DEPARTAMENT DE MEDICINA

UNIVERSITAT AUTÒNOMA DE BARCELONA

Autor: Joaquin Burgos Cibrián

Títol: Invasive pneumococcal disease among adults: Changes in clinical presentation and outcome after introduction of 7 valent pneumococcal conjugate vaccine in children.

Direcció: Vicenç Falcó Ferrer.

Treball de recerca.

Concocatòria de setembre. 2010

Annex 1
CERTIFICAT DEL DIRECTOR O CO-DIRECTOR DEL TREBALL DE RECERCA

Vicenç Falcó ferrer, Professor del Departament de Medicina de la Universitat Autònoma de Barcelona, (o el càrrec hospitalari que tingui el director del treball),

FA CONSTAR,

que el treball titulat "Invasive pneumococcal disease among adults: Changes in clinical presentation and outcome after introduction of 7 valent pneumococcal conjugate vaccine in children" ha estat realitzat sota la meva direcció pel llicenciat Joaquin Burgos Cibrián, trobant-se en condicions de poder ser presentat com a treball d'investigació de 12 crèdits, dins el programa de doctorat en Medicina Interna/Diagnòstic per la Imatge (curs 2009-2010), a la convocatòria de setembre.

Barcelona, 23 de agost de dos mil deu.

INDEX

ABSTRACT

Background.

The introduction of pneumococcal conjugate vaccine in children has changed the pattern of pneumococcal serotypes causing invasive pneumococcal disease (IPD). The aim of this study was to analyze the differences in clinical presentation and outcome between the pre and postvaccine era in adults with IPD.

Methods.

An observational study of all adults hospitalized with IPD in a university hospital, from 1997 to 2001 (prevaccine period), and from 2006 to 2009 (postvaccine period). Incidence rates, serotype distribution and clinical data were compared between both periods.

Results.

A total of 688 episodes of IPD were observed. In the postvaccine period IPD caused by vaccine serotypes decreased significantly (-54%; 95%CI, -66% to -38%) while IPD caused by non-vaccine serotypes increased (200%; 95%CI, 105% to 338%). Among patients aged 18-50 years, the incidence of IPD and empyema increased significantly (from 9.9 to 17.1 cases per 100,000 population-year and from 0.8 to 2.3 per 100,000 population-year respectively). The IPD in postvaccine period was associated to higher rates of septic shock (16.4% vs. 29.3%, p<.001), greater ICU admission (16.9% vs. 23.5%, p=.039) and, among patients aged 50-65 years, a higher score in the pneumonia severity index (score IV-V: 54.2% vs. 77.3%, p=.008). The overall case-fatality rate among patients aged 50-65 years increased from 11% to 24.1% (p=.023).

Conclusions. Our findings indicate that the emergence of new serotypes seems to be associated with increases of IPD incidence, especially in younger adults, and with clinical changes to a more severe illness.

INTRODUCTION

After the implementation of the 7-valent pneumococcal conjugate vaccine (PCV7) in USA significant declines in invasive pneumococcal disease (IPD) were reported in young children [1-4]. Moreover, decreased rates of IPD were also observed in groups of unvaccinated population, especially in adults, suggesting that PCV7 has both direct and indirect protective effects in vaccinated and unvaccinated people [3-5]. This protective effect in unvaccinated individuals is likely due to a reduction in transmission of vaccine-type pneumococci as a result of the reduction in carriage in the vaccinated pediatric population [6,7].

Simultaneously, increases in the incidence of IPD caused by non-PCV7 serotypes, both in children and adults, were observed [8-10]. The question is whether shifts in serotype distribution of IPD may be accompanied by changes in disease severity. In fact, high rates of empyema in children with pneumococcal pneumonia associated to the non-PCV7 serotypes 1 and 3, have been observed [11, 12].

PCV7 was introduced in Spain in June 2001 and, although it was not included in the routine pediatric vaccination schedule except for children at high risk, it has been extensively used in the private medicine for children aged < 2 years. In 2006 it was estimated that about 50% of children had been vaccinated [13]. In Spain, as in other geographic areas, the emergence of IPD caused by non-PCV7 serotypes after PCV7 introduction has also been described [10,14,15].

To our knowledge there are scarce data about the clinical impact of the emergence of IPD caused by non-PCV7 serotypes in adults after the introduction of the PCV7. The aim of our study was to analyze the differences in the disease characteristics, complications and clinical outcome between the pre and post PCV7 era in hospitalized patients with IPD.

PATIENTS AND METHODS

Study population and setting.

We performed an observational study of all adults hospitalized with IPD from January 1997 to December 2001, and from January 2006 to December 2009 in the University Hospital Vall d'Hebron, a 1200-bed terciary care teaching hospital in Barcelona that serves an estimated population of 500000 people. Patients were classified in two groups according to the introduction of PCV7 in our area: prevaccine period (1997-2001) and postvaccine period (2006-2009). The study was approved by the Commission of Medical Ethics of our institution.

Study variables and data collection.

The patients' records from 1997 to 1999 were reviewed retrospectively, and from 2000 onwards all data were collected prospectively. From each patient the following variables were recorded: (1) sociodemographic data; (2) underlying diseases; (3) immunosuppressive conditions; (4) clinical syndrome (pneumonia, meningitis, peritonitis, arthritis, endocarditis and primary bacteremia); (5) severity of the illness at presentation (septic shock, Pneumonia Severity Index (PSI) at the moment of admission to the Emergency Department); (6) microbiological data (serotype and antibiotic resistance pattern of the *Streptococcus pneumoniae* causal strain); (7) antimicrobial therapy and (8) variables related to clinical outcome (mortality, intensive care unit (ICU) admission, orotracheal intubation requirement, suppurative lung complications and length of hospital stay).

Definitions

IPD was defined as isolation of *S. pneumoniae* from a normally sterile site. Pneumococcal meningitis was considered when the patient had a positive CSF culture or a clinical diagnosis of meningitis in combination with a positive blood culture. Invasive pneumococcal pneumonia was diagnosed when a patient had consistent clinical findings plus a new pulmonary infiltrate on chest radiography and isolation of *S. pneumoniae* in blood and/or pleural fluid culture. If no clinical focus could be identified, it was recorded as bacteremia without focus.

Comorbid condition includes any of the following: chronic heart disease, chronic lung disease, cerebrovascular disease, cirrhosis, diabetes, chronic renal insufficiency or need for dialysis. An immunosuppressive condition was considered when any of the following was present: HIV infection, hematologic cancer, solid cancer, solid organ or bone marrow transplantation, immunoglobulin deficiency, splenectomy or current immunosuppressive therapy.

Septic shock was considered when vasoactive drugs were necessary to obtain appropriate arterial pressure values. Empyema was defined as loculated pleural effusion, positive results of

Gram staining or culture of the pleural fluid, purulent pleural fluid with a pH < 7.2 or a glucose level < 40mg/dl [16].

Microbiological procedures

S. pneumonia strains were identified by Gram staining, optoquin susceptibility, bile solubility testing and latex agglutination testing. Amtimicrobial susceptibility was tested using the microdilution method, in accordance with Clinical and Laboratory Standards Institute procedures (CLSI). Serotypes were performed by capsular swelling reaction using commercial serogrup and serotype-specific antisera, using the quellung reaction at the Spanish Reference Laboratory (Instituto Carlos III, Madrid, Spain). Serotypes were classified in two groups: PCV7 serotypes were those that matched serotypes included in the vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F); and all other serotypes were designated as non-PCV7 serotypes.

Calculation of incidence of IPD

Crude and group age incidence rates were calculated using as the denominator the number of people, by age group per year, of the reference area of the hospital in accordance with the public database of the Web de l'Estadística Oficial de Catalunya and is expressed as cases per 100000 people per year [17]. To compare the incidence rates between pre and postvaccine periods we used the mean of the yearly incidence during the period. To estimate the incidence of IPD due to vaccine or nonvaccine serotypes, we assumed that the distribution of serotypes for cases missing serotype information (15% of cases) was the same as the distribution for those cases with serotype information.

Statistical analysis

Statistical analyses were performed using the statistical software package SPSS for Windows, version 15.0.

Differences in means of incidence between prevaccine and postvaccine periods were tested using Mantel-Haenszel test. Their relative risks were reported as the percent changes ((relative risk-1) x 100) in rates with their associated 95% CI.

The X2 test or Fischer's exact test when appropriate, were used to compare the distribution of categorical variables and the Student's T test or the Mann-Whitney U test for continuous variables. Results were considered statistically significant if the 2-tayled p value was <.05. A multivariate analysis using a forward stepwise binary logistic regression model was performed to identify variables independently associated with IPD in postvaccine period. Significant and

nearly significant (P<0.1) variables from univariate analysis were included in the multivariate analysis.

RESULTS.

Changes in disease burden

During the period of the study 668 episodes of IPD were diagnosed in adults, 345 of them in the prevaccine period and 323 in the postvaccine period. The overall incidence of IPD did not change significantly between both periods (19.1 and 20.8 per 100,000 population-year respectively). However, the incidence of IPD due to PCV7 serotypes decreased significantly in the postvaccine period (-54%; 95% CI, -66% to -38%) while the incidence of IPD caused by non-PCV7 serotypes increased significantly (60%; 95% CI, 33% to 93%) (Table 1). Non-vaccine serotypes comprised 55.4% of the isolates in the prevaccine period and 81.2% in the postvaccine period (p<.001).

Reductions in PCV7 serotypes in the postvaccine era were due mostly to a 77% reduction of IPD caused by serogrup 6 (from 2 to 0.5 episodes per 100,000 population-year; 95% CI, -90% to -49%), and a 51% reduction of infections by serogrup 9 (from 1.4 to 0.7 episodes per 100,000 population-year; 95% CI, -76% to -0.1%). In non PCV7 serotypes we found a 94 % increase of IPD caused by serotype 1 (from 1.5 to 2.9 episodes per 100,000 population-year; 95% CI, 20% to 213%) and a 250% increase of infections by serogrup 7 (from 0.5 to 1.7 episodes per 100,000 population-year; 95% CI, 65% to 644%). Although serotype 3 is a non vaccine serotype, we found a significant decrease in its incidence in the postvaccine period from 2.2 to 1.3 episodes per 100,000 population-year (-42%, 95% CI, -66% to -0,2%). No changes in other specific serotypes were observed.

In patients aged 18-50 years, the IPD incidence increased significantly from 9.9 to 17.1 cases per 100,000 persons-year (71.6%; 95% CI, 30%-126%), mainly due to an increase in infections caused by non-PCV7 serotypes (200%; 95% CI, 105% to 338%). Among people aged > 65 years, the IPD incidence decreased from 56.3 to 44.3 cases per 100,000 persons-year (-21%, 95% CI, -38% to -0.6%) associated to a decreased IPD incidence of infections by PCV7 serotypes (-66%; 95% CI, -79% to -45%) without significant changes in infections caused by non PCV7 serotypes. In patients aged 50-65 years there was a significant decrease in infections caused by PCV7 serotypes and a significant increase in infections by non PCV7 serotypes although the overall incidence of IPD did not change in this age group (Table 1).

Sociodemographic variables and underlying diseases

The main baseline variables are shown in table 2. Comparing the two periods, the mean age of the patients decreased from 62.7 to 57.7 years (p=.001). Although we did not observe significant differences in the comorbid conditions between pre and post vaccine periods, the pattern of underlying diseases varied depending on the age. In younger patients (aged

between 18 and 50 years) we found a significant reduction in the proportion of HIV infections (53.1% vs. 26.6%, p<.001). In the other hand, patients aged 50-65 years had greater proportions of chronic medical illness (42.9% vs. 60%, p=.03), and solid cancer (13.1% vs. 36.3%, p=.001) in the postvaccine period. In contrast, no significant differences regarding underlying diseases were observed in the older patients (aged > 65 years).

Clinical syndromes

The most common clinical presentation of IPD was bacteremic pneumonia which accounted for 81.2% of all 668 episodes, followed by meningitis for 8.6% and bacteremia without focus for 6%. The incidence of bacteremic pneumonia increased significantly from 14.7 to 17.4 cases per 100,000 population-year in the postvaccine period. We did not find significant changes in the incidence of meningitis and bacteremia without focus in both periods except for a 61% reduction in primary bacteremia in older population (Table 3).

Overall 11.7% of all patients developed empyema. Both the proportion of patients with empyema and the incidence of empyema were unchanged in the postvaccine compared to the prevaccine period. However, when we analyzed patients according to age groups, in those aged between 18 and 50 years old we found a significant increase (183%; 95% CI, 17% to 583%) of empyema from 0.8 to 2.3 cases per 100,000 persons-year.

Clinical presentation and outcome

The proportion of patients with IPD who presented with septic shock was significantly higher (16.4% vs. 29.3%, p<.001) in the postvaccine era and as a consequence the proportion of patients who required ICU admission was also higher (16.9% vs. 23.5%, p=.039). Although theses changes tended to occur in all age groups, they specially affected to patients aged 50-65 years in whom the proportion of them with septic shock increased from 10.8% to 39.2% (p<.001) and they tended to require ICU admission more frequently (16.9% vs. 29.1%, p=.091) (Table 4). When we analyzed only the whole group of patients with pneumonia we found similar findings. Once again the group of patients with 50-65 years had a higher PSI score (score IV or V: 54.2% vs. 77.3%, p=.008).

The overall case-fatality rate remained unchanged in both periods (18.3% vs. 19.3%). However, among patients aged 50-65 years we found a significant increase in case-fatality rate, from 11% in the prevaccine period to 24.1% in the postvaccine period (p=.023). Although not significant, mortality showed a downward trend in younger patients (19.5% vs. 9.4%, p=.057).

Multivariate analysis showed that patients aged younger than 50 years, septic shock and IPD caused by non vaccine serotypes were independently associated to IPD in the postvaccine era (Table 5).

DISCUSSION

In this study we have observed significant changes not only in the incidence but also in the clinical presentation and severity of IPD in adults after the implementation of pneumococcal conjugate vaccine. These clinical changes seem to be caused by a shift in the pattern of pneumococcal serotypes causing IPD in adults.

In the United States, in the first years after the introduction of pneumococcal conjugate vaccine the overall incidence of IPD decreased significantly not only in children but also in adults [1-5]. This beneficial effect on the incidence of IPD in adults persisted in USA 7 years after the introduction of the vaccine in all age groups [1]. However, in other geographical areas theses changes in the burden of IPD in adults have not been so evident. In a population-based surveillance study in Canada, while there was a significant 37% reduction in the incidence of IPD in adults > 65 years, the incidence in adults aged 16 to 64 years increased by 73% [18]. In France the pneumococcal conjugate vaccine was introduced in 2003 and by 2006 the incidence of IPD not only had not decreased but also increased significantly in adults of all age groups [19]. A similar situation has been observed in Holland and in Spain [10, 15, 20]. In our study the overall incidence of IPD in adults has remained stable from 1997 to 2009, however we found a significant increase of IPD incidence in patients aged 18-50 years in the years following PCV implementation.

Several reasons can be argued to explain the differences in the burden of IPD in adults in United States and Europe. The first reason may be attributed to the different vaccine coverage between USA and Europe. While 93% of children had been vaccinated in 2006 in USA, the estimated coverage was 60% in France and about 50% in Spain by the same period [1, 13, 19]. Differences in the methodology of the studies should also be taken into account. In hospital based studies, like ours, the estimation of incidence rates of IPD may be biased by a higher proportion of severe cases. In contrast the extensive surveillance studies performed in USA may show a more realistic view of the burden of disease in the general population. Finally other factors like fluctuations of serotypes or outbreaks of infections in a specific geographical area may play a role [10].

The question why the disease is increasing in younger adults may be related to the emergence of specific non vaccine serotypes. Brueggemann et al classified pneumococcal serotypes according to their capacity of produce invasive disease [21, 22]. Non vaccine serotypes 1, 5 and 7F have been associated both to invasive disease and also to IPD in younger adults [23, 24]. In

our study we observed a significant increase in infections caused by serotype 1 and serogroup 7 which could explain the increases in incidence of IPD in younger adults.

Our study confirms the findings of previous reports about increasing proportions of patients with IPD who have comorbidities [5, 25]. In our setting this finding has had impact mainly in persons aged 50-65 years. Some authors have suggested that persons with comorbid conditions may be more susceptible to invasive disease caused by the non-PCV7 serotypes [5]. On the other hand, the percentage of patients with HIV infection has decreased in the postvaccine era among young adults, probably because of the generalization of HAART and the implementation of polysaccharide vaccine [10,26,27].

In the postvaccine period we have found significant variations in the incidence of the different clinical syndromes. Incidence of invasive pneumonia has increased, especially in young people, while the incidence of bacteremia without focus has decreased in older patients. Different American studies performed in children have noticed significant increases in rates of empyema and necrotizing pneumonia [11, 28, 29]. Data published in Spain in children also show a trend to higher incidence of empyema [12, 14]. However, to our knowledge there are no published data about suppurative lung complications in adults. We have also found a significant increase in the incidence of empyema in younger patients. Although the reasons behind these changes in the clinical syndromes are not entirely clear, it seems reasonable to explain them by changes in serotypes of pneumococccus causing IPD. It is well known the propensity of various serotypes to cause one type of disease manifestation rather than another [23, 34, 30, 31]. Thus, decreased in bacteremia without focus is probably associated to a decrease in infections caused by serogrup 6 in the postvaccine period, as it has been previously published [5]. In the same way the higher rates of infections by serotype 1, which has propensity to cause suppurative complications, explains the higher rates of empyema both in children and adults in the postvaccine period [11, 28, 29].

In our opinion one of the most important findings of our study is that not only the serotype distribution but also the severity of pneumococcal disease has changed in the postvaccine period. We have found higher rates of septic shock, greater proportion of patients who require ICU admission and, among patients aged 50-65 years, a higher score in the pneumonia severity index and a longer length of hospital stay. When we have analyzed overall mortality we have not found significant changes between pre and postvaccine periods. However the evolution of mortality rates differs depending on the age group analyzed. While mortality rate in younger people has tended to decrease, we have observed a significant increase in case-fatality rates in

patients aged 50-65 years in the postvaccine era. Lexau et al also found an increase in mortality rates in adults aged 50 years or older from 15.7% in 1998 to 19.5% in 2003 [5]. Once again, the explanation for these findings is probably related to the emergence of new serotypes. A recently published study has suggested that initial presentation with septic shock is associated to illness caused by serotype 3 [32]. A previous study found that the presence of a comorbid condition, but also the non-vaccine serotypes 3, 11A, 19A and the vaccine serotype 23F were independently associated to higher mortality in the postvaccine era [5]. More studies are necessary to confirm this data, however it seems that, with the emergence of new serotypes, the clinical presentation and outcome of IPD are changing to a more severity illness.

In conclusion, since the introduction of PCV7 vaccine, there has been a profound decrease in the overall incidence of IPD caused by PCV7-serotypes, nevertheless a replacement by non vaccine serotypes has been produced. The emergence of these new serotypes seems to be associated with increases of IPD incidence in some settings, especially in younger adults, and with changes in clinical presentation and outcomes. These last findings are novel and deserve additional investigation with studies focused on the clinical and outcomes of IPD in order to understand the real impact of PCV7 and the upcoming PCV10 and PCV13 vaccines.

REFERENCES

1. Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis **2010**; 201:32-41.
2. Poehling KA, Talbot TR, Griffin MR, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. JAMA **2006**; 295:1668-74.
3. Hsu HE, Shutt KA, Moore MR, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. N Engl J Med **2009**; 360:244-56.
4. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med **2003**; 348:1737-46.
5. Lexau CA, Lynfield R, Danila R, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. JAMA **2005**; 294:2043-51.
6. O'Brien KL, Millar EV, et al. Effect of pneumococcal conjugate vaccine on nasopharyngeal colonization among immunized and un-immunized children in a community-randomized trial. J Infect Dis **2007**; 196:1211-20.
7. Millar EV, Watt JP, Bronsdon MA, et al. Indirect effect of 7-valent pneumococcal conjugate vaccine on pneumococcal colonization among unvaccinated household members. Clin Infect Dis **2008**; 47:989-96.
8. Singleton R, Hennessy T, Bulkow L, et al. Invasive pneumococcal disease caused by nonvaccine serotypes among alaska native children high levels of 7-Valent pneumococcal conjugate vaccine coverage. JAMA **2007**; 297:1784-92.
9. Jacobs MR, Good CE, Bajaksouzian S, Windau AR. Emergence of *Streptococcus pneumoniae* serotypes 19A, 6C, and 22F and serogroup 15 in Cleveland, Ohio, in relation to introduction of the protein-conjugated pneumococcal vaccine. Clin Infect Dis **2008**; 47:1388-95.
10. Ardanuy C, Tubau F, Pallares R, et al. Epidemiology of invasive pneumococcal disease among adult patients in Barcelona before and after pediatric 7-valent pneumococcal conjugate vaccine introduction, 1997-2007. Clin Infect Dis **2009**; 48:57-64
11. Byington CL, Samore MH, Stoddard GJ, et al. Temporal Trends of Invasive Disease Due to *Streptococcus pneumoniae* among Children in the Intermountain West: Emergence of Nonvaccine Serogroups. Clin Infect Dis **2005**; 41:21-9.

12. Calbo E, Díaz A, Cañadell E, et al. Invasive pneumococcal disease among children in a health district of Barcelona: early impact of pneumococcal conjugate vaccine. Clin Microbiol Infect **2006**; 12:867-72
13. Enfermedad invasiva por *Streptococcus pneumoniae*. Implicación de la vacunación con la vacuna conjugada heptavalente.Madrid: Ministerio de Sanidad y Consumo. **2006**. Available at: http://www.msc.es/ciudadanos/proteccionSalud/infancia/vacunaciones/home.htm
14. Muñoz-Almagro C, Jordan I, Gene A, Latorre C, García-García JJ, Pallares R. Emergence of invasive pneumococcal disease caused by nonvaccine serotypes in the era of 7-valent conjugate vaccine. Clin Infect Dis **2008**; 46:174-82.
15. Guevara M, Barricarte A, Gil-Setas A, et al. Changing epidemiology of invasive pneumococcal disease following increased coverage with the heptavalent conjugate vaccine in Navarre, Spain. Clin Microbiol Infect **2009**; 15:1013-9.
16. Light RW. Parapneumonic effusions and empyema. Proc Am Thorac Soc **2006**; 3:75-80.
17. Web de l'estadística oficial de Catalunya. Idescat. Available at: http://www.idescat.cat. Accessed 15 march **2010**.
18. Kellner JD, Vanderkooi OG, MacDonald J, Church DL, Tyrrell GJ, Scheifele DW. Changing epidemiology of invasive pneumococcal disease in Canada, 1998-2007: update from the Calgary-area *Streptococcus pneumoniae* research (CASPER) study. Clin Infect Dis **2009**; 49:205-12.
19. Lepoutre A, Varon E, George S, Gutmann L, Lévy-Bruhl D. Impact of infant pneumococcal vaccination on invasive pneumococcal diseases in France, 2001-2006. Euro Surveill **2008**; 13:pii: 18962.
20. Rodenburg GD, de Greeff SC, Jansen AG, et al. Effects of pneumococcal conjugate vaccine 2 years after its introduction, the Netherlands. Emerg Infect Dis **2010**; 16:816-23.
21. Brueggemann AB, Griffiths DT, Meats E, Peto T, Crook DW, Spratt BG. Clonal relationships between invasive and carriage *Streptococcus pneumoniae* and serotype- and clones-specific differences in invasive disease potential. J Infect Dis **2003**; 187:1424-32.
22. Brueggemann AB, Peto TE, Crook DW, Butler JC, Kristinsson KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of *Streptococcus pneumoniae* in children. J Infect Dis **2004**; 190:1203-11.
23. Sjöström K, Spindler C, Ortqvist A, et al. Clonal and capsular types decide whether pneumococci will act as a primary or opportunistic pathogen. Clin Infect Dis **2006**; 42:451-9.

24. Jansen AG, Rodenburg GD, van der Ende A, et al. Invasive pneumococcal disease among adults: associations among serotypes, disease characteristics, and outcome. Clin Infect Dis **2009;** 49:e23-9.
25. Albrich WC, Braughman W, Schmotzer B, Farley MM. Changing characteristics of invasive pneumococcal disease in metropolitan Atlanta, Georgia, after introduction of a 7-Valent Pneumococcal Conjugate Vaccines. Clin Infect Dis **2007**; 44:1569-76.
26. Peñaranda M, Falcó V, Payeras A, et al. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control study. Clin Infect Dis **2007**; 45:e82-7.
27. Jordano Q, Falcó V, Almirante B, et al. A Invasive pneumococcal disease in patients infected with HIV: still a threat in the era of highly active antiretroviral therapy. Clin Infect Dis **2004**; 38:1623-8.
28. Byington CL, Korgenski K, Daly J, Ampofo K, Pavia A, Mason EO. Impact of the pneumococcal conjugate vaccine on pneumococcal parapneumonic empyema. Pediatr Infect Dis J **2006**; 25:250-4.
29. Bender JM, Ampofo K, Korgenski K, Daly J, Pavia AT, Mason EO. Pneumococcal necrotizing pneumonia in Utah: does serotype matter? Clin Infect Dis **2008**; 46:1346-52.
30. Heffron R, Varley FM. A Study of Lobar Pneumonia in Massachusetts: Methods and Results of Pneumococcus Type Determination, 1931-1932. Am J Public Health Nations Health. **1932**; 22:1230-48.
31. Colman G, Cooke EM, Cookson BD, Cooper PG, Efstratiou A, George RC. Pneumococci causing invasive disease in Britain 1982-1990. J Med Microbiol **1998**; 47:17-27.
32. Garcia-Vidal C, Ardanuy C, Tubau F, et al. Pneumococcal pneumonia presenting with septic shock: host- and pathogen-related factors and outcomes. Thorax **2010**; 65:77-81.

TABLE 1. Mean incidence of invasive pneumococcal disease by serotype, age group and time period among adult patients.

PNEUMOCOCCAL DISEASE	*PREVACCINE PERIOD*		*POSTVACCINE PERIOD*		*PRE vs POSTVACCINE PERIOD*	
	No. of cases	*Cases per 100000 population-year*	*No. of cases*	*Cases per 100000 population-year*	*Change, % (95% CI)*	*P value*
All serotypes						
All adults	*345*	*19.1*	*323*	*20.8*	*9.3% (-6% to 27%)*	*.25*
Adults aged 18-50 years	*85*	*9.9*	*125*	*17.1*	*73% (30% to 126%)*	*<.001*
Adults aged 50-65 years	*84*	*13.1*	*80*	*14.5*	*11% (-18% to 51%)*	*.5*
Adults aged > 65 years	*176*	*52.8*	*118*	*44.3*	*-21% (-38% to -0,6%)*	*.043*
Conjugate vaccine serotypes						
All adults	*154*	*8.5*	*61*	*3.9*	*-54% (-66% to -38%)*	*<.001*
Adults aged 18-50 years	*48*	*5.6*	*30*	*4.1*	*-27% (-54% to 15%)*	*.17*
Adults aged 50-65 years	*33*	*5.1*	*10*	*1.8*	*-65% (-83% to -28%)*	*.003*
Adults aged > 65 years	*73*	*23.5*	*21*	*7.9*	*-66% (-79% to -45%)*	*<.001*
Non-Conjugate vaccine serotypes						
All adults	*191*	*10.6*	*262*	*16.9*	*60% (33% to 93%)*	*<.001*
Adults aged 18-50 years	*37*	*4.3*	*95*	*13*	*200% (105% to 338%)*	*<.001*
Adults aged 50-65 years	*51*	*7.9*	*70*	*12.7*	*60% (12% to 130%)*	*.01*
Adults aged > 65 years	*103*	*32.8*	*97*	*36.4*	*11% (-16% to 46%)*	*.46*

TABLE 2: Basal characteristics, underlying diseases and clinical presentation by time period among adult patients.

	Prevaccine period (n=345)	***Postvaccie period (n=323)***	***P value***
Sociodemographic variables			
Age (years, mean)	*62.65*	*57,67*	*.001*
Sex male	*65,2%*	*61%*	*.262*
Underlying diseases			
Immunosuppressive condition [a]	*37.7%*	*33.4%*	*.259*
HIV infection	*13.8%*	*12.1%*	*.562*
Hematological cancer	*12.6%*	*8.4%*	*.098*
Solid cancer	*12.6%*	*16%*	*.220*
Chronic medical illness [b]	*48.4%*	*50.2%*	*.699*
Clinical Presentation			
Pneumonia	*78%*	*84.6%*	*.036*
Meningitis	*7.9%*	*9.4%*	*.492*
Primary bacteremia	*8%*	*3.8%*	*.031*

[a] *Includes any of the following: HIV infection, Hematologic cancer, Solid cancer, solid organ or bone marrow transplant, immunoglobulin deficiency, splenectomy or current immunosuppressive therapy (including systemic steroids).*

[b] *Includes any of the following: chronic heart disease, chronic lung disease, cerebrovascular disease, cirrhosis, diabetes or chronic renal insufficiency.*

TABLE 3. Mean incidence of different pneumococcal syndromes by age group and time period among adult patients.

PNEUMOCOCCAL DISEASE	*PREVACCINE PERIOD*		*POSTVACCINE PERIOD*		*PRE vs POSTVACCINE PERIOD*	
	% of all IPD	*Cases per 100000 population-year*	*% of all IPD*	*Cases per 100000 population-year*	*Change, % (95% CI)*	*P value*
Pneumonia						
All adults	*78%*	*14.7*	*84.6%*	*17.4*	*18% (0% to 40%)*	*.049*
Adults aged 18-50 years	*75.9%*	*7.4*	*84.4%*	*14.1*	*91% (39% to 161)*	*<.001*
Adults aged 50-65 years	*75%*	*9.8*	*87.5%*	*12.7*	*30% (-8% to 82%)*	*.134*
Adults aged > 65 years	*80.3%*	*44.7*	*82.9%*	*36.4*	*-19% (-37% to 6%)*	*.12*
Meningitis						
All adults	*7.9%*	*1.5*	*9.4%*	*1.9*	*29% (-23% to 118%)*	*.32*
Adults aged 18-50 years	*12.3%*	*1.3*	*7.4%*	*1.2*	*-4% (-60% to 130%)*	*.918*
Adults aged 50-65 years	*9.5%*	*1.2*	*12.5%*	*1.8*	*56% (-42% to 269%)*	*.423*
Adults aged > 65 years	*4.6%*	*2.6*	*9.5%*	*4.1*	*60% (-35% to 299%)*	*.304*
Primary bacteremia						
All adults	*8%*	*1.5*	*3.8%*	*0.8*	*-48% (-74% to 2%)*	*.054*
Adults aged 18-50 years	*3.7%*	*0.4*	*3.3%*	*0.5*	*56% (-65% to 595%)*	*.56*
Adults aged 50-65 years	*2.5%*	*0.9*	*2,5%*	*0.4*	*-61% (-92% to 93%)*	*.23*
Adults aged > 65 years	*5.1%*	*5.8*	*5.1%*	*2.3*	*-61% (-85% to -2%)*	*.03*
Empyema						
All adults	*11.3%*	*1.5*	*12.1%*	*2.2*	*42% (-14% to 134%)*	*.170*
Adults aged 18-50 years	*11.7%*	*0.8*	*15.6%*	*2.3*	*183% (17% to 583%)*	*.015*
Adults aged 50-65 years	*15.5%*	*1.4*	*11.3%*	*1.5*	*4% (-60% to 169%)*	*.94*
Adults aged > 65 years	*9.2%*	*3.9*	*9%*	*3.4*	*-12% (-63% to 108%)*	*.762*

TABLE 4: Clinical presentation and outcomes by age group and time period among adult patients

	ALL ADULTS			ADULTS 18-50 YEARS			ADULTS 50-65 YEARS			ADULTS > 65 YEARS		
	Prevaccine period (n=345)	Postvaccine period (n=323)	P value	Prevaccine period (n=85)	Postvaccine period (n=125)	P value	Prevaccine period (n=84)	Postvaccine period (n=80)	P value	Prevaccine period (n=176)	Postvaccine period (n=118)	P value
Clinical presentation												
Septic shock	16.4%	29.3%	<.001	18.6%	24.8%	.369	10.8%	39.2%	<.001	18%	27%	.096
PSI ≥ 4 [a]	67.7%	64.5%	.453	62.7%	65.3%	.864	54.2%	77.3%	.008	87.7%	87%	1
Outcomes variables												
ICU admission	16.9%	23.5%	.039	24.7%	26.5%	.869	16.9%	29.1%	.091	13.25	16.5%	.269
Length of ICU stay[b]	6	7,5	.195	4,5	7	.185	6	9	.165	9	8	.715
Orotracheal intubation	12.1%	14.9%	.354	13.6%	19.1%	.330	11%	16.5%	.363	12%	9.6%	.567
Length of hospital stay[b]	9	9	.603	7	8	.544	6	10	.753	11	9	.56
Hospital mortality	18.3%	19.3%	.751	19.5%	9.4%	.057	11%	24.1%	.023	21.3%	26.4%	.383

[a] PSI: Pneumonia Severity Index only in patients with pneumonia.
[b] Expressed in days (median).

TABLE 5: Variables associated to invasive pneumococcal disease in the postvaccine period in multivariate analysis.

Risk factor	***RR (95% CI)***	***P value***
Age, 18-50 vs > 50 years	*2.027 (1.333-3.083)*	*.001*
Septic shock	*2.289 (1.449-3.615)*	*<.001*
Non-vaccine serotypes	*3.711 (2.402-5.733)*	*<.001*