# A national study of the epidemiology of pneumococcal disease among hospitalised patients in Singapore: 1995 to 2004

**Low S, Chan F L F, Cutter J, Ma S, Goh K T, Chew S K**


## ABSTRACT

**Introduction: Infections with *Streptococcus pneumoniae* cause significant morbidity and mortality. In this study, we describe the epidemiology of pneumococcal disease based on hospitalisation rates for all age groups in Singapore. This is important for evaluating prevention and control strategies of pneumococcal disease.**

**Methods: We conducted a retrospective study of hospitalisation cases admitted to all public and private hospitals from 1995 to 2004. 4,275 hospitalisation records were extracted, based on the International Classification of Diseases, Ninth Revision (ICD-9) codes for pneumococcal disease. We analysed the demographics, type of pneumococcal disease, length of stay and case fatality of these cases.**

**Results: Our study showed that the mean annual hospitalisation rate for pneumococcal disease was 10.9 per 100,000 population from 1995 to 2004. The mean annual hospitalisation rate was highest in the young and the elderly.**

**Conclusion: Baseline information on the epidemiology of pneumococcal disease is important for the formulation and evaluation of a national prevention and control programme.**


**Keywords: International Classification of Diseases, pneumonia, pneumococcal disease, *Streptococcus pneumoniae***

*Singapore Med J 2007; 48(9):824–829*

## INTRODUCTION

Infections with *Streptococcus pneumoniae* cause significant morbidity and mortality. Studies have shown that the incidence of pneumococcal disease is highest at the extremes of age.[1-4] Many studies on the epidemiology of pneumococcal disease have been conducted in western countries. Table I shows the reported incidence of invasive pneumococcal disease (IPD) in countries where routine childhood immunisation with pneumococcal conjugate vaccine (PCV) had not been carried out during their study period. Some of these countries subsequently incorporated PCVs into their routine childhood immunisation programmes, e.g. United States and Australia. Published data on the epidemiology of pneumococcal disease in Asian countries is, however, limited,[5] although there have been more studies on epidemiology conducted in Asia in recent years.[6-8] This paper aims to describe the epidemiology of pneumococcal disease based on the hospitalisation rates for all age groups in Singapore, as this is important for the evaluation of prevention and control strategies of this disease.

## METHODS

A retrospective study of hospitalisation records of patients admitted to all restructured and private hospitals in Singapore from 1995 to 2004 was conducted. We extracted 4,275 records with discharge diagnosis based on the International Classification of Diseases, Ninth Revision (ICD-9) codes for pneumococcal disease from the Central Claims Processing System, a national inpatient discharge database which covers all hospitals in Singapore. The system captures information on diseases coded using the ICD-9, date of birth, gender, ethnicity, nationality, episode outcome, admission date, discharge date and institution name. The following ICD-9 codes were included as pneumococcal disease: 320.1 (pneumococcal meningitis), 567.1 (pneumococcal peritonitis), 481 (pneumococcal pneumonia), 038.2 (pneumococcal septicaemia) and 041.2 (bacterial infection in conditions classified elsewhere and of unspecified site, pneumococcus). These are strictly pneumococcal disease codes; those which include other aetiological agents other than *Streptococcus pneumoniae* were excluded. The denominator for calculating the annual hospitalisation

**Communicable Diseases Division, Ministry of Health, College of Medicine Building, 16 College Road, Singapore 169854**

Low S, MBBS
Medical Officer (Policy)

Chan FLF, MPH, GradCertHSM, BNur
Public Health Executive (Policy)

Cutter J, MBBS, MMed, FAMS
Deputy Director (Policy)

**Epidemiology and Disease Control Division**

Ma S, BSc, MStat, PhD
Senior Biostatistician

Chew SK, MBBS, MSc
Deputy Director of Medical Services

**Director of Medical Services Office**

Goh KT, MSc, MD, FAMS
Senior Consultant

**Correspondence to:**
Dr Serena Low
Fax: (65) 6325 1168
Email: lowkiatmun@yahoo.com

**Table I. Reported incidence of invasive pneumococcal disease in countries where national childhood immunisation with pneumococcal conjugate vaccine had not been carried out during the study period.**

| | | Incidence per 100,000 population | | | |
|---|---|---|---|---|---|
| Study population | Year(s) | Overall | < 1 year old | < 5 years old | ≥ 65 years old |
| Australian capital territory and Queanbeyan region, Australia[17] | 1998–2000 | 15.2 | – | – | 38.9 |
| Sydney, Australia[18] | 1991–1996 | – | – | 31.7 | – |
| Austria[19] | 2001–2003 | – | – | 13.7 | – |
| Denmark[11] | 1995-–1999 | 17-27 | – | – | – |
| Denmark[20] | 1981–1999 | – | 39.4 | – | – |
| England and Wales[21] | 1995–1997 | 6.6* | 37.1* | 14.5* | 21.2* |
| Oxford, UK[21] | 1995–1999 | 9.1* | 48.1* | 21.2* | 36.2* |
| Finland[22] | 1983–1992 | – | – | – | 27.1 |
| Greece[23] | 1995–1999 | – | – | 100 | – |
| Catalonia, Spain[14] | 1997–1999 | 10.5* | – | – | 27.9* |
| Switzerland[24] | 1985–1994 | – | – | 7.6* | – |
| United States[25] | 1999 | 24.4 | 162.7 | 87.4 | 61.1 |
| Dallas County, Texas, United States[13] | 1995 | 22.2* | – | – | 80* |

* Number of cases/100,000 person-years

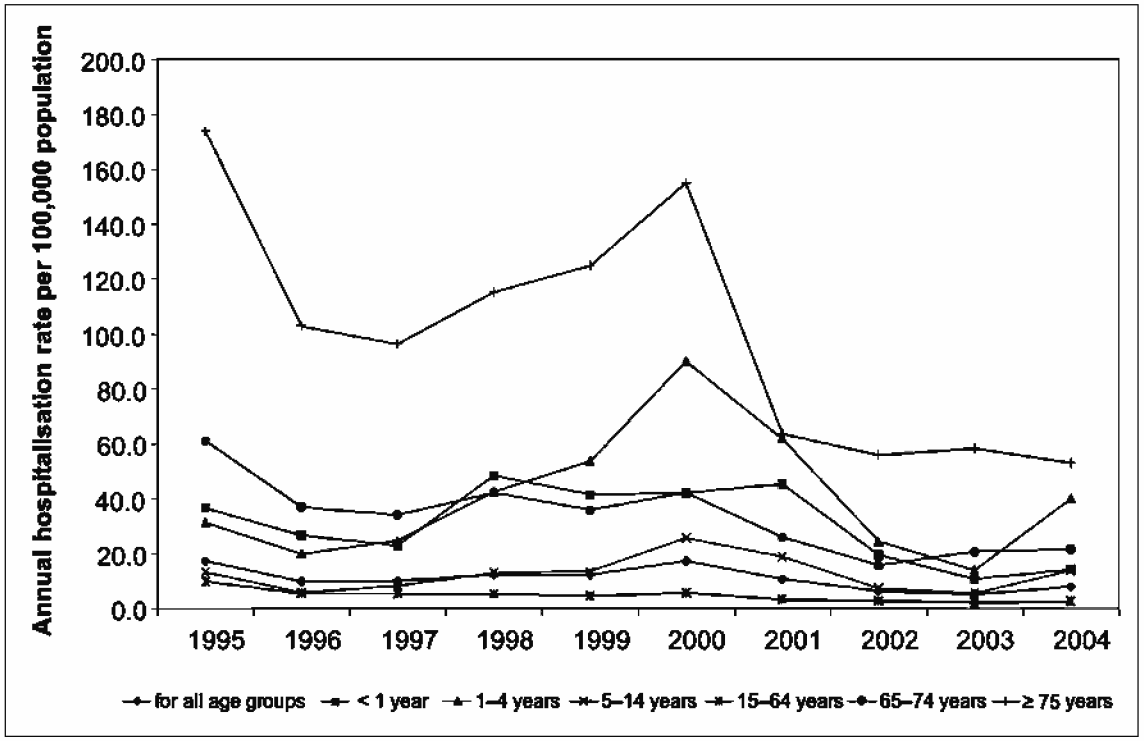


**Fig. 1** Annual hospitalisation rate for pneumococcal disease by age groups, from 1995 to 2004.

rate was derived from the mid-year population estimates (Source: Department of Statistics, Singapore). Using Microsoft Office Excel, we produced the graphs and analysed the annual hospitalisation rates and distribution by age, ethnicity, gender and case fatality rates. Analysis of data was also performed using the Statistical Package for Social Sciences, version 14.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics was used to characterise type of disease, length of stay and episode of outcome.

## RESULTS

The mean annual hospitalisation rate for pneumococcal disease was 10.9 per 100,000 population. During the study period, the rate reached its peak in 2000 and was at its lowest in 2003 (Fig. 1). The cases were

**Table II. Breakdown of pneumococcal disease by age and gender**

| Age group (years) | Gender | |
|---|---|---|
| | Female (%) | Male (%) |
| < 1 | 46 (33.3) | 92 (66.7) |
| 1–4 | 339 (45.3) | 410 (54.7) |
| 5–14 | 307 (48.2) | 330 (51.8) |
| 15–64 | 503 (36.4) | 880 (63.6) |
| 65–74 | 248 (46.4) | 286 (53.6) |
| ≥75 | 419 (50.2) | 415 (49.8) |
| Total | 1,862 (43.6) | 2,413 (56.4) |

There was a total of 4,275 cases for pneumococcal pneumonia, pneumococcal meningitis, pneumococcal septicaemia, pneumococcal peritonitis and bacterial infection in conditions classified elsewhere and of unspecified site, pneumococcus.

aged from less than one month to 111 years. The study population was divided into six age groups: < one year old, 1–4 years old, 5–14 years old, 15–64 years old, 65–74 years old, and ≥ 75 years old. The annual hospitalisation rate for these age groups from 1995 to 2004 is shown in Fig. 1. Of note, the annual hospitalisation rates for the elderly aged 75 years and above remained higher than the rest of the age groups over the ten-year period. The hospitalisation rates for most of the age groups reached their peak at 2000 and were on a decreasing trend from 2001 to 2004. The annual hospitalisation rate (per 100,000) ranged from 10.7 to 48.4 for children under one year old; 14.0 to 90.0 for 1–4 years old; 5.7 to 25.7 for 5–14 years old; 2.1 to 9.8 for 15–64 years old; 15.6 to 61.0 for 65–74 years old; and 53.0 to 173.7 for ≥ 75 years old.

Chinese accounted for 2,967 cases with pneumococcal disease in this study, followed by Malays (639 cases) and Indians (390 cases) from 1995 to 2004. The distribution of mean annual hospitalisation rate (per 100,000) of pneumoccoccal disease by ethnicity was as follows: Malays (12.9), Indians (11.2) and Chinese (10.8). Overall, there was no statistically significant difference in the hospitalisation rates among the three ethnic groups ($p > 0.2014$). The yearly trend of pneumococcal disease was similar for all the three ethnic groups from 1995 to 2004. The breakdown of pneumococcal disease by age and gender is shown in Table II. There were more males with pneumococcal disease than females for all age groups, except for those aged 75 years and above. Of note, there were more females than males in this age group 75 years and above among the general population in Singapore. Overall, males had a statistically significant higher mean annual hospitalisation rate of pneumococcal disease than females (12.0 per 100,000 versus 9.8 per 100,000) ($p = 0.0293$).

Pneumococcal pneumonia was the predominant type of pneumococcal disease as it accounted for 4,186 (97.9%) of all pneumococcal disease analysed in this study, followed by pneumococcal septicaemia (49 cases, 1.1%), pneumococcal meningitis (30 cases, 0.7%), pneumococcal peritonitis (seven cases, 0.2%) and bacterial infection in conditions classified elsewhere and of unspecified site, pneumococcus (three cases, 0.1%). The hospitalisation data for pneumococcal pneumonia, pneumococcal meningitis and pneumococcal septicaemia for the different age groups is shown in Table III. The hospitalisation rate for pneumococcal pneumonia was the highest among the elderly aged 75 years and above, whereas the hospitalisation rate for pneumococcal meningitis was the highest among infants under one year old. The hospitalisation rate for pneumococcal septicaemia was the same for both the very young (aged under one year) and the elderly (aged 75 years and above).

**Table III. Hospitalisation due to pneumococcal pneumonia (ICD-9 481), pneumococcal meningitis (ICD-9 320.1) and pneumococcal septicaemia (ICD-9 038.2) by age group in Singapore, 1995–2004.**

| Age group (years) | Pneumococcal pneumonia | | Pneumococcal meningitis | | Pneumococcal septicaemia | |
|---|---|---|---|---|---|---|
| | No. | Rate* | No. | Rate* | No. | Rate* |
| < 1 | 128 | 29.25 | 7 | 1.60 | 3 | 0.69 |
| 1–4 | 729 | 38.74 | 4 | 0.21 | 15 | 0.80 |
| 5–14 | 627 | 12.36 | 6 | 0.12 | 3 | 0.06 |
| 15–64 | 1,346 | 4.53 | 12 | 0.04 | 20 | 0.07 |
| 65–74 | 530 | 32.21 | 1 | 0.06 | 2 | 0.12 |
| ≥75 | 826 | 94.79 | 0 | 0.00 | 6 | 0.69 |
| Total | 4,186 | | 30 | | 49 | |

The total number of cases for pneumococcal pneumonia, pneumococcal meningitis and pneumococcal septicaemia was 4,265. The overall total number of pneumococcal cases, which also include pneumococcal peritionitis and bacterial infection in conditions classified elsewhere and of unspecified site, pneumococcus, was 4,275.

* Mean annual hospitalisation rate per 100,000 population

The median length of stay for pneumococcal disease for all ages was four days (mean 6.1, SD 7.4). The median length of stay for different age groups was as follows: < 1 year old, four days (mean 6.5, SD 10.7); 1–4 years old, three days (mean 4.7, SD 4.1); 5–14 years old, three days (mean 4.2, SD 3.8); 15–64 years old, four days (mean 6.0, SD 8.5); 65–74 years old, five days (mean 8.0, SD 9.6); and ≥ 75 years old, six days (mean 7.5, SD 7.1). The median length of stay was highest for pneumococcal meningitis, 13.5 days (mean 16.5, SD 19.9), followed by pneumococcal peritonitis, seven days (mean 15.7, SD 21.7), pneumococcal septicaemia, six days (mean 10.6, SD 12.1) and pneumococcal pneumonia, four days (mean 6.0, SD 7.1). There were 135 deaths among the hospitalisation cases analysed, accounting for 3.2% of these cases. The elderly aged 75 years and above had the highest case fatality rate of 8.4% which was twice that of those under one year old (3.6%). The case fatality rate for the other age groups was as follows: 1–4 years old (0.5%), 5–14 years old (0.6%), 15–64 years old (2.0%), and 65–74 years old (4.7%). Pneumococcal meningitis had the highest case fatality of 23.3%. This was followed by pneumococcal septicaemia and pneumococcal peritonitis (both 14.3%) and pneumococcal pneumonia (2.9%). There was no case fatality in bacterial infection in conditions classified elsewhere and of unspecified site, pneumococcus.

## DISCUSSION

Overall, the highest mean annual hospitalisation rate of pneumococcal disease in our study was observed in children under five years of age (38.4 per 100,000 population) and in the elderly 65 years and above (56.4 per 100,000 population). It was also observed that in our study, the annual hospitalisation rates for pneumococcal disease in Singapore from 1995 to 2004 were similar to the findings in the United States (9.1–10.2 per 100,000 population)[9] and the United Kingdom (10.8 per 100,000 population),[4] prior to the incorporation of PCV into the routine childhood immunisation programmes in the United States and United Kingdom.

Over the study period, the peak annual hospitalisation rate for pneumococcal disease was observed in 2000. The increase in annual hospitalisation rate for pneumococcal disease in our study coincided with the dramatic increase in the prevalence of infections with penicillin-non-susceptible *Streptococcus pneumoniae* (PNSSP) during 1996 to 2000 reported in studies conducted in other parts of Asia.[6-7] The emergence of pneumococcal resistance to penicillin and other microbial agents limits the treatment options of IPD.[6] Further investigations may be needed to determine the numbers and proportion of PNSSP infection in our study to ascertain if there was an increase in PNSSP infection, that contributed to the upward trend of annual hospitalisation rate of pneumococcal disease up to 2000.

The 23-valent polysaccharide pneumococcal vaccine, Pneumovax 23 and Pneumo 23, were approved by the Health Sciences Authority (HSA) for use in Singapore in 1988 and 1998 respectively.[10] This was followed by a downward trend in the annual hospitalisation rates for pneumococcal disease from 2000 onwards, most notably among elderly adults 75 years old and above. In 2002, PCV7 was approved by the HSA for use in Singapore.[10] Annual hospitalisation rates declined from 2002 to 2003 for children under five years of age. Part of the decline in numbers among the elderly, and in young children under the age of five years, might have been due to pneumococcal vaccination. However, there is no reliable data on vaccination coverage to substantiate this hypothesis. Further investigations might be needed to ascertain the reasons for the decline in hospitalisation rates for pneumococcal disease.

In this study, we showed that the young and the elderly were susceptible to pneumococcal disease, similar to the findings in previous studies done overseas.[4,11] The age-specific distribution of pneumococcal disease provides important information on the most susceptible age groups and guidance for potential future prevention strategies, such as effective treatment of pneumococcal disease and vaccination. Studies on the cost-effectiveness of pneumococcal vaccination might be useful for evaluating the potential benefits of vaccination. The reasons for the observed distribution of pneumococcal disease could include: firstly, children under five years of age are more likely to attend day care, where they could have a higher nasopharyngeal carriage of *Streptococcus pneumoniae*; studies have shown that there is a strong association between day care attendance and an increased risk of IPD.[12] Secondly, the young children and elderly may have underlying conditions which predispose them to pneumococcal disease. It has been shown that conditions such as cardiovascular disease, chronic lung disease and malignancy are associated with an increased rate of pneumococcal disease.[13]

The elderly had the highest case-fatality rate among all the age groups in our study, and this could be due to the presence of underlying chronic diseases and poorer immune responses. There was an overall male predominance in the hospitalisation rates for pneumococcal disease. This was also observed in previous studies,[14,15] raising the possibility of gender constituting a risk factor in pneumococcal disease. It is interesting to note in one study that suggested looking for

any gender-related effects on vaccine immunogenicity and protection.[15] There could also be confounding factors, such as underlying diseases, smoking and alcohol use, which may affect the distribution of pneumococcal disease by gender. In view of the national scope and extended duration of our study, our findings have provided us an insight into the trend and demographics of patients. This information is important in planning prevention strategies. The longer length of stay observed in the young and the elderly has also highlighted that more extensive utilisation of healthcare services occurred at the extremities of age.

There are a few limitations in our study. Firstly, there is lack of microbiological data in our study, as information on serotypes and antibiotic resistance is not captured in the inpatient discharge database. Some cases could be missed, as only ICD-9 codes were used in obtaining the records from the inpatient discharge database. However, we noted in a recent retrospective local study of pneumococcal isolates from children admitted to KK Women's and Children's Hospital, that pneumonia (63.3%, includes 14.3% empyema) accounted for the majority of the diagnoses at presentation, followed by bacteraemia (17%), meningitis (15.6%) and 4.1% others (endocarditis, orbital cellulites, mastoiditis and peritonitis). The overall antibiotic resistance was: penicillin 40%, ceftriaxone 11%, erythromycin or trimethoprim-sulfamethoxazole 63%–69%. According to a separate analysis of 68 isolates from 2001 to 2004 in the same study, the coverage of all invasive serotypes by the 7-valent PCV (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) would be 83.8%.[16]

Our findings could only show the burden of pneumococcal disease requiring hospitalisation. Patients with pneumococcal disease and treated as outpatients were not included in our study. As our study was based on computerised hospitalisation records, errors due to coding misclassification might have occurred. Of note, the distribution of the types of pneumococcal disease might not be well reflected in our study based on hospitalised data. For instance, 97.9% of pneumococcal diseases in this study were pneumonia, although in all likelihood, a significant proportion of pneumonia cases could also be septicaemic. Furthermore, there is lack of separate ICD-9 codes for pneumococcal otitis media and pneumococcal rhino sinusitis. These limitations are relevant in a study purporting to describe the epidemiology of pneumococcal infections. Another limitation is the lack of data which might have contributed to the trend of the annual hospitalisation rate in our study. This includes possible risk factors like day care attendance and underlying conditions. Further investigations are needed to ascertain the reasons for the trends in hospitalisation rates.

Baseline information on the epidemiology of pneumococcal disease is important for the formulation and evaluation of a national prevention and control programme. Ongoing surveillance is needed to monitor the trends of pneumococcal infections in order to allow for timely and appropriate intervention. Studies in serotypes and antibiotic resistance in pneumococcal disease for these hospitalisation cases are also needed to fill in the information gaps in our study. Pneumococcal vaccination may be potentially useful. Studies should be done to evaluate the cost-effectiveness of a pneumococcal vaccination programme in Singapore.

## ACKNOWLEDGEMENTS

We would like to express our gratitude to our colleagues at the Communicable Diseases Division and Epidemiology and Disease Control Division for their advice.

## REFERENCES

1. McIntyre P, Gilmour R, Watson M. Differences in the epidemiology of invasive pneumococcal disease, Metropolitan NSW, 1997-2001. N S W Public Health Bull 2003; 14:85-9.
2. Hogg G, Strachan J. Pneumococcal infections in Victoria, Australia. Vaccine 1999; 17 suppl 1:S119-21.
3. Mansoor O. Pneumococcal infections in New Zealand. Vaccine 1999; 17 suppl 1:S122-3.
4. 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.
5. Jamal F. Epidemiological data on pneumococcal infections in Asian countries. Vaccine 1999; 17 suppl 1:S75-8.
6. Ma JS, Chen PY, Chi CS, Lin JF, Lau YJ. Invasive Streptococcus pneumoniae infections of children in central Taiwan. J Microbiol Immunol Infect 2000; 33:169-75.
7. Sirinavin S, Vorachit M, Thakkinstian A, Hongsanguensri S, Wittayawongsruji P. Pediatric invasive pneumococcal disease in a teaching hospital in Bangkok. Int J Infect Dis 2003; 7:183-9.
8. Ho PL, Chiu SS, Chueng CH, et al. Invasive pneumococcal disease burden in Hong Kong children. Pediatr Infect Dis J 2006; 25:454-5.
9. Shah SS, Ratner AJ. Trends in invasive pneumococcal disease-associated hospitalizations. Clin Infect Dis 2006; 42:e1-5.
10. Health Sciences Authority, Singapore. In: Infosearch for medicinal products [online]. Available at: www.hsa.gov.sg/prism/common/enquirepublic/SearchDRBProduct.do?action=load. Accessed August 15, 2006.
11. Konradsen HB, Kaltoft MS. Invasive pneumococcal infections in Denmark from 1995 to 1999: epidemiology, serotypes, and resistance. Clin Diagn Lab Immuno 2002; 9:358-65.
12. Levine OS, Farley M, Harrison LH, et al. Risk factors for invasive pneumococcal disease in children: a population-based case-control study in North America. Pediatrics 1999; 103:E28.
13. Pastor P, Medley F, Murphy TV. Invasive pneumococcal disease in Dallas County, Texas; results from population-based surveillance in 1995. Clin Infect Dis 1998; 26:590-5.
14. Domínguez A, Salleras L, Cardeñosa N, et al. The epidemiology of invasive Streptococcus pneumoniae disease in Catalonia (Spain). A hospital-based study. Vaccine 2002; 20:2989-94.
15. Scheifele D, Halperin S, Pelletier L, Talbot J. Invasive pneumococcal infections in Canadian children, 1991-1998: implications for new vaccination strategies. Clin Infect Dis 2000; 31:58-64.
16. Chong CY, Mok YH, Tee N. Invasive pneumococcal disease in Singapore children. Poster (abstract) presented at the 5th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD5), Alice Springs, Central Australia, 2006 Apr 2-6.

17. Andresen DN, Collignon PJ. Invasive pneumococcal disease in the Australian Capital Territory and Queanbeyan region: do high infant rates reflect more disease or better detection? J Paediatr Child Health 2004; 40:184-8.
18. Liddle JLM, McIntyre PB, Davis CWC. Incidence of invasive pneumococcal disease in Sydney children, 1991-96. J Paediatr Child Health 1999; 35:67-70.
19. Rendi-Wagner P, Georgopoulos A, Kundi M, et al. Prospective surveillance of incidence, serotypes and antimicrobial susceptibility of invasive Streptococcus pneumoniae among hospitalized children in Austria. J Antimicrob Chemother 2004; 53: 826-31.
20. Kaltoft MS, Zeuthen N, Konradsen HB. Epidemiology of invasive pneumococcal infections in children aged 0-6 years in Denmark: a 19-year nationwide surveillance study. Acta Paediatr Suppl 2000; 89:3-10.
21. Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. J Infect Dis 2001; 183:239-46.
22. Sankilampi U, Herva E, Haikala R, et al. Epidemiology of invasive Streptococcus pneumoniae infections in adults in Finland. Epidemiol Infect 1997; 118:7-15.
23. Syriopoulou V, Daikos GL, Soulis K, et al. Epidemiology of invasive childhood pneumococcal infections in Greece. Acta Paediatr Suppl 2000; 89:30-4.
24. Venetz I, Schopfer K, Mühlemann K. Paediatric, invasive pneumococcal disease in Switzerland, 1985-1994. Int J Epidemiol 1998; 27:1101-4.
25. Centers for Disease Control and Prevention. Active bacterial core surveillance (ABCs) report: emerging infections program network. Streptococcus pneumoniae, 1999. Available at: www.cdc.gov/ncidod/dbmd/abcs/survreports/spneu99.pdf. Accessed May 20, 2006.