical analysis

Subjects were enrolled in the study in accordance with the inclusion and exclusion criteria. Absolute and relative frequencies were calculated for qualitative variables, while quantitative variables were summarized as mean \pm standard deviation. Incidence of IPD was estimated by the number of laboratory confirmed IPD cases divided by the number of children monitored in the

sampled population per year. Data were analyzed using the R statistical software package.

Results

As reported in table 1, a total of 31,618 (M/F ratio=1.05; mean age= 23.9 ± 17.8 months) and 31,109 children (M/F ratio= 1.04; mean age= 23.4±16.8 months) were observed during 2010 and 2011, respectively. The final observed sample accounted for 10.6% of the entire Sicilian population aged less than 5 years, ranging

from 7.3% in Enna to 11.8% in Palermo. Figure 1 shows IPD cases and vaccination coverage observed during the study period.

Regional pneumococcal vaccination coverage rates were 90.7% in 2010 and 92.0% in 2011.

During the surveillance period, 40 children (23 in 2010, accounting for 0.07% and 17 in 2011, accounting for 0.05%) met the inclusion criteria and were recruited in the study. None of the eligible subjects was confirmed as an IPD case. The overall inci-

	2010	2011
Sample population aged 0-59 months; n (% of the entire pediatric Sicilian population)	31,618 (10.7%)	31,109 (10.5%)
M/F ratio	1.05	1.04
Age in months; mean ± SD	23.9 ± 17.8	23.4 ± 16.8

Table 1: Characteristics of the pediatric sample population observed during the two years of surveillance.

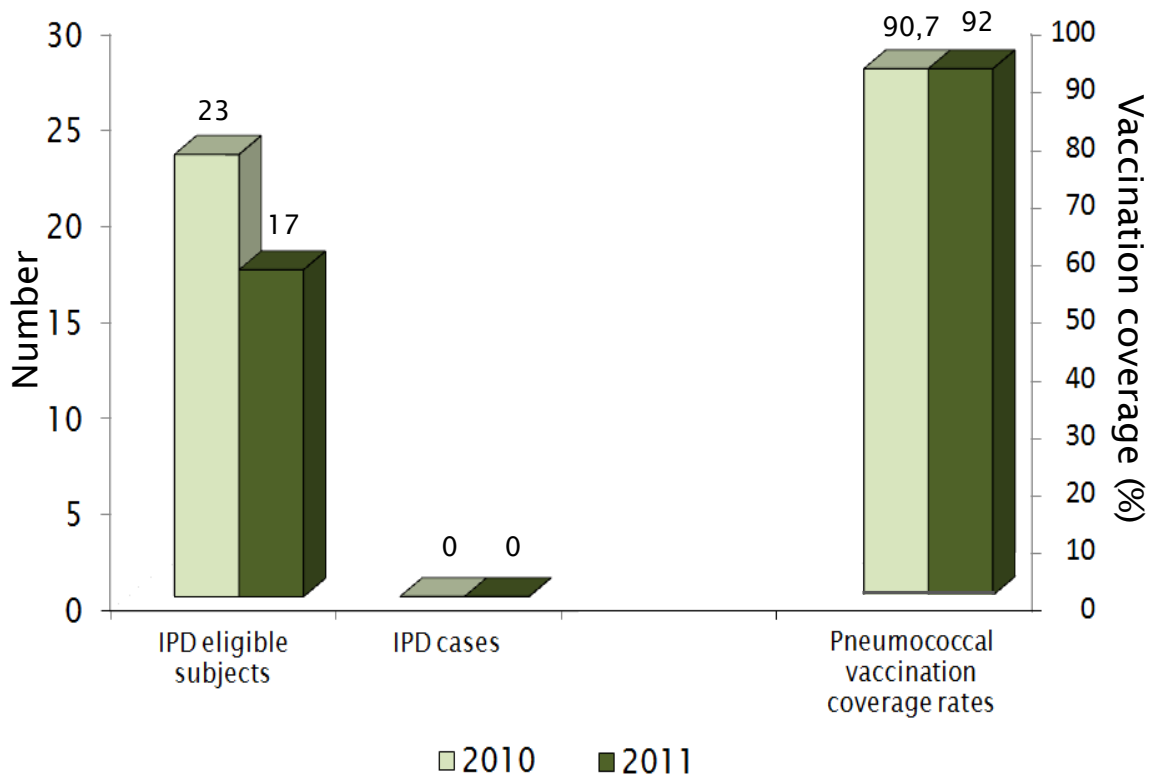


Figure 1: IPD cases and vaccination coverage observed during the study period.

dence rate of IPD cases was 0.0/100,000 in both years.

4. Discussion

Measuring the local burden of vaccine preventable disease using active surveillance models is of crucial importance in informing policy-makers regarding the implementation of evidence-based public health strategies such as vaccination campaigns. In Sicily, pneumococcal vaccination for infants began in 2004 but, to the best of our knowledge, this is the only study designed with the aim of evaluating the effects of pneumococcal vaccination in the reduction of the IPD burden in the pediatric general population. Our results show that invasive pneumococcal infections can be considered relatively rare in Sicilian children, suggesting a very effective regional control of the disease. This result was, at least in part, expected for two main reasons.

Firstly, our data seem to represent a trend whereby Italian regions with higher pneumococcal vaccination coverage such as Sicily (>90%) and Puglia (81.9%) [8] report lower IPD incidence rates than regions such as Lombardia, where only 27.1% of infants were vaccinated against *S. pneumoniae* [8]. Indeed, other Italian studies report IPD rates from 2.8/100,000 per year in Puglia and 5.7/100,000 in Piemonte [9], but rates of 50.0/100,000 cases per year in Lombardia [10].

Secondly, the total absence of IPD cases in our study population is expected since, at the beginning of this study, universal pneumococcal vaccination of Sicilian infants had already been in place for more than 5 years with very high vaccination coverage (> 90%). As a consequence, a very large majority of subjects included in the surveillance was expected to have been vaccinated against pneumococcal infection. Moreover, several authors have observed a reduction of nasopharyngeal carriage of vaccine strains in both vaccinated and unvaccinated children after the introduction of conjugate pneumococcal vaccines [11, 12]. Although the indirect effect cannot easily be measured and a vaccine induced replacement has been reported by some authors [13], the fact that the very high vaccine coverage in our study population could have reduced the rate of pneumococcal diseases also in non-immunised individuals as a consequence

of the herd effect, should be taken into consideration.

Finally, the present study could have some limitations due primarily to the relatively small number of subjects recruited. As a result, incidence could be significantly distorted by changes in the numbers of isolates. Moreover, it is not possible to be certain that family pediatricians captured all potential eligible subjects, which could result in a possible underestimation of disease burden.

Despite these possible limitations, the present study is the first that estimates IPD incidence in an Italian region where pneumococcal vaccination has both been in place for a relatively long time and has a high coverage. The absence of IPD cases during the surveillance period, in comparison with higher IPD incidence rates observed in other Italian regions with lower pneumococcal vaccination coverage, suggests the importance of maintaining very high immunization levels against *S. pneumoniae*.

Acknowledgment: This study is supported by a grant from Pfizer Italia (Protocol number 0887X1-4432). Thanks are due to the participating children and their families, family pediatricians involved in this study and medical direction of Pfizer.

References

1. Melegaro A, Edmunds WJ, Pebody R, Miller E, George R. The current burden of pneumococcal disease in England and Wales. *J Infect.* 2006;52:37-48.
2. O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, Lee E, Mulholland K, Levine OS, Cherian T. Hib and Pneumococcal Global Burden of Disease Study Team. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet.* 2009 Sep 12;374(9693):893-902. Review.
3. World Health Organization Pneumococcal conjugate vaccine for childhood immunization – WHO position paper. *Wkly Epidemiol Rec.* 2007;82:93-104.
4. Piano Nazionale Vaccini 2005-2007. Available on http://www.salute.gov.it/imgs/C_17_pubblicazioni_543_allegato.pdf, accessed 10/10/2012.
5. ISTAT. Available at <http://www.istat.it/it/sicilia/dati?>

q=gettable&dataset=DCIS_ASSBASE&dim=120,0,0&lang=2&tr=0&te=1

6. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, Reingold A, Cieslak PR, Pilishvili T, Jackson D, Facklam RR, Jorgensen JH, Schuchat A. Active Bacterial Core Surveillance of the Emerging Infections Program Network Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med.* 2003;348(18):1737-1746.

7. Italian National Institute of Health. Protocollo per la sorveglianza nazionale delle malattie

invasive da meningococco, pneumococco ed emofilo in Italia. 2007. Available at http://www.salute.gov.it/imgs/C_17_pubblicazioni_744_allegato.pdf, last access on 12/31/2013.

8. Nicolotti N, Gualano MR, Kheiraoui F, Castiglia P, Pessina EA, Ricciardi W, La Torre G. Introduction of a new vaccine in the context of Italian and regional prevention. *Italian Journal of Public Health.* Volume 6, Issue 4 SUPPL. 5, 2009, Pages 34-51. Available at <http://www.ijph.it/pdf/27/034.pdf>

9. D'Ancona F, Salmaso S, Barale A, Boccia D, Lopalco PL, Rizzo C, Monaco M, Massari M, Demicheli V, Pantosti A, Italian PNC-Euro working group. Incidence of vaccine preventable pneumococcal invasive infections and blood culture practices in Italy. *Vaccine* 2005, 23:2494-2500.

10. Riva E, Salvini F, Garlaschi ML, Radaelli G, Giovannini M. The status of invasive pneumococcal disease among children younger than 5 years of age in north-west Lombardy, Italy. *BMC Infect Dis.* 2012 May 3 and 12:106.

11. Dagan R, Patterson S, Juergens C, Greenberg D, Givon-Lavi N, Porat N, Gurtman A, Gruber WC, Scott DA. Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccines in reducing nasopharyngeal colonization: a randomized double-blind trial. *Clin Infect Dis.* 2013 Oct;57(7):952-962.

12. Fleming-Dutra KE, Conklin L, Loo JD, Knoll MD, Park DE, Kirk J, Goldblatt D, Whitney CG, O'Brien KL. Systematic Review of the Effect of Pneumococcal Conjugate Vaccine Dosing Schedules on Vaccine-type Nasopharyngeal Carriage. *Pediatr Infect Dis J.* 2014 Jan;33 Suppl 2:S152-60.

13. Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. *Lancet.* 2011 Dec 3;378(9807):1962-1973.