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Influence of pneumococcal serotype group on outcome in adults with bacteremic pneumonia.

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ABSTRACT

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Background: The influence of infecting serotype group on outcome in bacteremic pneumococcal pneumonia remains unclear.

Methods: Prospective, 10-year observational study in an 800-bed teaching hospital. 299 adults diagnosed with pneumonia, and whose blood cultures showed growth of *Streptococcus pneumoniae* were included in the study. "High invasive disease potential" (H serotypes) included serotypes 1, 5 and 7F, which served as a reference category and were compared with "low invasive disease potential" (L serotypes: 3, 6A, 6B, 8, 19 F, and 23 F) and "other serotypes" (O serotypes: non-H, non-L). The influence on outcome was determined for each group of serotypes after adjusting for underlying conditions and severity-of-illness at admission.

Results: Overall 30-day mortality was 11%. H serotypes (n=93) infected primarily younger people and presented a higher risk of complicated parapneumonic effusion or empyema (17.2%vs5.1%, p=0.01), with lower mortality (3.2%). The isolation of L serotypes (n=78) was an independent risk factor for 30-day mortality (OR=7.02, 95%CI 1.72-28.61), as were Charlson Score (OR= 1.30, 95%CI 1.08-1.58), alcohol abuse (OR= 3.99 95%CI 1.29-11.09) and severity-of-illness measured by ATS/IDSA criteria (OR=4.8, 95%CI 1.89-12.13).

Conclusions: A vaccination strategy including serotypes 3, 6A, 6B, 8, 19 F, and 23 F may improve survival in adults.

Key Words: Bacteremic pneumococcal pneumonia, conjugated vaccines, serotypes, *Streptococcus pneumoniae*,

INTRODUCTION.

Bacteremic pneumococcal pneumonia (BPP) accounts for 9 to 18 cases per 100,000 adults [1]. The outcome is a complex process that depends on interactions between factors related to the host [2,3], therapy [4-6], and the microorganism [7,8], including the bacterial pneumococcal load [9]

The polysaccharide capsule is considered to be the primary virulence factor of the pneumococcus, protecting it against phagocytosis. The classification of pneumococci into serotypes is based on the differences in the structure of the capsule and, to date, 90 different serotypes have been described [10]. Individual serotypes appear to have different clinical manifestations, but the data available to clarify whether different serotypes are associated with differing mortality rates are limited and sometimes contradictory.

In the pediatric population, Brueggeman and coworkers [11] described the invasive disease potential of several serotypes and the case-fatality rates for each group. According to their findings, a group of serotypes including 1, 5 and 7F (known as "invasive serotypes" in the literature) rarely cause oropharyngeal colonization but commonly cause bacteremia (with a lower case-fatality rate). A second group of serotypes (3, 6A, 6B, 8, 19 F, and 23 F) are frequently associated with colonization but rarely cause bacteremia, acting as "opportunistic pathogens" or microorganisms with "low invasive disease potential" (LIDP). Higher case-fatality rates were reported in children infected by these serotypes. In adults, the influence of serotypes on mortality remains controversial: some studies [12] found higher case-fatality rate for certain serotypes whereas others did not [13]. These results deserve attention in an era of the design and licensure of new formulations of pneumococcal conjugate vaccines (PCV).

The objective of our study was to determine the influence of infecting serotypes on the severity of clinical presentation and outcome in a cohort of adults with bacteremic pneumococcal pneumonia, after adjusting for underlying disease and severity of illness at admission. Our hypothesis was that the outcome for specific groups of serotypes would be different when adjusted for baseline conditions of the host and severity-of-illness at admission.

METHODS

Study population.

This study was performed between January 1999 and March 2009 in an 800-bed teaching hospital. All patients aged ≥ 18 years with a diagnosis of pneumonia (fever, productive cough, chest pain, shortness of breath, and crackles on auscultation in addition to a chest radiograph interpreted as pneumonia) and whose blood cultures obtained within the first 48 hours of hospitalization showed growth of *Streptococcus pneumoniae* were included. Exclusion criteria were bacteremia from other sources, presence of concurrent meningitis or endocarditis at admission and growth of other pathogenic microorganisms in blood cultures. The study was approved by the institutional research board and informed consent was waived.

The following variables were recorded at admission: age, sex, tobacco and alcohol abuse, underlying diseases, vaccination status with the 23-valent polysaccharide (PPV-23) vaccine (patients who received the last administration of the vaccine in the five years before pneumonia were considered as vaccinated) symptoms in the days prior to and at admission, relevant physical findings, blood gases, white and red blood cell count, blood urea nitrogen, serum creatinine, and chest radiograph pattern. The Charlson Score and PSI score were calculated as reported elsewhere [14, 15]. Severity of pneumonia was assessed according to the prediction rule of the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) considering severe pneumonia those cases that met at least 1 of 2 major criteria or 3 of 9 minor criteria [16].

During hospitalization, the following variables were also recorded: *in vitro* susceptibility for strains, need for ICU admission, vasoactive drugs and mechanical ventilation, major complications (respiratory failure, septic shock, empyema), outcome

(30-day mortality), length of stay (LOS) for survivors, and antibiotic therapy prescribed. Antibiotic therapy was not standardized and was left to the criteria of the attending physician.

Definitions: Underlying conditions: alcohol consumption: > 60 gr/day, history of lung comorbidity included chronic obstructive pulmonary disease and interstitial lung disease; cardiac comorbidity: diagnosis of congestive heart failure, coronary artery disease or advanced valvulopathy; renal disease: chronic renal failure, with creatinine levels $\geq$ 1.5 mg/100; liver disease: biopsy-proven cirrhosis or diagnosis of viral or toxic chronic liver disease; diabetes mellitus: treatment with oral hypoglycemics or insulin; immunocompromise: corticosteroid therapy with 4 mg prednisolone/day or equivalent for more than 1 month, HIV infection, hematological disease with immune defects or recent therapy with other immunosuppressors, including antineoplastic agents.

Antibiotic treatment was considered concordant if at least one of the antibiotics administered during the first 8 hours showed full *in vitro* susceptibility against the isolated strain [5]. Complicated pleural effusion and empyema were defined according to current criteria [17]

Microbiologic evaluation: Blood samples were processed using the BacT-Alert® system (bioMerieux, Lyon, France). Identification was carried out by colonial morphology on blood agar, Gram stain, susceptibility to optochin and detection of the colony antigen. MIC values were determined by the microdilution method in cation-adjusted Mueller-Hinton broth, supplemented with 5% lysed horse blood. Penicillin and erythromycin susceptibility was assessed post-hoc, converting MIC values to categories of susceptibility according to the 2008 CLSI breakpoints [18]. All strains were sent to the Pneumococci Reference Laboratory of the Instituto de Salud Carlos III in Majadahonda for verification of sensitivity to the antibiotics and serotyping using the

Quellung reaction and/or dot blot assay, with the use of antisera provided by the Statens Serum Institute (Copenhagen, Denmark).

Serotypes were analyzed individually and classified as follows:

- Serotypes with "high invasive disease potential" (H group) or "invasive serotypes" [11]: 1, 5 and 7 F
- "Low invasive potential" (L group) or "opportunistic serotypes": 3, 6A, 6B, 8, 19 F, and 23 F [11].
- Serotypes not included in the H and L groups were denominated as "other serotypes" (O group).

For the analysis of impact of PPV-23, serotypes were classified as "vaccine serotypes" (included in PPV-23) and "non- vaccine serotypes".

Statistical analyses*:*

For quantitative variables (age, Charlson Score), means $\pm$ standard deviation were given and were compared in three groups of serotypes by means of ANOVA test with Bonferroni's post hoc analysis. Dichotomous variables were evaluated using the Chi-square test, and Fisher's test when appropriate. Variables with $p<0.05$ (two tailed) were considered as significant. Severity according PSI class and serotype groups was assessed by logistic ordinal regression, being H serotypes the reference category. Survival was analyzed with the Kaplan-Meier method, and curves for groups of serotypes were compared with the log-rank analysis. A multivariate logistic regression analysis was performed, considering variables with $p< 0.1$ in the univariate analysis. We restricted the number of variables included in the multivariate model following the rule of at least 5-7 events (deaths) per variable [19]. Thus, variables showing colinearity (ATS/IDSA or PSI scores and individual criteria contained in them, individual comorbidities and Charlson score) were not included together in the model. The

appropriateness of the model was assessed by Hosmer-Lemeshow goodness-of-fit. Data were analyzed using the SPSS-17 statistical package (SPSS Inc; Chicago, IL).

RESULTS.

During the study, 299 consecutive adults were included. Mean age was 62.2 ± 19.5 years (range 18-92). Overall 30-day mortality was 11% (33/299). Details on comorbidities and the main clinical, radiological and laboratory findings are shown in Table 1. The most frequently prescribed antibiotic therapies were combination therapy including ceftriaxone or cefotaxime plus a macrolide (133, 44.4%), amoxicillin-clavulanate (60, 20%), ceftriaxone or cefotaxime (35, 11.7%) and levofloxacin (34, 11.6%) in monotherapy. Combination therapy was prescribed in 51% of patients who survived and in 67 % of patients who died (p=0.08)

Using the 2008 CLSI breakpoints, non-susceptibility to penicillin (MIC $\geq$ 4 mg/ml) was documented in only 4 (1.3%) episodes and resistance to macrolides in 15.7%. Only 4 patients received discordant empirical therapy (1 died, 25 % versus 11% p=0.37).

The infecting serotype was determined in 294/299 patients. Fig 1 shows the distribution of serotypes between two age groups (< 60 and $\geq$ 60 years old). Serotypes 1 (18.9%), 3 (12.3%) and 14 (7.6%) were the most prevalent in the cohort. L serotypes infected mainly people aged $\geq$ 60 years old (32 versus 17.8% p<0.05, OR= 3.92, 95% CI 2.05-7.51) Serotypes in patients who died were listed in table 2.

Table 3 compares underlying conditions, severity-of-illness on clinical presentation, antibiotic susceptibility and outcome for each group of serotypes. Patients with pneumonia caused by group H serotypes were significantly younger, with better baseline status (lower Charlson Score) and presented a significantly higher incidence of complicated parapneumonic effusion or empyema (50% of these complicated effusions were associated with serotype 1).

Otherwise, although we did not find statistically significant differences in age or baseline conditions between groups L and O, patients with pneumonia due to L serotypes not only presented higher mortality, but also had severe pneumonia (ATS/IDSA criteria and PSI class V) more frequently, were more likely to have a PaO2/FiO2 ratio below 250 at admission, and had a greater need for vasopressors and mechanical ventilation (table 3). Moreover, differences in ATS/IDSA criteria were found both in major (31 % in L, 17.2 % in H and 18 % in O group, $p<0.05$) and minor criteria (51.2 % in L group, 23.6 % in H and 32.5 % for O group, $p<0.01$). Fig 2 reflects the proportion of PSI class for each group of serotypes. Both O and L serotype isolates presented an increased likelihood to be associated with higher PSI classes when compared with H group (ordinal OR = 3.25, 95 % CI 1.97-5.37, $p<0.001$ for O serotypes and ordinal OR= 5.86, 95 % CI 3.26-10.53, $p<0.001$ for L serotypes). At same time, an increased likelihood was also documented when L were compared with O serotypes (ordinal OR= 1.97, 95%CI 1.04-3.09, $p<0.05$).

Univariate analysis (table 4) revealed that 30-day mortality was influenced by several underlying conditions, such as Charlson Score and alcohol consumption, and by others related to severity of the clinical presentation (level of consciousness, need for vasopressors, multilobar involvement, PaO2/FiO2 ratio) and infecting serotype (group L). Kaplan-Meier curves of patients infected by L serotypes versus those infected with O and H serotypes are shown in fig 3; there were statistically significant differences in survival (log-rank 26.55, p value <0.001). Finally, details of a logistic regression analysis after adjusting for baseline conditions and severity-of-illness that reached statistical significance in the univariate analysis are summarized in table 5. Two different models were analyzed, with ATS/IDSA criteria in model A (Hosmer

Lemeshow goodness-of-fit 0.712) and PSI in model B (Hosmer-Lemeshow goodness-of-fit 0.682).

DISCUSSION

In our cohort, serotypes 3, 6A, 6B, 8, 19 F and 23 F (L serotypes) were involved in only 26% of adults with bacteremic pneumococcal pneumonia, but in two-thirds of fatal episodes. The L serotype group emerged as an independent variable of death, with a 7-fold increase compared with H serotypes and a 4-fold increase compared with O serotypes. Moreover, patients infected with L serotypes also presented more hypoxemia and higher need for vasopressors and mechanical ventilation and were most likely to develop severe pneumonia (ATS/IDSA criteria and PSI class V). For their part, H serotypes (1, 5, 7F) infected younger people and presented a higher incidence of complicated parapneumonic effusion or empyema.

The excess of mortality attributable to certain pneumococcal serotypes in pneumococcal invasive disease has been a subject of controversy. In an unadjusted model, Henriques et al. [20] found increased case-fatality rates for serotypes 3, 6B and 19 F. Using the same classification as in our study, Sjostrom et al [12] reported that invasive serotypes (1,5 and 7F) were associated with lower mortality. Less invasive serotypes (3, 6A, 6B, 8, 19F and 23F) infected patients with comorbidity and presented an increased case-fatality rate. In a retrospective study of 464 patients with pneumococcal invasive disease, Martens and coworkers [21] found that serotype 3 was linked to higher mortality in the global cohort (OR=2.63), but found only a trend (p=0.06) in patients with pneumonia.

Differences in the clinical behavior of serotypes are supported by a population-based study involving more than 18,000 patients with invasive pneumococcal disease. Harboe et al [22] reported different OR for each serotype after adjusting for age, gender, meningitis and comorbidity level. Interestingly, not only the mortality, but also the probability of infection by specific serotypes varied among different levels of

comorbidity measured by the Charlson Score. Moreover, infection by serotypes 3, 19 F and 23 F was independently associated with mortality in patients with high comorbidity level. Unfortunately, the authors did not present data for serotype distribution between different age groups among their adult population. In our study, as shown in fig 1, the distribution between patients aged ≥ or < 60 years old is clearly different.

A recent retrospective study [23] found that serotypes with low invasive disease potential presented higher prevalence of meningitis and primary bacteremia and higher case-fatality rate, but it remains unclear whether this mortality was associated with the infecting serotypes or with the source of the bacteremia. In contrast, our study included only bacteremic pneumonia: patients with meningitis or bacteremia of unknown source at admission were excluded, demonstrating that infection by L serotypes influenced mortality by itself, irrespective of the source of infection.

Conversely, in a multicenter study involving 760 patients with pneumococcal bacteremia and after adjusting for baseline conditions and severity-of-illness, Alanee et al [13] did not find an independent association between mortality and specific serotypes or groups of serotype (pediatric, conjugated and invasive serotypes), suggesting that host factors were more important than serotypes in determining severity and outcome.

In our study, serotypes 1, 5 and 7F were associated with lower severity according to PSI score (only 18% of patients showed PSI class V). Similar severity patterns have been reported in a study of patients with meningitis [24]. These serotypes were associated with an increased risk of complicated parapneumonic effusion or empyema, although serotype 1 accounts for 50% of episodes. Some authors have reported this association in pediatric populations [25], but not in adults [13].

Vaccination strategy is a key point to improve outcome in pneumococcal pneumonia. Unfortunately, the rate of PPV-23 vaccination in our cohort was low.

Despite the effectiveness of PPV-23 vaccine in reducing the severity of the infection, some vulnerable cohorts remain: for instance COPD patients and the elderly, who respond poorly to active immunization with polysaccharide 23-valent vaccine and who might be a potential target population for PCV vaccines [26]. Our data suggest that the inclusion of some L serotypes (mainly serotype 3) in PCV vaccines would improve survival in patients with high degrees of comorbidity.

Our study has several limitations. First, the great variability of isolated serotypes was a serious handicap to determining whether individual serotypes might have different degrees of influence on mortality or severity-of-illness. Second, the distribution of serotypes may differ in other geographic areas, especially with higher levels of immunization with PPV 23. Third, our findings may not be applicable to hospitalized patients without bacteremia or to the pediatric population, in which different serotypes (mainly 7F) seem to be associated with excess-of-mortality [27]. Finally, the invasiveness or virulence of pneumococci may be different even among strains with the same serotype, suggesting that these properties are also associated to the genotype of the isolates. Recent studies demonstrated that multi-invasive locus sequence typing and comparative genomic hybridization are promising techniques to distinguish strains that causes invasive disease from carrier strains [28]

In summary, our findings suggest that there is a group of serotypes associated with severe bacteremic pneumococcal pneumonia in adults in Spain. These serotypes were independently associated with death. Therefore, they should be included in new vaccines. Our data suggest that the global impact of the newer 13-valent vaccine in reducing mortality would be high in elderly population.

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Table 1. Demographic data, underlying conditions, clinical, radiological and microbiologic findings in 299 patients with bacteremic pneumococcal pneumonia, stratified by age.

Variables	Overall. N=299 .	< 60 yr old N=119	≥ 60 yr old N=180
Gender (male patients)	171 (57.2%)	71 (59.6%)	100 (55.6%)
Vaccinated with PPS23*	47/227 (20.7%)	23/95(24.2%)	24/132 (18%)
Infected by 23-VS**	270/294 (91%)	112 (94.1%)	158 (87.8%)
Current or former smokers	164 (54.8%)	79 (66.4%)	85 (47.2%)
Alcoholism	42 (14%)	27 (22.7%)	15 (8.3%)
Comorbidities:			
- Cardiomyopathy	64 (21.2%)	4 (3.4%)	60 (33.3%)
- Lung disease	84 (28.1%)	17 (14.3%)	67 (37.2%)
- Liver disease	47 (15.6%)	26 (21.8%)	21 (11.7%)
- Renal	28 (9.3%)	3 (2.5%)	25 (13.9%)
- Immunocompromise	38 (12.6%)	26 (21.8%)	12 (6.7%)
Charlson Score	2.03 ± 2.28	1.9 ± 2.84	2.12 ± 1.82
ICU admission	70 (23.4%)	34 (28.6%)	36 (20%)
PaO2/FiO2 ratio < 250	104 (34.8%)	28 (23.5%)	76 (42.2%)
Vasopressors	49 (16.4%)	22 (18.5%)	27 (15%)
Multilobar involvement	131 (43.8%)	50 (42%)	81 (45 %)
Pleural effusion	90 (30.1%)	36 (30.3%)	54 (30%)
Complicated effusion or empyema	26 (8.7%)	13 (10.9%)	13 (7.2%)
Penicillin resistance	4 (1.3%)	1 (0.8%)	3 (1.7%)
Macrolide resistance	47 (15.7%)	13 (10.9%)	34 (18.9%)
Therapy:			
- Combination therapy.	157 (52.5%)	60 (50.4%)	97 (53.9%)
PSI class V	116 (38.7%)	21 (17.6%)	95 (52.8%)
ATS/IDSA criteria	110 (36.8%)	36 (30 %)	74 (41.1%)
30-day mortality	33 (11%)	9 (7.6%)	24 (13.3%)

*Patients vaccinated within the last five years among the 194 who fulfilled vaccination criteria.

**VS = serotypes included in PPV-23 vaccine

Table 2. Serotypes in patients who died (n=33) within 30 days of diagnosis of BPP

Serotype	Number of isolates (%)	Deaths
3	37 (12.5%)	8
19 F	8 (2.6%)	6
23 F	8 (2.6%)	3
5	16 (5.3%)	2
4	15 (4.9%)	2
6B	5 (1.6%)	2
14	23 (7.6%)	1
7F	20 (6.6%)	1
19A	15 (4.9%)	1
8	11 (3.6%)	1
9V	10 (3.3%)	1
11A	5 (1.6%)	1
12F	5 (1.6%)	1
24	4 (1.3%)	1
16F	1 (0.3%)	1
Unknown	5 (1.6%)	1

Table 3. Univariate analysis (Chi-square test, ANOVA test) of the underlying conditions, clinical presentation, complications, and outcome for 294 patients according the presence of several groups of serotypes:

	Group 1: H serotypes * (n=93)	**Group 2: L serotypes * (n=78)**	**Group 3: O serotypes * (n=123)**
Mean age (SD) years	54.2 ± 20 [e]	66.4 ± 17.2	65.2 ± 18.5
Comorbidities: n (%)			
Cardiopathy	10 (10.7%) [a]	23 (29.4%)	30 (24.3%)
Lung Disease	18 (19.3%)[c]	21 (26.9%)	44 (35.7%)
Liver disease	7 (7.5%) [a]	15 (19.2%)	24 (19.5%)
Renal disease	5 (5.3%)	7 (8.9%)	16 (13%)
Immunocompromise	6 (6.4%)	12 (15.3%)	20 (16.2%)
Mean Charlson Score (SD)	1.04 (1.6) [e]	2.44 (2.3)	2.49 (2.2)
PaO2/FiO2 (< 250)	24(25.8%)	35 (44.8%) [b]	42 (34%)
Need for vasopressors	15 (16.1%)	21 (26.9%) [b]	13 (10.5%)
Multilobar involvement	42 (45.1%)	42 (53.8%)	46 (37.3%)
ICU admission	20 (21.5%)	25 (32%)	24 (19.5%)
Mechanical ventilation	12 (12.9%)	20 (25.6%) [b]	17 (13.8%)
Severe pneumonia (ATS/IDSA)*	25 (26.8%)	40 (51.2%) [b]	43 (34.9%)
Pleural effusion	33 (35.4%)	23 (29.4%)	32 (26%)
Complicated parapneumonic effusion or empyema	16 (17.2%) [e]	5 (6.4%)	5 (4%)
Combination therapy	44 (47%)	49 (63%)	63 (51%)
PSI class V	17 (18.2%) [d]	47 (60.2%)	49 (39,8%)
LOS for survivors	12.72 ± 12.1	17.2 ±16.7	14.21 ± 11.1
30-day mortality	3 (3.2%)	20 (25.6%) [f]	9 (7.3.%)

H serotypes: 1, 5 and 7 F
L serotypes: 3, 6A, 6B, 8, 19 F and 23 F
O: Other serotypes.
*Severe pneumonia was considered when patients met at least 1 of 2 major criteria or 3 of 9 minor criteria [16].
a: $p<0.05$ between group H and the other two groups (Chi-square test)
b: $p<0.05$ between group L and the other two groups.
c: $p<0.05$ between groups H and O
d: $p<0.05$ between three groups.
e: $p<0.001$ between group H and the other two groups.
f: $p<0.001$ between group L and the other two groups

Table 4. Univariate model (Chi-square test) for 30-day mortality, including potential risk factors influencing outcome related to underlying conditions, severity of the clinical presentation, and microbiologic and therapy-related factors.

	OR for death (95% CI)	**p value**
Underlying and demographic conditions:		
- Male sex	4.81 (1.80-12.55)	< 0.01
- Age	1.02 (0.99-1.04)	0.08
- Alcoholism	3.79 (1.67-8.56)	< 0.01
- Tobacco consumption	2.03 (0.94-4.45)	0.07
- Charlson Score	1.25 (1.09-1.44)	< 0.01
- Immunocompromise	2.51 (1.04-6.08)	0.05
Severity at admission (individual variables):		
- PaO2/FiO2 < 250	6.20 (2.75-13.93)	< 0.001
- Multilobar involvement	5.59 (2.38-13.59)	< 0.001
- Need for vasopressors	4.15 (1.90-9-07)	< 0.001
- Need for mechanical ventilation	3.53 (1.70-7.79)	0.01
Severity of illness scores		
- PSI class V	14.91 (5.08-43.9)	< 0.001
- ATS/IDSA criteria	6.65 (2.88-15.36)	< 0.001
Antibiotic resistance:		
Penicillin	----------	-------
Macrolide	4.43 (2.02-9.72)	<0.01
Microbiology:		
- H serotypes (reference category)	1	--------
- O serotypes	2.36 (0.63-9.05)	0.2
- L serotypes	10.34 (2.94-36.5)	< 0.001
Antibiotic therapy		
- Monotherapy	1.94 (0.90-4.16)	0.1
- Combination therapy	1	-----

PSI: Pneumonia Severity Index
H serotypes includes serotypes 1,5 and 7F
L serotypes includes serotypes 3, 6A, 6B, 8, 19 F and 23 F.

O serotypes includes non –L, non-H serotypes

Table 5. Logistic regression analysis for 30-day mortality.

	Model A: with ATS/IDSA criteria			Model B: with PSI		
Variables	OR for death	95% CI	p value	OR for death	95% CI	p value
- Serotypes:						
- H serotypes	1	--------	--------	1	----------	---------
- O serotypes	1.72	0.40-7.41	0.46	1.28	0.29-5.60	0.73
- L serotypes	7.02	1.72-28.61	<0.01	5.28	1.29-21.58	<0.05
- ATS/IDSA criteria	4.80	1.89-12.13	<0.01	--------	----------	----------
- PSI class V	--------	----------	----------	9.50	3.06-29.46	<0.001
- Alcohol abuse	3.99	1.39-11.39	0.01	3.16	1.18-8.46	<0.05
- Charlson score	1.30	1.08-1.57	<0.01	1.22	1.01-1.46	<0.05
- Age	1.02	0.99-1.05	0.11	---------	----------	---------

H serotypes includes serotypes 1, 5 and 7 F. L serotypes includes serotypes 3, 6A, 6B, 8, 19 F and 23 F. O serotypes includes non-L, non-H serotypes. OR = Odds ratio. CI = confidence interval. PSI = Pneumonia severity index.

Figure 1

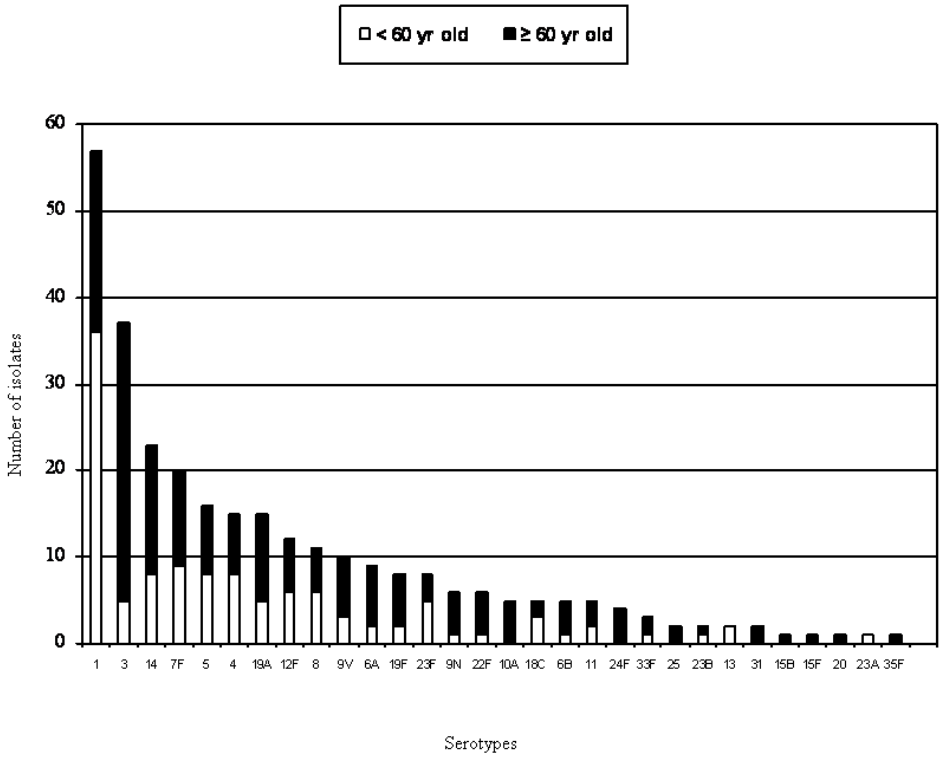


Figure 2

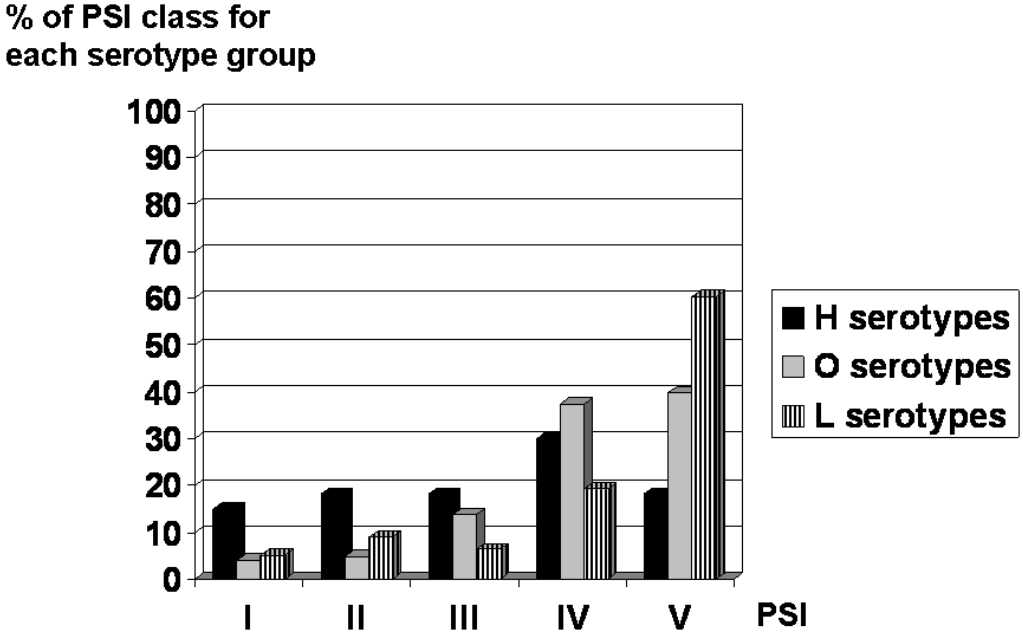
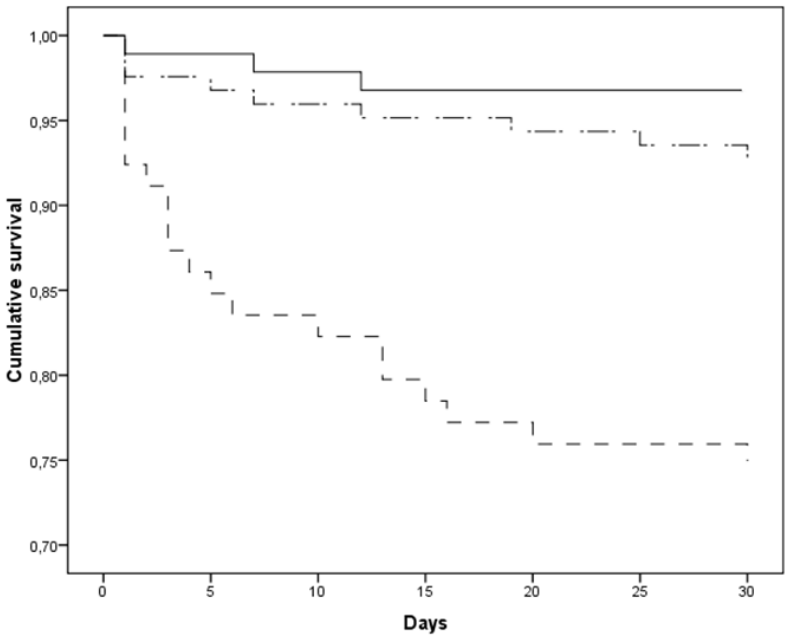


Figure 3



HIDP serotypes
Other serotypes
LIDP serotypes

Log-rank p<0.001