Penicillin-resistant pneumococcus and risk of treatment failure in pneumonia

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ABSTRACT

Objective: To determine whether the presence of in vitro penicillin-resistant *Streptococcus pneumoniae* increases the risk of clinical failure in children hospitalised with severe pneumonia and treated with penicillin/ampicillin.

Design: Multicentre, prospective, observational study.

Setting: 12 tertiary-care centres in three countries in Latin America.

Patients: 240 children aged 3–59 months, hospitalised with severe pneumonia and known in vitro susceptibility of *S pneumoniae*.

Intervention: Patients were treated with intravenous penicillin/ampicillin after collection of blood and, when possible, pleural fluid for culture. The minimal inhibitory concentration (MIC) test was used to determine penicillin susceptibility of the pneumococcal strains isolated. Children were continuously monitored until discharge.

Main outcome measures: The primary outcome was treatment failure (using clinical criteria).

Results: Overall treatment failure was 21%. After allowing for different potential confounders, there was no evidence of association between treatment failure and in vitro resistance of *S pneumoniae* to penicillin according to the Clinical Laboratory Standards Institute (CLSI)/National Committee for Clinical Laboratory Standards (NCCLS) interpretative standards ($_{adj}$RR = 1.03; 95%CI: 0.49–1.90 for resistant *S pneumoniae*).

Conclusions: Intravenous penicillin/ampicillin remains the drug of choice for treating penicillin-resistant pneumococcal pneumonia in areas where the MIC does not exceed 2 μg/ml.

Acute respiratory infections (ARI) are among the five leading causes of death in children less than 5 years old in developing countries, causing more than 2 millions deaths per year.[1 2] *Streptococcus pneumoniae* is the bacteria that causes the most ARI (especially pneumonia) in this age group.[3 4] The World Health Organization (WHO) and the Pan American Health Organization (PAHO) have developed a strategy to reduce the burden of ARI among children, and it is based on standard case-management with appropriate empirical antibiotic treatment.[5] This approach, when optimally applied, has been effective in reducing childhood pneumonia-related mortality by 50% and overall child mortality by 25%.[6]

However, the emergence of penicillin-resistant pneumococcal strains has made the choice of empirical antibiotic therapy more difficult. Penicillin resistance has resulted in poor clinical

outcomes for bacterial meningitis and has changed the recommendation for the empirical treatment of this disease.[7] Controversy still exists as to whether or not penicillin resistance influences the outcome in pneumococcal pneumonia. No prospective study has been conducted to directly address this question.

Our aim was to determine whether the presence of penicillin-resistant *S pneumoniae* increases the risk of clinical failure in children aged 3–59 months who are hospitalised with severe pneumonia and treated with penicillin/ampicillin.

METHODS

Study design, definitions and procedures

This was a multicentre, prospective, observational investigation carried out simultaneously in 12 centres in three countries (six centres in Argentina, five in Brazil and one in the Dominican Republic) from July 1998 to December 2002. Conjugate pneumococcal vaccine was not available for the study population at that time and is not yet routinely administered in any of these countries.

In this study, cases were defined as children aged 3 to 59 months who were hospitalised with severe pneumonia according to the WHO guidelines,[5] that is, children with a cough or difficulty breathing and lower chest indrawing. The exclusion criteria were signs of very severe disease (severe malnutrition, stridor in calm child, unconsciousness, convulsions, nasal flaring, central cyanosis),[5] meningitis, sepsis, other infections requiring antibiotic therapy, current measles or pertussis, known penicillin allergy, miliary tuberculosis, congenital heart disease, known immunodeficiency, cancer, neurological or neuromuscular diseases, HIV-positive mother and hospitalisation in the previous two weeks before enrolment in this study.

On admission, a complete history was recorded and a full clinical examination with a chest X-ray was carried out. Venous blood samples were collected for culture and blood studies before therapy was initiated. When possible, pleural fluid was also collected for culture.

Blood and pleural fluid specimens were immediately inoculated into appropriate broth media for culture, and isolates were identified by standard methods.[8] All isolates were sent to the National Reference Laboratory of each country for the determination of the MIC for penicillin, using the broth micro-dilution method according to the

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CLSI/NCCLS.[9] Penicillin MIC data were interpreted according to the CLSI/NCCLS standards, that is, susceptible is ⩽0.06 µg/ml, intermediate is 0.12 µg/ml to 1 µg/ml and resistant is ⩾2 µg/ml. Serotypes were determined by the Neufeld–Quellung reaction using sera from the Statens Seruminstitut, Copenhagen, Denmark. All the National Reference Laboratories participate in an external Quality Assurance Programme for the SIREVA network (PAHO)[10] established by the National Centre for Streptococcus (NCS) in Edmonton, Alberta (Canada).

The patients received either penicillin G intravenously (200,000 IU/kg/day) or ampicillin intravenously (150 mg/kg/day) divided into four doses, in accordance with local policies. They were monitored for fever, tachypnea, hypoxaemia (oxygen saturation by pulse oximetry ⩽95% while breathing room air)[11] and the occurrence of disease progression until discharge. Fever was defined as axillary temperature >37.5°C[12] and tachypnoea as respiratory rate ⩾50 breaths/min in children aged 3–11 months and ⩾40 breaths/min in children aged 12 months or more.[5] The primary study outcome was treatment failure, defined as either no improvement (persistence of fever, tachypnoea, dyspnoea or hypoxaemia) after at least 48 hours of antibiotic therapy or deterioration of patients during antimicrobial therapy. Deterioration included development of pneumothorax, pneumatocele, pleural effusion for those without pleural effusion on admission, respiratory failure or sepsis. When treatment failed, the antibiotic was changed in accordance with local policies.

Ethical aspects

This study was approved by the Ethical Committee of every centre and by the ethical review board of the WHO (Subcommittee on Research Involving Human Subjects). We obtained written informed consent from parents or legal guardians of children before enrolment.

Statistical analysis

The sample size was estimated for a cohort study design to compare the risk of treatment failure in cases presenting in vitro penicillin-resistant isolates (exposed) with the risk of treatment failure in cases with in vitro susceptible strains (non-exposed). We assumed a ratio of non-exposed to exposed of 4:1 and assumed that among non-exposed patients the treatment failure rate would be 15%. Thus, 196 isolates would be sufficient to detect a statistically significant relative risk of 2.5 or greater associated with risk factors for treatment failure at a significance level of 0.05 and power of 0.80.

Analysis was conducted using a multiple logistic regression model. This model was developed in steps so that the more distant determinants of the outcome were first entered and, afterwards, the model progressively included the more proximal variables. The age of the child was included in the model on a priori grounds.

Thus, initially we included in our model the variables related to socioeconomic condition (eg, parent's schooling, parent's occupation, family income, country of residence, place of residence). Afterwards, we included the mother's age, length of exclusive breast feeding, day-care centre attendance, use of antibiotics prior to admission to the study, history of hospitalisation, exposure to passive smoking and overcrowding. The variables that were included in the last steps were the presence and susceptibility of S pneumoniae to penicillin, the initial signs and symptoms of disease (eg, clinical, laboratory

and X-ray findings) and, finally, the clinical evolution markers. Variables were selected for this analysis on the basis of a literature review for factors shown to be related to treatment failure in children with pneumonia.

Variables were selected for the final model if p⩽0.05 in each step and if there was a clear change (10% or more) in the estimate of the effect of in vitro penicillin-resistant isolates produced by the other variables not selected in the first steps of the analysis. The statistical significance of variables in the model was assessed by the likelihood ratio test (LRT). The odds ratios obtained were corrected to relative risks according to Zhang and Yu.[13] The analyses were performed using the STATA package, version 9.0.

RESULTS

Out of the 2566 patients included, 284 (11%) had pneumococcal strains isolated (179 from blood, 102 from pleural fluid and three from both). In vitro susceptibility was obtained, for 263 (93%) strains out of which 138 (52%) were susceptible, 68 (26%) had intermediate resistance and 57 (22%) were resistant (49 with MIC = 2 µg/ml and eight strains with MIC = 4 µg/ml).

After excluding patients for whom the antibiotic was changed in the first 48 hours of therapy (23), 240 cases constituted the study sample. Serotype data were available for 227 (95%) of these cases, and the following serotypes were the most common: 14 (118 strains), 1 (22 strains), 6B (16 strains), 5 (15 strains), 6A (9 strains), 9V (9 strains), 19A (6 strains), 18C (5 strains), 19F (5 strains) and 23F (3 strains). Table 1 presents selected demographic and clinical characteristics of these patients according to pneumococcal susceptibility. Overall, the median age was 15.7 months and the mean age 19.9 months (SD = 13.2 months).

We observed treatment failure in 51 (21%) children. For 12 of these patients their clinical condition deteriorated on the day that treatment failure was documented (one with respiratory failure, two with pneumatocele, one with pneumothorax and pleural effusion, one with pneumothorax and sepsis, two with sepsis and five with pleural effusion). Four patients needed to be referred to an intensive care unit (ICU), but no death occurred in this study group. The treatment failure occurred, on average, 5.8 days after the beginning of the therapy (median = 5 days).

No statistically significant association between in vitro resistance of S pneumoniae to penicillin and treatment failure was observed (p = 0.75), even after stratifying according to the presence of pleural effusion on admission (table 2).

The final multiple logistic regression model for the analysis of the effect of in vitro resistance of S pneumoniae on treatment outcome included 236 children, owing to missing values for the variable "previous antibiotic use" included in the model. Pleural effusion and lethargy on admission were statistically associated with treatment failure (table 3). No association between S pneumoniae resistance to penicillin, according to the CLSI/NCCLS breakpoints, and treatment failure was found (table 3).

DISCUSSION

Despite the availability of excellent antimicrobial therapy and adequate healthcare systems, respiratory diseases and invasive infections caused by pneumococci are still a major public health problem.[14 15] The introduction of penicillin in the 1940s greatly reduced the fatality rate of those infections.[16] Resistance to penicillin among S pneumoniae was initially recognised in 1967,[17] but only at the beginning of the 1990s did the penicillin resistance began to increase at an alarming rate.[18] Nevertheless,

Table 1 Number of children (%) in selected demographic and clinical characteristics with severe pneumonia in each pneumococcal penicillin susceptibility group

Characteristic	Pneumococcal penicillin susceptibility			Total* 240 (100)
	Susceptible 120 (50)	Intermediate 64 (27)	Resistant 56 (23)	
Age (months)				
3–11	31 (26)	31 (48)	22 (39)	84 (35)
12–23	43 (36)	21 (33)	24 (43)	88 (37)
24–35	21 (17)	10 (16)	7 (12)	38 (16)
36–47	14 (12)	2 (3)	1 (2)	17 (7)
48–59	11 (9)	–	2 (4)	13 (5)
Sex (male)	64 (53)	36 (56)	33 (59)	133 (55)
Country of residence				
Argentina	46 (38)	32 (50)	15 (27)	93 (39)
Brazil	56 (47)	20 (31)	8 (14)	84 (35)
Dominican Republic	18 (15)	12 (19)	33 (59)	63 (26)
Urban residence	108 (91)	59 (94)	49 (89)	216 (91)
Day-care centre attendance	14 (12)	5 (8)	6 (11)	25 (11)
Hospitalisation in the past 12 months	18 (16)	16 (25)	12 (21)	46 (20)
Report of previous antibiotic use	14 (12)	21 (33)	16 (30)	51 (22)
Fever on admission	89 (74)	47 (73)	35 (66)	171 (72)
Tachypnoea on admission	100 (85)	51 (80)	44 (82)	195 (83)
Dyspnoea on admission	89 (77)	49 (77)	49 (88)	187 (79)
Hypoxaemia on admission	67 (58)	35 (57)	35 (64)	137 (59)
Pleural effusion on admission	64 (53)	32 (50)	33 (59)	129 (54)
Hospitalisation >5 days (no., %)	95 (79)	53 (83)	39 (70)	187 (78)
Mean (SD) haemoglobin (g/dl) on admission	8.92 ($\pm$1.78)	8.35 ($\pm$1.62)	7.45 ($\pm$1.55)	8.43 ($\pm$1.78)
Mean (SD) WBC ($\times10^3$/l) on admission	18.53 ($\pm$9.53)	21.05 ($\pm$9.09)	20.93 ($\pm$11.03)	19.77 ($\pm$9.83)

*Totals may not add up 240 owing to missing values.

the clinical relevance of antimicrobial resistance in pneumococcal respiratory-tract infections remains surprisingly uncertain.[14 18]

To the authors' knowledge, this is the first prospective, multicentre investigation conducted among children with severe pneumonia in which patients were categorised according to the level of in vitro penicillin resistance to assess the association between resistance in vitro and clinical outcome after penicillin administration.[19] There was a large number of patients in our study and the sample size was therefore appropriate. The treatment was standardised at the same dose of penicillin/ampicillin for all eligible patients, the analysis was adjusted for confounding variables, there was no co-morbidity and patients presented with the same level of severity.

The evidence presented here shows that there is no association between penicillin resistance in vitro and treatment failure of penicillin in children up to 5 years old hospitalised with severe pneumonia (table 3). Austrian and Gold[20] reported, 40 years ago, that even with appropriate therapy and no resistance, 10–15% of hospitalised patients with pneumococcal bacteraemic pneumonia would fail therapy. This means that there will always be anecdotal evidence of treatment failure with various drugs because of the intrinsic pathogenicity of *S pneumoniae*.[18]

In a study of 504 adult patients with culture-proven pneumococcal pneumonia, Pallares et al.[21] found that mortality was 25% in patients who had penicillin-resistant *S pneumoniae* and were treated with penicillin G or ampicillin during the first 48 hours (discordant therapy), whereas mortality was 19% in those with penicillin-susceptible strains who were treated with the same drugs (concordant therapy) (p = 0.51). By contrast, Turett et al.[22] found an association between high-level (MIC$\geqslant$2 µg/ml) penicillin resistance and mortality. However,

the HIV-infection rate among these penicillin-resistant cases was high (70%).

Several experts believe that the aim of antimicrobial therapy in respiratory-tract infections, including pneumonia, should be the eradication of the infecting organism,[23] and the pharmacodynamics/pharmacokinetics (PK/PD) of an antimicrobial agent against the infecting pathogen can be used to predict the potential for bacterial eradication.[24] The penetration of beta-lactam antibiotics into lung tissue is generally similar to that of the serum concentration that provides a bactericidal effect at the site of infection; in addition, pneumococcal resistance to beta-lactams is not absolute, and increased doses can achieve the required PK/PD parameters for the treatment of resistant strains.[23]I have changed

All patients included in this study received Ampicillin intravenously (150 mg/kg/day) or Penicillin G intravenously (200 000 units/kg/day), doses that were reported to achieve serum concentrations above the MIC for highly penicillin-resistant strains (MIC$\geqslant$2 µg/ml) for >50% of the dosing interval (3 h).[23] Giachetto et al.[25] reported adequate interdose time serum concentrations higher than 4 µg/ml using Ampicillin (400 mg/kg/day) or Penicillin G IV (200 000 units/kg/day).

Friedland and Klugman[26] reported no difference in mortality rates between bacteraemic children infected with susceptible (n = 124) or resistant (n = 83) pneumococcal strains treated with intravenous penicillin or ampicillin. In 1995, Friedland[27] conducted a subsequent prospective non-interventional study to compare the clinical response in bacteraemic children with pneumonia, excluding meningitis, infected with susceptible or intermediate-resistant pneumococcal strains treated with intravenous ampicillin or an equivalent beta-lactam agent. Ninety three percent of children with penicillin-susceptible infections

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Table 2 Number of children (%) classified by treatment outcome and *S pneumoniae* in vitro susceptibility to penicillin (CLSI/NCCLS interpretative standards)

Treatment outcome	Susceptible	Intermediate	Resistant	Total	P
All children (n = 240)					0.75*
Success	94 (78)	49 (77)	46 (82)	189 (79)	
Failure	26 (22)	15 (23)	10 (18)	51 (21)	
Children without pleural effusion on admission (n = 111)					0.87*
Success	48 (86)	29 (91)	20 (87)	97 (87)	
Failure	8 (14)	3 (9)	3 (13)	14 (13)	
Children with pleural effusion on admission (n = 129)					0.37*
Success	46 (72)	20 (63)	26 (79)	92 (71)	
Failure	18 (28)	12 (37)	7 (21)	37 (29)	

*Fisher's exact test.

Table 3 Prognostic factors for treatment failure among children admitted with severe pneumonia who had *S pneumoniae* isolated and were treated with penicillin/ampicillin

Variables	Success n = 187(79%)	Failure n = 49(21%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	P*
Susceptibility					0.92
Susceptible	94	25	1	1	
Intermediate	49	14	1.05 (0.57–1.76)	1.14 (0.58–1.97)	
Resistant	44	10	0.88 (0.44–1.60)	1.03 (0.49–1.90)	
Age (months)			1.01 (0.99–1.02)	1.00 (0.98–1.02)	0.84
Pleural effusion on admission	90	35	2.21 (1.30–3.41)	2.31 (1.33–3.61)	0.003
Lethargy on admission	50	21	1.75 (1.06–2.63)	1.84 (1.10–2.79)	0.02
Previous antibiotic use	42	9	0.82 (0.41–1.49)	0.77 (0.35–1.46)	0.44

*Log likelihood ratio test.
RR, relative risk.

had improved by day 7 of therapy compared with 88% with resistant infections (no association was found).

A recent South Korean study,[28] enrolling children with pneumococcal pneumonia treated with pencillin 150 000–200 000 units/kg/day or cefotaxime 100 mg/kg/day, showed that the initial clinical condition was predictive of clinical response and mortality, and that there was no clear relationship between the outcome and the penicillin resistance of the infecting organism. In a study conducted in Uruguay and Argentina,[29] 75 children with pneumonia were treated with penicillin 150 000–200 000 units/kg/day or intravenous ampicillin and there was no significant difference in mortality between 52 patients infected with penicillin-susceptible *S pneumoniae* and 23 patients infected with highly penicillin-resistant strains (penicillin MIC⩾2 µg/ml) (RR = 1; 95%CI:0.8–1.1).

The overall high failure rate (21%) in this study can be partly explained by the stringent clinical criteria used to define the primary outcome. The association found between treatment failure and pleural effusion on admission (table 3) may be caused by the protracted response of children with pleural effusion.[18] Tan *et al*.[11] showed, in a retrospective study, that children with complicated pneumococcal pneumonia (mainly because of pleural effusion) were not more likely to be infected by antibiotic-resistant bacteria. Wexler *et al*.[30] did not observe any association between isolation of penicillin-resistant *S pneumoniae* and complicated pneumonia defined as the presence of pleural fluid on a chest radiograph, radiographic evidence of atelectasis, pneumatocele, pneumothorax and/or empyema (ie, purulent pleural fluid collection). Our results corroborate their studies.

This study has potential limitations that must be clarified. First, the heterogeneity of the study sites from different countries. Second, a great number of observers monitored the patients and collected the data. However, before and during the implementation of the study, meetings among the site investigators were promoted to agree the standardisation of the procedures. We believe the bias that might have been introduced was counteracted by the strict clinical criteria used and the agreement of the site investigators on all treatment failures.

The percentage (69%) of the strains that belonged to serotypes included in the seven-valent vaccine (4, 9V, 6B, 14, 18C, 19F and 23F) and the great frequency of serotype 14 (52%) are in agreement with data previously published from that region.[30] It is worth noting that an investigational vaccine including serotype 1 would be very beneficial in improving the protection afforded by the vaccine.

The contribution of this study was to present evidence that high-level penicillin resistance was not associated with treatment failure with penicillin. In areas where pneumococcal strains present with MIC up to 2 µg/ml, penicillin remains the drug of choice for the treatment of children with severe pneumonia, when administrated at a dose of 200 000 units/kg/day. This is in agreement with Bishai's[32] statement that in vitro findings do not seem to be predictive of in vivo outcomes in this range of MIC. The authors, thus, emphasize the importance of continuous surveillance of pneumococcal infections and the need to implement preventive measures for halting the increase of the frequency of pneumococcal strains with greater MIC.[33]

What is already known on this topic

The increase in penicillin-resistant pneumococcal strain frequency has made the choice of empirical antibiotic therapy for pneumonia difficult. Controversy still exists as to whether or not penicillin resistance influences the outcome of pneumococcal pneumonia infection.

What this study adds

Diminished susceptibility of *Streptococcus pneumoniae* to penicillin was not associated with treatment failure with penicillin in children with pneumonia. Penicillin, when administered at a dose of 200 000 units/kg/day, remains the drug of choice for the treatment of children with severe pneumonia in areas where the MIC does not exceed 2 μg/ml.

REFERENCES

1. **Williams BG,** Gouws E, Boschi-Pinto C, *et al*. Estimates of worldwide distribution of child deaths from acute respiratory infections. *Lancet Infect Dis* 2002;**2**:25–32.
2. **World Health Organization**. The World Health Report 2005. Make every mother and child count. Geneva: World Health Organization, 2005.http://www.who.int/whr2005_en.pdf.
3. **World Health Organization (WHO)**. Technical bases for the WHO recommendations on management of pneumonia in children at first level health facilities. Geneva: WHO 1991, WHO/ARI/91.20.
4. **Michelow IC,** Olsen K, Lozano J, *et al*. Epidemiology and characteristics of community-acquired pneumonia in hospitalized children. *Pediatrics* 2004;**113**:701–7.
5. **World Health Organization (WHO)**. ARI in children: case management in small hospitals in developing countries. A manual for doctors and other senior health workers. Programme for the Control of ARI.Geneva: WHO, 1990.
6. **Sazawal S,** Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. *Lancet Infect Dis* 2003;**3**:547–56.
7. **Friedland IR,** Klugman KP. Failure of chloramphenicol therapy in penicillin-resistant pneumococcal meningitis. *Lancet* 1992;**339**:405–8.
8. **Facklam RR,** Washington JA. Streptococcus and related catalase-negative Gram positive cocci. In: Balows A, Hausler WJ Jr, Hermann KL, Isenberg HD, Shadomy HJ, eds. *Manual of clinical microbiology*. 5th ed. Washington (DC): American Society for Microbiology, 1991.
9. **Clinical and Laboratory Standards Institute (CLSI)**. *Performance standards for antimicrobial susceptibility testing; Fifteenth informational supplement*. Document M100-S15.Wayne, USA: CLSI/NCCLS, 2005.
10. **Di Fabio JL,** Homma A, de Quadros C. Pan American Health Organization epidemiological surveillance network for Streptococcus pneumoniae. *Microb Drug Resist* 1997;**3**:131–3.
11. **Tan TQ,** Mason Jr EO, Wald ER, *et al*. Clinical characteristics of children with complicated pneumonia caused by *Streptococcus pneumoniae*. *Pediatrics* 2002;**110**:1–6.
12. **El-Radhi AS,** Barry W. Thermometry in paediatric practice. *Arch Dis Child* 2006;**91**:351–6.
13. **Zhang J,** Yu KF. What's the relative risk?: a method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;**280**:1690–1.
14. **File Jr TM.** Appropriate use of antimicrobials for drug-resistant pneumonia: focus on the significance of beta-lactam-resistant *Streptococcus pneumoniae*. *Clin Infect Dis* 2002;**34**(Suppl 1):s17–26.
15. **Bogaert D,** Hermans PW, Adrian PV, *et al*. Pneumococcal vaccines: an update on current strategies. *Vaccine* 2004;**22**:2209–20.
16. **Dowell SF,** Kupronis BA, Zell ER, *et al*. Mortality from pneumonia in children in the United States, 1939 through 1996. *N Engl J Med* 2000;**342**:1399–407.
17. **Hansman D,** Bullen MM. A resistant pneumococcus. *Lancet* 1967;**ii**:264–5.
18. **Bishai W.** The in vivo-in vitro paradox in pneumococcal respiratory tract infections. *J Antimicrob Chemother* 2002;**49**:433–6.
19. **Kaplan SL.** Review of antibiotic resistance, antibiotic treatment and prevention of pneumococcal pneumonia. *Paediatr Respir Rev* 2004;**5**(Suppl A):S153–8.
20. **Austrian R,** Gold J. Pneumococcal bacteremia with special reference to bacteremic pneumococcal pneumonia. *Ann Intern Med* 1964;**60**:759–76.
21. **Pallares R,** Linares J, Vadillo M, *et al*. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *N Engl J Med* 1995;**333**:474–80.
22. **Turett GS,** Blum S, Fazal BA, *et al*. Penicillin resistance and other predictors with high human immunodeficiency virus seroprevalence. *Clin Infec Dis* 1999;**29**:321–7.
23. **Dagan R,** Klugman KP, Craig WA, *et al*. Evidence to support the rationale that bacterial eradication in respiratory tract infection is an important aim of antimicrobial therapy. *J Antimicrob Chemother* 2001;**47**:129–40.
24. **Garau J.** Clinical failures: the tip of the iceberg? *Respir Med* 2001;**95**(Suppl A): S5–11.
25. **Giachetto G,** Pirez MC, Nanni L, *et al*. Ampicillin and penicillin concentration in serum and pleural fluid of hospitalized children with community-acquired pneumonia. *Pediatr Infect Dis J* 2004;**23**:625–9.
26. **Friedland IR,** Klugman KP. Antibiotic-resistant pneumococcal disease in South African children. *Am J Dis Child* 1992;**146**:920–3.
27. **Friedland IR.** Comparison of the response to antimicrobial therapy of penicillin-resistant and penicillin-susceptible pneumococcal disease. *Pediatr Infect Dis J* 1995;**14**:885–90.
28. **Choi EH,** Lee HJ. Clinical outcome of invasive infections by penicillin-resistant Streptococcus pneumoniae in Korean children. *Clin Infect Dis* 1998;**26**:1346–54.
29. **Deeks SL,** Palacio R, Ruvinsky R, *et al*. Risk factors and course of illness among children with invasive penicillin-resistant *Streptococcus pneumoniae*. *Pediatrics* 1999;**103**:409–13.
30. **Wexler ID,** Knoll S, Picard E, *et al*. Clinical characteristics and outcome of complicated pneumococcal pneumonia in a pediatric population. *Pediatr Pulmonol* 2006;**41**:726–34.
31. **Brandileone M-CC,** Casagrande ST, Guerra M-LLS, *et al*. Increase in numbers of beta-lactam-resistant invasive *Streptococcus pneumoniae* in Brazil and the impact of conjugate vaccine coverage. *J Med Microbiol* 2006;**55**:567–74.
32. **Bishai WR.** Clinical significance of pneumococcal resistance and factors influencing outcomes. *Treat Respir Med* 2005;**4**(Suppl 1):19–23.
33. **Cunha BA.** Therapeutic implications of antibacterial resistance in community-acquired respiratory tract infections in children. *Infection* 2004;**32**:98–108.

APPENDIX

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