

# The Impact of Penicillin Resistance on Short-Term Mortality in Hospitalized Adults with Pneumococcal Pneumonia: A Systematic Review and Meta-Analysis

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(See the editorial commentary by File et al. on pages 798–800)

**Background.** The clinical impact of penicillin resistance on the outcome of pneumococcal pneumonia has remained controversial. We performed a meta-analysis of prospective cohort studies to examine the association between penicillin resistance and short-term all-cause mortality for pneumococcal pneumonia.

**Methods.** We retrieved studies published in any language by a comprehensive search of the Medline, Current Contents, and Embase databases for all appropriate articles published up to January 2005. We also manually reviewed bibliographies of retrieved articles, recent national treatment guidelines, and review articles. We included prospective cohort studies that involved adult subjects, and we examined the association between penicillin resistance and short-term mortality for pneumococcal pneumonia. Two reviewers independently extracted data on crude and adjusted risk estimates of all-cause mortality for pneumococcal infections with different levels of penicillin resistance and assessed the methodological quality of selected studies. We also contacted authors to obtain additional information. We performed meta-analyses using a random-effect model.

**Results.** Of 1152 articles identified in the search, 10 studies that involved 3430 patients (most of whom were hospitalized) were included. The mortality rate was 19.4% in the penicillin-nonsusceptible *Streptococcus pneumoniae* group and 15.7% in the penicillin-susceptible *S. pneumoniae* group. The combined relative risks of all-cause mortality for the penicillin-nonsusceptible, -intermediate, and -resistant *S. pneumoniae* groups, compared with the penicillin-susceptible *S. pneumoniae* group, were 1.31 (95% confidence interval [CI], 1.08–1.59), 1.34 (95% CI, 1.13–1.60), and 1.29 (95% CI, 1.01–1.66), respectively. The combined adjusted relative risks of mortality for penicillin-nonsusceptible versus penicillin-susceptible *S. pneumoniae* group was 1.29 (95% CI, 1.04–1.59) for the 6 studies that adjusted for age, comorbidities, and severity of illness. There was minimal between-study heterogeneity in these analyses.

**Conclusion.** Penicillin resistance is associated with a higher mortality rate than is penicillin susceptibility in hospitalized patients with pneumococcal pneumonia. Additional efforts are needed to understand the mechanisms of this association.

The global morbidity and mortality due to pneumococcal pneumonia, the most common type of community-acquired pneumonia (CAP), remain striking [1]. The mortality rate ranges from 6.4% among patients treated in an ambulatory and hospital setting to >37% among patients treated in intensive care units

[2]. The development of multidrug resistance among clinical *Streptococcus pneumoniae* isolates has posed more challenges in treating some syndromes of infection caused by this organism. Several surveillance programs that span numerous countries indicate that the proportion of drug-resistant *S. pneumoniae* isolates continues to increase worldwide. In 2 recent multinational studies, the prevalence of penicillin resistance among *S. pneumoniae* isolates ranged from 18.2% to 22.1% [3, 4].

The clinical impact of in vitro antibiotic resistance on outcome of pneumococcal CAP remains a critical question that is worthy of the attention it has garnered for >1 decade. Despite this attention, the topic has re-

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mained controversial because studies have been underpowered or results have conflicted. Therefore, we performed a systematic review of the literature following the Meta-analysis of Observational Studies in Epidemiology guidelines [5]. We sought to examine the association between different levels of penicillin resistance and short-term mortality for pneumococcal pneumonia.

## METHODS

**Identification of relevant literature.** A literature search was performed to identify all published cohort studies of nonmeningeal *S. pneumoniae* infection with the help of an experienced medical librarian. The search included Medline and Embase databases (for relevant articles published up to January 2005) and Current Contents/Science Edition (for articles published from 1996 to January 2005). We searched the Medline database using the search terms “pneumonia, bacterial” and “streptococcus pneumonia or diplococcus or pneumococcus or pneumonia, pneumococcal or pneumococcus,” and “bacterial/and drug resistance” and “mortality” (Appendix A). Two investigators (H.M.T. and L.M.B.) independently reviewed abstracts of all identified references. We reviewed any study that could be considered to be relevant on the basis of findings that were described in the respective abstract. We manually reviewed bibliographies of retrieved articles, recent national treatment guidelines, and review articles for additional citations, and we obtained the full text of all potentially relevant articles. There was no restriction to language of publication. We did not seek unpublished investigations.

**Inclusion and exclusion criteria.** To be included, a study had to include (1) a cohort of prospectively enrolled patients and collected data, (2) adult patients with pneumonia, and (3) data outlining penicillin resistance and short-term, all-cause mortality. Short-term mortality included all deaths within 30 days after diagnosis or during hospitalization. Investigations were excluded if the study population contained only immunocompromised patients (i.e., HIV-infected patients or transplant recipients) or elderly patients (i.e., those aged >65 years), who are at high risk for mortality.

**Data collection.** A data collection form was developed and used to retrieve information on relevant features and results of pertinent studies. Two reviewers independently extracted and recorded data on a predefined checklist. Data included the following items: study characteristics (i.e., country and year of study), characteristics of the cohort, and case definitions. We hypothesized that the purported factors of bacteremia, concordance of therapy, and severity of illness could influence the relative risk (RR) of mortality. Therefore, we extracted the total number of patients infected with and number of deaths among patients infected with penicillin-susceptible *S. pneumoniae* (PSSP), penicillin-resistant *S. pneumoniae* (PRSP), penicillin-

intermediate *S. pneumoniae* (PISP), penicillin-nonsusceptible *S. pneumoniae* (PNSSP), and highly penicillin-resistant *S. pneumoniae* (HPRSP) for the total cohort and for the following subgroups: bacteremia, concordant therapy, discordant therapy, and penicillin-discordant therapy groups (Appendix B). We also collected adjusted ORs and 95% CIs based on the multivariable regression model used in each study. Seven of 10 corresponding authors of the primary studies who were contacted for clarification of data or to obtain additional information provided available data [6–12]. Two reviewers (I.M.T. and H.M.T.) independently assessed the methodological quality of selected studies using the Newcastle-Ottawa quality assessment scale for cohort studies [13]. Disagreement among reviewers was discussed, and agreement was reached by consensus.

**Statistical analysis.** The meta-analytic comparison was based on the adjusted summary OR estimate from each cohort study and the crude unadjusted relative risk (RR) for mortality in different subgroups. A random-effects model was used to pool the effect estimates. RRs for all-cause mortality were calculated with the 95% CI. Pooled estimates of adjusted OR were obtained by combining the separate estimates of inverse variance-weighted log OR from each study. The adjusted OR from the logistic regression was converted to RR using the following formula:  $RR = OR / [(1 - P) + (P \times OR)]$ , where P is the incidence of the outcome event in the nonexposed group [14].

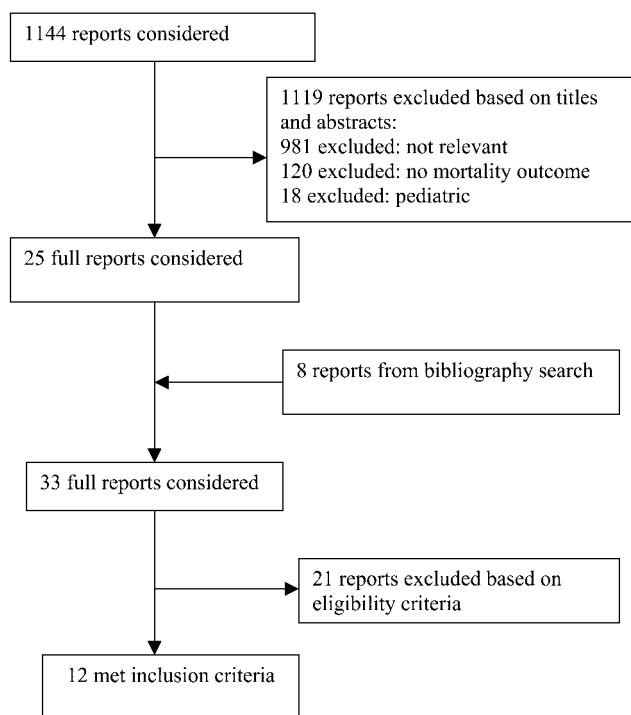
Subgroup analyses, hypothesized a priori, were conducted by using a statistical test of interaction [15]. Studied subgroups included the study population (invasive infections vs. broader microbiologic inclusion criteria) and outcome measures (in-hospital vs. 30-day mortality). Sensitivity analysis was performed to examine the effect of study quality on combined risk estimates.

Between-study inconsistency was analyzed by means of  $I^2$ , which defines the variability percentage in effect estimates that is due to heterogeneity rather than to chance [16]. A funnel plot was not constructed because of the small number of identified studies. All meta-analyses were performed with RevMan Analyses, version 4.2.7 (Cochrane Collaboration).

## RESULTS

Figure 1 summarizes the process of identifying eligible studies. Twelve prospective cohort studies met inclusion criteria [6–12, 17–21]. The  $\kappa$  statistic for interobserver agreement on study eligibility was 0.9. Disagreement was resolved by consensus. The study by Falco et al. [7] was a combination of a retrospective cohort (from 1997–1999) and a prospective cohort (from 1999–2001).

Two studies [11, 21] were subsequently excluded because outcome and susceptibility data were missing for >30% of patients and were not readily available for either of the study



**Figure 1.** Flow diagram of eligible studies of penicillin resistance and short-term mortality for pneumococcal pneumonia.

authors. Their effect on the pooled estimate was examined by sensitivity analysis.

**Study characteristics.** Table 1 summarizes the characteristics of all studies included in our analysis. The studies were geographically heterogeneous. Study samples were from Argentina, different Asian countries, Brazil, France, Israel, New Zealand, Spain, South Africa, Sweden, and the United States. The 10 cohorts included a total of 3430 patients. Sample sizes ranged from 22 to 793 patients. In all studies, >95% of patients were hospitalized. Eight of 10 studies included only patients with CAP; in the 2 other studies [9, 12], >85% of the patients had underlying pneumonia. These 2 studies also included nosocomial infections, but the authors adjusted for the mode of acquisition in the multivariate analysis. Thirty-four patients (5.3%) in the study by Aspa et al. [6] and 24 patients (24%) in the study by Ewig et al. [17] had mixed infections. The effect of the latter study on the combined RR was examined by sensitivity analysis. The remaining studies included only patients with monobacterial pneumococcal infections.

Microbiologic inclusion criteria for study participants were either strict or broad. Strict criteria included only patients with *S. pneumoniae* recovered from blood, pleural fluid, or lower respiratory specimens (i.e., bronchoalveolar lavage or protected brush samples). Broad criteria also included patients with *S. pneumoniae* recovered from sputum specimens.

The proportion of PISP isolates ranged from 2% to 37%,

the proportion of PRSP isolates ranged from 0% to 29.6%, and the proportion of HPRSP isolates ranged from 0% to 3.4%. The mortality rates ranged from 10.9% to 36.4%.

The extent of adjustment for potential confounding factors in the association between penicillin resistance and mortality varied among studies. All 6 studies that reported an adjusted OR for mortality used variables that were associated with mortality by univariate analysis, including age, comorbidity measures, and severity of illness in the final logistic regression model. The assessment of severity of illness varied among studies. Three studies used pneumonia severity index score, 1 study used Pitt bacteremia and APACHE II scores, and 2 studies used surrogate markers for severity of illness (table 2).

**Quality assessment.** Table 3 summarizes the different levels of study quality. The Newcastle-Ottawa quality assessment scale for cohort studies is intended to assess for selection bias, comparability of the exposed and unexposed groups of each cohort, outcome assessment, and attrition bias. Included studies differed in the representativeness of the cohorts and comparability of the exposed and nonexposed groups when exposure represents penicillin resistance. Two reviewers independently evaluated these 2 components of the scale. There was 100% agreement ( $\kappa = 1$ ). All studies had both adequate follow-up and outcome assessment methods.

All study populations were selected groups of consecutive hospitalized patients and not representative of the average patient with pneumococcal CAP. Six of the 10 investigations [6–9, 12, 19] adjusted for possible confounders when exposed and nonexposed cohorts were compared.

**Quantitative summary of mortality risk.** Table 4 summarizes results of analyses using unadjusted mortality data. The mortality rate was 19.4% in the PNSSP group and 15.7% in the PSSP group. The combined RRs of mortality for the PNSSP, PISP, and PRSP groups, compared with the PSSP group, were 1.31 (95% CI, 1.08–1.59), 1.34 (95% CI, 1.13–1.60), and 1.29 (95% CI, 1.01–1.66), respectively (figure 2a and 2b). There were only a total of 51 patients infected with HPRSP, with a combined RR of mortality of 1.68 (95% CI, 0.68–4.16).

The combined unadjusted and adjusted ORs of mortality for penicillin-nonsusceptible versus penicillin-susceptible *S. pneumoniae* CAP were 1.50 (95% CI, 1.21–1.85) and 1.37 (95% CI, 1.05–1.78), respectively, for the 6 studies that adjusted for age, comorbidities, and severity of illness (figure 3), with corresponding RRs of 1.39 (95% CI, 1.18–1.65) and 1.29 (95% CI, 1.04–1.59). Excluding the study by Falco et al. [7], which had a retrospective cohort component, the combined adjusted OR was 1.28 (95% CI, 0.98–1.68).

**Subgroup analyses and assessment for heterogeneity.** There was minimal and statistically nonsignificant between-study heterogeneity in different analyses, as suggested by low  $I^2$ . We hypothesized a priori that estimates of RRs might vary

**Table 1. Characteristics of included cohort studies of pneumococcal pneumonia.**

Reference	Period	Country	Inclusion criteria <sup>a</sup>	Age, mean years	No. of patients	Percentage of isolates			Bacteremia, % of patients	Mortality definition	Mortality rate, %
						PISP	PRSP	HRSP			
Jehl et al. [18]	1998–2000	France	Invasive and noninvasive pneumococcal pneumonia	65	465	32.9	10.5	0	47.5	30-day	16.3
Pallares et al. [8]	1984–1993	Spain	Invasive pneumococcal pneumonia	...	456	15.1	10.3	2.6	78	In-hospital	23.5
Yigla et al. [20]	1989–1990	Israel	Invasive and noninvasive pneumococcal pneumonia	60.2	22	13.6	0	0	68	In-hospital	36.4
Ewig et al. [17]	1996–1998	Spain	Invasive and noninvasive pneumococcal pneumonia	...	101	2	5.9	0	55	In-hospital	10.9
Pallares et al. [9]	1994–2000	Spain and Switzerland	Invasive nonmeningeal pneumococcal infection	...	429	12.1	17.9	0	> 50%	30-day	16.8
Sangthawan et al. [10]	1998–2001	Thailand	Invasive and noninvasive pneumococcal pneumonia	52.5	46	37	4.3	2.2	...	In-hospital	26.1
Yu et al. [12]	1998–2001	International	Pneumococcal bacteremia	52.1	793	15	9.6	1.6	100	14-day in-hospital	17
Aspa et al. [6]	1999–2000	Spain	Invasive pneumococcal pneumonia	61.5	638	25.7	10.2	0.5	73.6	30-day	14.4
Falco et al. [7]	1997–2001	Spain	Invasive pneumococcal pneumonia	62.8	247	20.6	6.1	0	95	In-hospital	15.8
Song et al. [19]	2000–2001	9 Asian countries	Invasive pneumococcal pneumonia	60.8	233	25.3	29.6	3.4	31	30-day	13.3

**NOTE.** HPRSP, highly penicillin-resistant *Streptococcus pneumoniae*; PISP, penicillin-intermediate *S. pneumoniae*; PRSP, penicillin-resistant *S. pneumoniae*.

<sup>a</sup> Invasive pneumococcal pneumonia was diagnosed if *S. pneumoniae* was recovered from blood, pleural fluid, or lower respiratory tract specimens (i.e., bronchoalveolar lavage fluid or protected brush specimens).

**Table 2. Variables adjusted for in univariate/multivariate analyses.**

Reference	Variables
Aspa et al. [6]	PSI score, age, ICU admission, mechanical ventilation, shock, DIC, renal failure, empyema, lung abscess, extrapulmonary focus, chronic pulmonary disease, suspected aspiration, discordant/concordant penicillin therapy, and previous hospitalization <sup>a</sup>
Falco et al. [7]	PSI score, age, serotypes, malignancy, HIV infection, ICU admission, and need for mechanical ventilation
Pallares et al. [8]	Age, comorbidities, multilobar involvement, shock, nosocomial infection, and leukopenia
Pallares et al. [9]	Charlson comorbidity index and age, as well as shock and multilobar involvement (in cases of pneumonia) <sup>a</sup>
Yu et al. [12]	Pitt bacteremia and APACHE II scores, comorbidities, age, immunosuppression, and nosocomial infection
Song et al. [19]	PSI score, age, and comorbidities

**NOTE.** DIC, disseminated intravascular coagulation; ICU, intensive care unit; PSI, pneumonia severity index.

<sup>a</sup> Determined by personal communication with authors.

on the basis of the study population (i.e., strict vs. broad microbiologic inclusion criteria) or outcome measures (i.e., in-hospital vs. 30-day mortality). There was no heterogeneity in exposure definition, because all studies used Clinical and Laboratory Standards Institute guidelines to define penicillin susceptibility. We performed subgroup analyses to test these hypotheses. There was no statistically significant difference among the different subgroups ( $P = .86$  and  $.67$ , respectively, for statistical test of interaction).

Sensitivity analysis was performed to examine the effect of the 2 excluded studies and the quality of included studies on the combined risk estimate. Addition of the 2 excluded studies [11, 21] to the analysis did not change the results significantly. The pooled RR for mortality for PNSSP versus PSSP groups was 1.25 (95% CI, 1.03–1.51). Exclusion of the study by Ewig et al. [17], in which 24% of patients had mixed infections, resulted in a combined RR of 1.22 (95% CI, 1.01–1.48).

Studies differed in their quality on the basis of comparability criteria of the Newcastle-Ottawa quality assessment scale. Six investigations performed multivariate analysis when comparing mortality rates of PNSSP and PSSP. The combined OR for mortality of PNSSP versus PSSP infection was 1.37 (95% CI, 1.05–1.78).

## DISCUSSION

Our meta-analysis suggests an increase in short-term mortality across different levels of penicillin resistance among *S. pneumoniae* infections. The mortality rate for PNSSP infection is ~30% higher than that for PSSP disease. This association was similar for infections due to both PISP and PRSP and was present across different subgroups, including the total cohort, the subgroup of bacteremic patients, and the concordant and discordant therapy groups. Given the high incidence of strep-

tococcal pneumonia—the most common cause of CAP—this association can be translated into a large absolute number of deaths annually.

**Internal validity of the results.** The possibility that the observed association between penicillin resistance and mortality was associated with bias should be considered. First, selection bias can distort the results if hospitalization rates differ for different exposure groups (PSSP vs. PNSSP). Because of the difficulty of ascertaining the microbiologic diagnosis of CAP in the outpatient setting, this meta-analysis included studies that recruited patients from the hospital setting only.

Second, exposure misclassification is another potential bias. Several studies have used broad microbiologic inclusion criteria and have recruited patients with *S. pneumoniae*-positive sputum cultures [10, 17, 18, 20]. The sputum isolates could represent colonizing strains. Moreover, patients can be colonized with >1 strain of pneumococcus, which causes difficulties in identifying an infecting strain. Third, knowledge of the patient's poor status may influence the decision to search for a specific microbiologic etiology, because susceptibility testing is not routinely performed on pneumococci isolated from sputum specimens. However, we do not believe that these biases distorted our results, because the 6 studies that used multivariate analysis to report the OR for mortality relied on strict microbiologic inclusion criteria.

Confounding effect should also be examined. Comorbidities are known confounders that are associated with pneumococcal penicillin resistance and mortality [22]. Severity of illness is a complex interaction of host defenses, preexisting conditions, and bacterial virulence and can be either a confounder or in the causal pathway of this association if PNSSP isolates are more virulent than PSSP isolates. The combined RR from the 6 studies that used logistic regression models to adjust for pos-

**Table 3. Newcastle-Ottawa quality assessment scale for cohort studies.**

Reference	Selection				Comparability <sup>e</sup>	Outcome		
	Representativeness of the exposed cohort <sup>a</sup>	Selection of the nonexposed cohort <sup>b</sup>	Ascertainment of exposure <sup>c</sup>	Incident disease <sup>d</sup>		Assessment of outcome <sup>f</sup>	Length of follow-up <sup>g</sup>	Adequacy of follow-up <sup>h</sup>
Jehl et al. [18]	C	A	A	A	C	B	A	A
Pallares et al. [8]	C	A	A	A	A and B	B	A	A
Yigla et al. [20]	C	A	A	A	C	B	A	A
Ewig et al. [17]	C	A	A	A	C	B	A	A
Pallares et al. [9]	C	A	A	A	A and B	B	A	A
Sangthawan et al. [10]	C	A	A	A	C	B	A	A
Yu et al. [12]	C	A	A	A	A and B	B	A	A
Aspa et al. [6]	C	A	A	A	A and B	B	A	A
Falco et al. [7]	C	A	A	A	A and B	B	A	A
Song et al. [19]	C	A	A	A	A and B	B	A	A

<sup>a</sup> A, truly representative of the average patient with community-acquired pneumonia; B, somewhat representative of the average patient with community-acquired pneumonia; C, selected group; D, no description of the derivation of the cohort.

<sup>b</sup> A, drawn from the same community as the exposed cohort; B, drawn from a different source; C, no description of the derivation of the non exposed cohort.

<sup>c</sup> A, secure record (e.g., surgical record); B, structured interview; C, written self-report; D, no description.

<sup>d</sup> For demonstration that the outcome of interest was not present at start of study: A, yes; B, no.

<sup>e</sup> For comparability of cohorts on the basis of the design or analysis: A, study controls for any additional factor (e.g., age and severity of illness); C, not done.

<sup>f</sup> A, independent blind assessment; B, record linkage; C, self-report; D, no description.

<sup>g</sup> For determination of whether follow-up was long enough for outcomes to occur: A, yes (i.e., in-hospital or up to 30 days); B, no.

<sup>h</sup> A, complete follow-up and all subjects accounted for; B, subjects lost to follow-up was unlikely to introduce bias, because a small number were lost (i.e., >90% were available for follow-up) or a description was provided of those lost; C, follow-up rate of <90% (select an adequate percentage) and no description of those lost; D, no statement.

sible confounders, including age, comorbidities, and severity of illness, although the models were not uniform, supports an increased mortality rate in the PNSSP group.

As with any prognostic cohort study, residual confounding cannot be fully excluded, particularly when the observed association is not strong. The combined unadjusted and adjusted RRs of mortality for PNSSP versus PSSP CAP were 1.39 (95% CI, 1.18–1.65) and 1.29 (95% CI, 1.04–1.59), respectively. Adjustment for known important confounders only resulted in a 0.1-unit decrease in the RR. An unknown confounder would be unlikely to cause a large change in the RR.

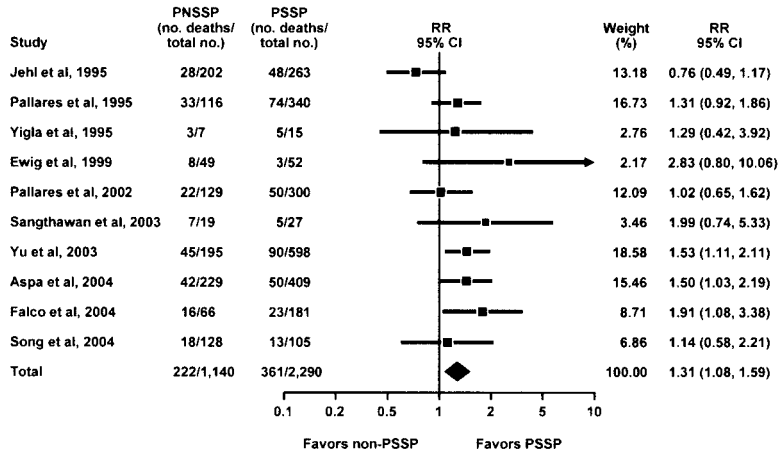
Discordant antibiotic therapy does not appear to have contributed to increased mortality in the PNSSP group. We were not able to examine penicillin-discordant therapy, because the

cumulative number of patients who were in this group was small. This is in part the result of the recommended use of broad-spectrum antibiotics for empirical treatment of CAP in more seriously ill patients. Nevertheless, the success of penicillin therapy for PISP infection is supported by its pharmacokinetic and pharmacodynamic principles. An antibiotic concentration in the serum exceeding the MIC of a microorganism for at least 40%–50% of the dosing interval is predictive of microbiologic eradication with most  $\beta$ -lactam antibiotics, including penicillin that is administered in routine doses. Therefore, our meta-analysis does not dictate a shift in current antimicrobial treatment for pneumococcal pneumonia. Nevertheless, it suggests that penicillin resistance is a prognostic factor. This observation could help physicians assess patients' risks and im-

**Table 4. Summary of combined relative risks (RRs) of mortality for the penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSSP), penicillin-intermediate *S. pneumoniae* (PISP), and penicillin-resistant *S. pneumoniae* (PRSP) groups, compared with the penicillin-susceptible *S. pneumoniae* (PSSP) group.**

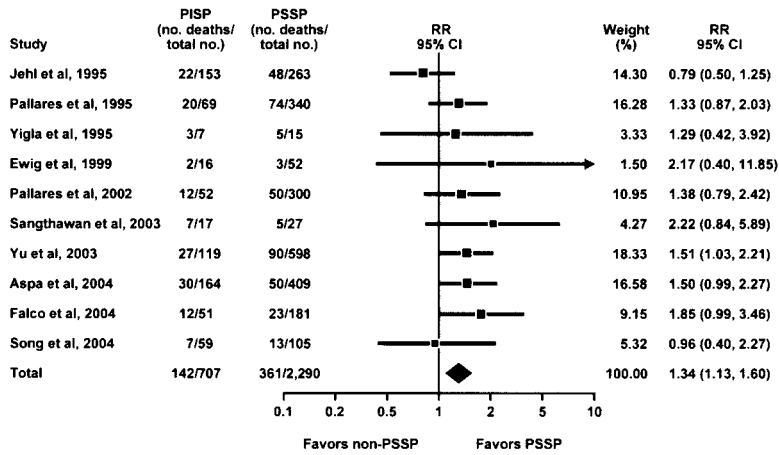
Group	PNSSP group				PISP group				PRSP group				References
	No. of studies	No. of patients	RR (95 %CI)	I <sup>2</sup>	No. of studies	No. of patients	RR (95 %CI)	I <sup>2</sup>	No. of studies	No. of patients	RR (95 %CI)	I <sup>2</sup>	
Total cohort	10	1140	1.31 (1.08–1.59)	29	10	707	1.34 (1.13–1.60)	0	10	433	1.29 (1.01–1.66)	13	[6–10, 12, 17–20]
Bacteremic group	5	545	1.50 (1.22–1.84)	9	5	327	1.61 (1.28–2.03)	0	5	218	1.38 (0.99–1.93)	20	[6–9, 12]
Concordant therapy group	5	293	1.60 (1.07–2.40)	34	5	218	1.54 (0.99–2.41)	33	5	75	1.84 (1.15–2.97)	0	[6, 7, 10, 12, 17]
Discordant therapy group	5	164	1.61 (1.12–2.31)	0	5	91	1.72 (1.10–2.70)	0	5	73	1.88 (1.15–3.08)	0	[6, 7, 10, 12, 17]

**PNSSP**



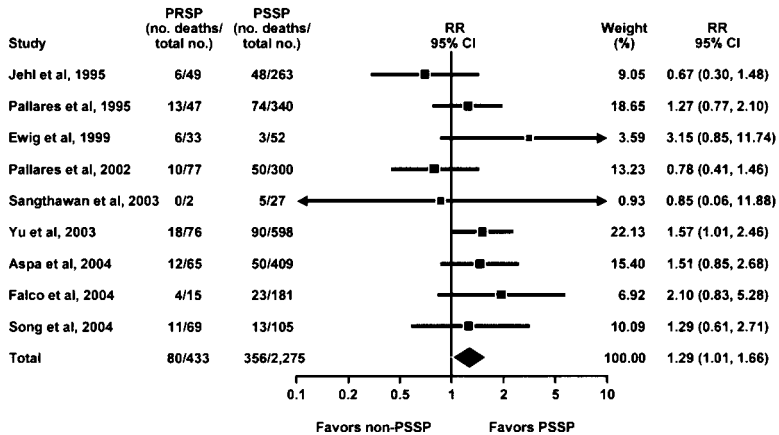
Test for heterogeneity:  $\chi^2 = 12.73$ ,  $df = 9$  ( $P = .18$ ),  $I^2 = 29.3\%$   
 Test for overall effect:  $Z = 2.75$  ( $P = .006$ )

**PISP**



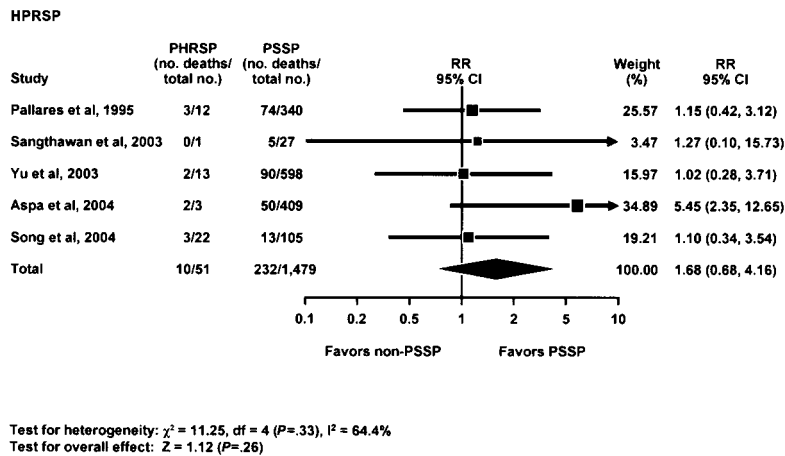
Test for heterogeneity:  $\chi^2 = 8.70$ ,  $df = 9$  ( $P = .47$ ),  $I^2 = 0\%$   
 Test for overall effect:  $Z = 3.29$  ( $P = .001$ )

**PRSP**



Test for heterogeneity:  $\chi^2 = 9.19$ ,  $df = 8$  ( $P = .33$ ),  $I^2 = 13.0\%$   
 Test for overall effect:  $Z = 2.03$  ( $P = .04$ )

**Figure 2a.** Forest plot of unadjusted relative risks (RRs) of mortality (with 95% CIs) for penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSSP), penicillin-intermediate *S. pneumoniae* (PISP), penicillin-resistant *S. pneumoniae* (PRSP) infections, and highly penicillin-resistant *S. pneumoniae* (HPRSP) infections, compared with penicillin-susceptible *S. pneumoniae* (PSSP) infections.



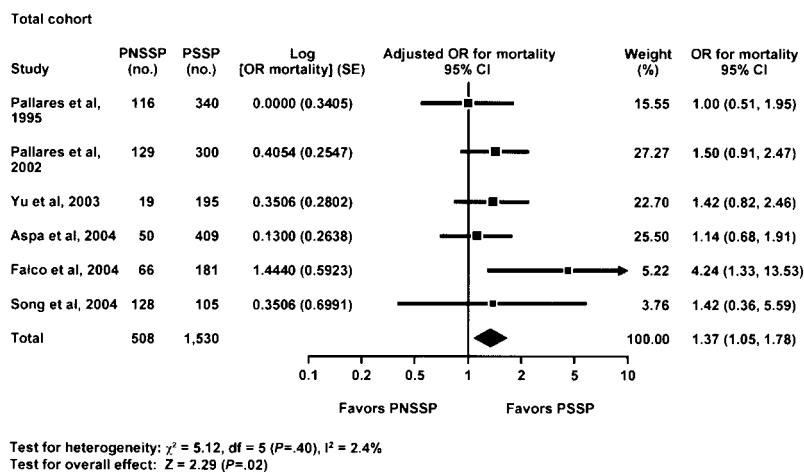
**Figure 2b.** Forest plot of unadjusted relative risks (RRs) of mortality (with 95% CIs) for penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSSP), penicillin-intermediate *S. pneumoniae* (PISP), penicillin-resistant *S. pneumoniae* (PRSP) infections, and highly penicillin-resistant *S. pneumoniae* (HPRSP) infections, compared with penicillin-susceptible *S. pneumoniae* (PSSP) infections.

prove the decisions about treatment. It can also help improve the design and analysis of clinical trials, such as risk stratification, and assist in comparing outcome between treatment groups in nonrandomized studies by allowing adjustment for this prognostic factor.

**Mechanisms.** This observed association could be hypothetically attributed to 4 clinical factors: virulence of the resistant organism, associated host comorbidities, severity of illness, and discordance of antibiotic therapy [23]. Whether mechanisms conferring drug resistance come at a significant cost to the virulence of the organism is debatable. Animal models of infection have not been helpful in clarifying whether virulence and pneumococcal antibiotic resistance are associated, because it has been difficult to establish pneumococcal pneumonia in animals. Moreover, results of studies investigating the relation-

ship between antibiotic resistance and virulence among pneumococcal strains have not been definitive, in part because of the different serotypes that can cause invasive disease in humans [24]. PNSSP selected in the clinical setting can possibly acquire additional compensatory factors that restore their virulence [25]. It has been suggested that unfit mutants were able to survive in the nasopharynx of children and immunocompromised adults long enough to regain virulence, allowing transmission and infection to occur [26]. Regardless, it has been well documented that PNSSP can cause serious infections in humans.

**Limitations.** Our analysis has possible limitations. The only end point examined in this meta-analysis is short-term all-cause mortality. This is the most reliable and clinically relevant outcome. Other important outcomes, including bacterial eradi-



**Figure 3.** Forest plot for adjusted ORs of mortality (with 95% CIs) for penicillin-nonsusceptible *S. pneumoniae* (PNSSP) infection versus penicillin-susceptible *S. pneumoniae* (PSSP) infection.



cation, development of infection-related complications, time to clinical response, and length of hospitalization, are subject to several limitations and have not been routinely described in individual studies [27].

Applicability of the results is another limitation. The patient populations examined in this systematic review involved predominately hospitalized patients. Therefore, results cannot be applied to ambulatory patients with mild CAP who are at low risk of mortality. This limitation reflects the types of studies that are being conducted, in part because it is difficult to ascertain the causative organism in cases of milder infection.

Publication bias is another possible limitation. The small number of studies, however, limits our ability to assess for publication bias (for instance, using a funnel plot) or to draw conclusions regarding such bias.

**Implications.** The results of our study are in parallel with the observations from 2 meta-analyses, which showed that methicillin-resistant *S. aureus* and vancomycin-resistant enterococcal bacteremia are associated with higher mortality rates than are methicillin-susceptible *S. aureus* and vancomycin-susceptible enterococcal bacteremia, respectively [28, 29]. These results highlight the grave clinical consequences of antimicrobial resistance and emphasize the importance of efforts designed to limit their emergence and spread. Judicious use of antimicrobial drugs is necessary if we are to avoid providing a selective advantage for these drug-resistant organisms. Several approaches have been suggested to improve antimicrobial drug prescription practices that involve both patient and physician education [30, 31].

**Conclusion.** In conclusion, our meta-analysis suggests that penicillin resistance is associated with a higher mortality rate than penicillin susceptibility in cases of pneumococcal CAP. Additional studies are needed to understand the mechanisms of this association.

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**Potential conflicts of interest.** All authors: no conflicts.

## APPENDIX A

Medline search history

1. exp pneumonia, bacterial/
2. streptococcus pneumonia/
3. diplococcus.mp
4. pneumococcus.mp
5. pneumonia, pneumococcal/or pneumococcus.mp
6. bacterial pneumonia.mp or pneumonia, bacterial/
7. 1 or 2 or 3 or 4 or 5 or 6

8. exp clinical trials/
9. exp epidemiologic studies
10. exp evaluation studies
11. 8 or 9 or 10
12. 7 and 11
13. Drug resistance, multiple, bacterial/
14. 12 and 13
15. exp mortality/ or short term mortality.mp or exp prognosis
16. 12 and 15
17. 14 or 16
18. exp cross infection/ or hospital acquired.mp
19. 17 and 18
20. 7 and 18
21. 17 or 20
22. 14 or 19
23. limit 22 to human
24. 22 not 23

Embase search history

1. exp pneumonia/
2. bacterial infection/
3. exp bacterium/
4. exp hospital infection/
5. 1 and 4
6. 5 and (3 or 2)
7. exp drug resistance/
8. 6 and 7
9. cross infection
10. 1 and 9 and (2 or 3)
11. 8 or 10
12. exp mortality
13. 30 day mortality.mp
14. 11 and (12 or 13)

Current Contents/Science Edition search history

1. pneumonia.mp
- [mp = abstract, title, author keywords, keywords plus]
2. resistant.mp
  3. resistance.mp
  4. 1 and (2 or 3)
  5. (bacteria or strep or lobar or diplococi or pneumococci or pneumococcus).mp
  6. 4 and 5

## APPENDIX B

PRSP isolates had an MIC of  $\geq 2.0$   $\mu\text{g}/\text{mL}$ , PISP isolates had an MIC of 0.12–1.0  $\mu\text{g}/\text{mL}$ , and HPRSP isolates had an MIC of  $>4.0$   $\mu\text{g}/\text{mL}$ . PNSSP included PRSP and PISP.

“Concordant therapy” was defined as therapy that was given

for the first 2 days after obtainment of a culture specimen and that consisted of at least a single empirical antimicrobial with in vitro activity (i.e., neither intermediate nor resistant in vitro) against the respective *S. pneumoniae* isolate. “Discordant therapy” was defined as therapy given for the first 2 days after obtainment of the culture specimen and that consisted of a single empirical antimicrobial that was inactive in vitro against the respective *S. pneumoniae* isolate. “Penicillin-discordant therapy” was defined as only penicillin or penicillin derivatives given to a patient infected with PNSSP.

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