

Correspondence

Case-Control Studies to Assess Vaccine Effectiveness? Yes, but Not This Way

TO THE EDITOR—Barricarte et al. [1] concluded in their article that the effectiveness of the vaccination with 7-valent pneumococcal conjugate vaccine (PCV7) in Navarre is limited because of a higher risk of invasive pneumococcal disease (IPD) caused by non-PCV7 serogroups among vaccinated children. After reading the article carefully, we have the following comments.

In the Methods section of Barricarte et al. [1], 2 possible biases can be observed, an information bias and a selection bias of controls. The information about both case and control subjects derives only from computerized databases, without the subsequent verification by study personnel with parents of the subjects included in the study. Not even the information relating to the PCV7 vaccination history, based only on the Primary Care Vaccination Register, has been verified. This fact is especially important, because this vaccine is not included in the Navarre vaccination calendar. Although the pediatrician individually makes the recommendation, it is the parent who makes the final decision about the vaccine purchase, and there are several places where the vaccine can be administered to the child. Therefore, it is likely that some information, like number of doses or dates of vaccination, may not be included in the Primary Care Vaccination Register. This information bias may result in raising or lowering the OR, dependent on the direction of the bias [2].

The bias in selection of control subjects is caused by an absence of established matching criteria a priori, other than being born in the same hospital and on the same

date as the case patients. Factors as important as number of siblings, presence of chronic diseases, use of breast-feeding, day care attendance, and/or exposure to cigarette smoke were not taken into account, probably because this information is not included in any database. In case-control studies, selection bias implies that case and control subjects differ importantly in ways other than the disease in question [2]. What is more, the Results section of Barricarte et al. [1] reports that the age of the case patients did not differ from the age of control subjects, but that could not have been otherwise, since it is assumed that, at least, that variable was “adjusted.” The term “matching” is being used in a merely “cosmetic” sense on too many occasions, meaning that the 2 groups are similar only in the distribution of supposedly adjusted variables. Studies of this type must not be considered as matched [3].

Our comments about the Conclusions section of the work by Barricarte et al. [1] are set forth in decreasing order of importance. Those authors state that “vaccinated children had a 6 times greater risk of IPD due to nonvaccine serogroups than did those who were not vaccinated” [1, p. 1439]. However, such calculation was done with consideration of subjects who had received at least 1 vaccine dose (see the table 2 title, “Vaccination status of case patients and control subjects and the association between receipt of at least 1 dose of 7-valent pneumococcal conjugate vaccine (PCV7) and occurrence of invasive pneumococcal disease (IPD), by serotype” [1, p. 1439])—that is, data included vaccinated and incompletely vaccinated subjects, so this conclusion cannot be extrapolated to children who have received vaccination appropriate for their age. It is further stated that these findings are consistent with those shown in the IPD sur-

veillance study from Navarre [4], where it is observed that “the incidence of cases caused by non-PCV7 serotypes increased by 36%” [1, p. 1440]). The authors do not mention that this finding is not significant ($P = .405$), omitting what was published in the mentioned article [4]. In other words, with use of their data, the incidence of IPD due to nonvaccine serotypes in Navarre has not significantly changed after the licensure of the vaccine. Our third comment is related to the interpretation of the OR by the authors [1]. They repeatedly interpret the OR as an attributable risk, which cannot be estimated from case-control studies.

Finally, we believe the conclusions are alarmist and unsuitable, given that Navarre is a small region (6000 births/year, for 1.5% of the total Spanish cohort), with an unknown PCV7 vaccine coverage and without IPD surveillance in place before the license of the vaccine. Only prospective population-based IPD surveillance and follow-up in populations with high vaccine coverage can establish the possible impact of serotype replacement. Although increased rates of nonvaccine disease have been noted, especially among adult patients with HIV infection [5] and among Alaska natives [6], even in these high-risk populations, increased rates of nonvaccine serotype disease have not outweighed the beneficial impact of vaccination—that is, the overall decrease in IPD incidence.

The evidence from prospective surveillance studies for which the incidence can be calculated (from the United States [7], Canada [8], Australia [9], and Spain [10]) has demonstrated PCV7's beneficial impact on the incidence of IPD, in vaccinated children and unvaccinated persons (through a herd effect). Increases in nonvaccine serotype disease (especially serotype 19A) have been noted, but the impact

of these increases has been relatively small in comparison with the magnitude of decrease in IPD.

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Pitfalls in Case-Control Studies of Vaccine Effectiveness

TO THE EDITOR—Barricarte et al. [1] concluded that vaccination with the 7-valent pneumococcal conjugate vaccine (PCV7) is associated with a 6-fold increased risk of invasive pneumococcal disease (IPD) caused by non-PCV7 serogroups. This conclusion contrasts with other studies that found little or no increased risk of non-PCV7-type IPD among healthy vaccinated children [2–6]. We believe that the analysis and inferences by Barricarte et al. [1] have 2 important limitations.

First, methodological biases and uncontrolled confounding may explain some of the study findings. In observational studies of vaccine effectiveness, the non-random allocation of vaccination introduces bias regarding who receives—and who is recorded to have received—vaccine. Vaccination status was collected from a Primary Care registry, but there is no statement about the completeness of vaccine reporting or verification of case and control vaccination status. If control subjects were less likely than case patients to have their vaccinations recorded, this misclassification bias would reduce the estimate of effectiveness against PCV7-type IPD while inflating the odds of vaccination among children with non-PCV7-type IPD. This bias may explain the authors' surprising observation that vaccine effectiveness against PCV7-type IPD was higher among partially vaccinated children than among fully vaccinated ones [1].

Unexpected findings can also occur because of uncontrolled confounding, especially when opportunities for exposure (vaccination) and disease detection (i.e., access to care or access to a diagnostic test) differ among case and control subjects. It

seems that the authors did not control for confounders related to temporal changes in case ascertainment or vaccine uptake. In the study region, reporting of IPD was not mandatory, the number of blood cultures performed for sick children increased 3-fold during 2001–2005 [7], and the proportion of case patients with isolates available for serotyping ranged from 35% to 73% within some hospitals [8]. Were case patients among vaccinated subjects more likely to be reported and serotyped than case patients among unvaccinated subjects? If case reporting and isolate submission improved over time, this should have been controlled for in the analysis (see p. 151 of the work by Rothman and Greenland [9]).

Second, the authors do not adequately guide the interpretation of the reported OR, which is only a *relative* measure of increased risk. For example, a 10-fold increase in an uncommon disease can represent substantially less in absolute case numbers than a 2-fold increase in a common disease. The authors' discussion suggests that the 6-fold increased odds of vaccination among children with non-PCV7-type IPD provides information about the *absolute* rate increase in the population. However, documenting such an increase would require knowing rates of non-PCV7-type IPD derived from active, population-based surveillance among vaccinated and unvaccinated children. The authors' conclusion that “the overall effectiveness of PCV7 for IPD prevention may be greatly reduced” [1, p. 1436] is therefore not supported by their data.

The preponderance of evidence shows that pneumococcal conjugate vaccines have overwhelming benefits for public health in various settings and with a range of vaccine coverage [2, 4–6, 10, 11]. Surveillance for pneumococcal disease caused by non-PCV7 serotypes, as the authors of this report have done, is critical for the monitoring of vaccine impact. As national immunization programs consider the use of pneumococcal conjugate vaccines, we urge readers to consider the full scope of

published observations and to use caution when interpreting findings inconsistent with other evidence.

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Reply to Bernaola et al. and Moore et al.

TO THE EDITOR—The points made by Bernaola et al. [1] are interesting and some that we also considered [2]. The 7-valent pneumococcal conjugate vaccine (PCV7) is dispensed in pharmacies in Navarre, Spain, but it is administered in primary health care centers. All doses administered are recorded in the patient's computerized clinical history, which automatically updates the vaccination registry. The number of doses of PCV7 recorded represents 98.7% of the doses sold. The vaccination status was ascertained in a blind review of the registry. Any bias would be small and nondifferential—that is, toward the null effect.

Our study was individually matched, both in design and analysis. The failure to adjust for chronic diseases, socioeconomic class, breast-feeding, day care attendance, or exposure to tobacco smoke is a potential limitation [2]. There are 4 reasons showing that, in the case of our analysis, the lack of adjustment does not have an important effect on the conclusions. First, none of the case patients had a previous pathology for which PCV7 would be especially indicated. Second, we found both an important protective effect of PCV7 against vaccine and vaccine-related serotypes and an increased risk from nonvac-

cine serogroups. It seems highly unlikely that, with the use of the same design, confounding factors would explain a risk of invasive pneumococcal disease (IPD) from nonvaccine serogroups 6 times higher among vaccinated children without the reduction of the estimated effectiveness against vaccine serotypes. Third, to evaluate the possibility that differences in the selection of controls could have given rise to confounding in one analysis but not in the other, we repeated the 2 analyses by comparing the case patients in each one with the pooled control subjects, and the conclusions were unchanged. Fourth, exposure to tobacco smoke, lack of breast-feeding, and low socioeconomic class have been related with a higher incidence of IPD and may be also associated with a lower probability of being vaccinated. Thus, this bias would overestimate the effectiveness of the vaccine.

We interpret the OR as a relative risk. Children who received at least 1 dose of vaccine had a 6-fold greater risk of IPD due to nonvaccine serogroups than did those who were not vaccinated, and complete vaccination was associated with a 13-fold higher risk of developing IPD caused by non-PCV7 serogroups.

The results are consistent with those of the active population-based surveillance of IPD in children aged <5 years. In the same period, the incidence of IPD from vaccine serotypes decreased by 69%, the incidence of cases from non-PCV7 serotypes showed a nonstatistically significant increase of 36%, and the overall incidence of IPD showed a nonsignificant decrease of only 12% [3].

We agree with Moore et al. [4] that our results [2] are somewhat different from those of other published studies. The effectiveness of PCV7 depends greatly on local factors; therefore, the discrepancy with what has been found in other places is not an argument against the validity of our results.

In 2000, before the licensure of PCV7, an active population-based surveillance of IPD was initiated in Navarre. All pneu-

mococcal isolates from patients with IPD were sent to the National Microbiology Center for serotyping. In the 2000–2002 seasons, when PCV7 was initially not available, and later, when it was available only to a limited extent, PCV7 serotypes caused only 43% of IPD cases in children aged <5 years [3].

The observation that vaccine effectiveness against PCV7-serotype IPD was higher among partially vaccinated children than among fully vaccinated children was not statistically significant and is explained by a single vaccine failure.

We did separate analyses for 2 periods: the 2001–2003 and 2003–2005 epidemiological seasons. The matched OR for occurrence of IPD from all serotypes with at least 1 dose of vaccine was 0.46 (95% CI, 0.13–1.58) in the 2001–2003 seasons and 0.81 (95% CI, 0.39–1.70) in 2003–2005. The matched OR for IPD from non-PCV7 serogroups was 5.58 (95% CI, 0.48–65.0) in 2001–2003 and 6.41 (95% CI, 1.30–31.5) in 2003–2005. These results rule out the confounding effect of temporal changes and suggest a loss of PCV7 effectiveness over time.

Performance of blood cultures for sick children increased in Spain. If more cases of IPD were detected as a result, it is reasonable that these would have been primarily less severe forms. In Navarre, the percentage of cases of occult bacteremia has remained stable, with no significant changes between 2000 and 2005 [3]. In any case, this circumstance has little relevance to the validity of our case-control study [2].

Aristegui et al. [5] analyzed cases from several hospitals in the Basque Country and Navarre. Theirs was a hospital-based study that was independent of the active population-based surveillance in Navarre. The IPD incidence among children aged <5 years found in the active population-based surveillance [3] was systematically higher than that estimated by Aristegui and colleagues. We were able to determine the serotype of all cases, with the exception of

one strain that could not be revived and another nontypable case [2].

Our conclusion is correct as applied to Navarre and may be of value for other places with similar conditions. We included all cases of IPD detected by active surveillance. The preventive effect of PCV7 against vaccine serotypes is partially neutralized by the risk of IPD from non-PCV7 serogroups, in both relative and absolute terms.

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Polymorphisms at Position 245 of HIV Reverse Transcriptase Do Not Accurately Predict the Presence of Human Leukocyte Antigen B*5701

TO THE EDITOR—We read with interest the article by Chui et al. [1] supporting the use of screening for polymorphisms at position 245 of HIV reverse transcriptase. The authors propose that this relatively cheap and simple test could be used as an alternative to screening for the HLA-B*5701 polymorphism to ascertain the risk of developing the abacavir hypersensitivity reaction. Following the initial presentation of this data at the 2006 Inter-science Conference on Antimicrobial Agents and Chemotherapy, we tested the association between the presence of a polymorphism at position 245 and the presence of the HLA-B*5701 allele in 2 London-based clinic cohorts.

We have used prospective HLA-B*5701 screening prior to commencing abacavir therapy since September 2005 at Chelsea and Westminster Hospital (London, UK) and since April 2006 at St. Mary's Hospital (London, UK). At both centers, the incidence of abacavir hypersensitivity reaction has decreased since the introduction of this test [2, 3]. As outlined by Chui et al. [1], the HLA class I plays a key role both in immune-mediated hypersensitivity reaction and in exerting selective pressures that shape HIV sequence evolution; codon 245 lies within an HLA-B*5701–restricted epitope, and non-wild-type (i.e., valine) identity was deemed to be an alternative to HLA screening to estimate abacavir hypersensitivity reaction risk.

We analyzed data from 2 groups of patients who had undergone HLA-B*5701 screening and full reverse transcriptase sequencing as part of baseline drug-resistance testing. Of 117 individuals, 64 tested HLA-B*5701 positive, and 53 tested HLA-B*5701 negative. Overall, 37 (57.8%) of 64 HLA-B*5701–negative isolates and 49 (90.7%) of 54 HLA-B*5701–positive isolates had a polymorphism at position 245. Of the clade B samples, 22 (50%) of 44

Table 1. Sensitivity, specificity, and positive and negative predictive values for a polymorphism at position 245 as a marker of the presence of HLA-B*5701.

Variable	Percentage (95% CI)		
	All isolates (n = 117)	Clade B isolates (n = 83)	Non-clade B isolates (n = 34)
Sensitivity	92.5 (81.8–97.9)	89.7 (75.8–97.1)	100.0 (76.8–100.0)
Specificity	42.2 (29.9–55.2)	50.0 (34.6–65.4)	25.0 (8.7–49.1)
Positive predictive value	57.0 (45.9–67.6)	61.4 (47.6–74.0)	48.3 (29.5–67.5)
Negative predictive value	87.1 (70.2–96.4)	84.6 (65.1–95.6)	100.0 (47.8–100.0)

HLA-B*5701–negative isolates and 35 (89.7%) of 39 HLA-B*5701–positive isolates had a polymorphism at position 245; of the non-clade B viruses, 5 (25%) of 20 HLA-B*5701–negative isolates and 14 (100%) of 14 HLA-B*5701–positive isolates had a polymorphism at position 245. The sensitivity, specificity, and positive and negative predictive values for a polymorphism at position 245 as a marker of the presence of HLA-B*5701 are presented in table 1 for all isolates and for clade B and non-clade B viruses separately. The higher rate of position 245 polymorphisms in HLA-B*5701–positive isolates, compared with HLA-B*5701–negative isolates, was statistically significant by the χ^2 test ($P < .001$).

We believe that, particularly for patients with infection due to clade B virus, the sensitivity and specificity of a polymorphism at position 245 is insufficient as a marker for the presence of HLA-B*5701. The low specificity rates would necessitate an HLA-B*5701 test for up to 50% of individuals to avoid their being denied abacavir treatment unnecessarily. Among subjects with infection due to clade B virus, >10% of those individuals with isolates with the HLA-B*5701 allele have wild-type 245 virus; again, in our opinion, this is unacceptably high. The higher sensitivity rates among patients with non-clade B virus may warrant further investigation, because the number of such subjects in our analyses was small. We do not feel that, at present, screening for polymorphisms at position 245 should replace HLA screening.

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Reply to Waters et al.

TO THE EDITOR—We agree that HIV reverse-transcriptase (RT) codon 245 polymorphisms should not be used to deny abacavir therapy to patients [1]. As has

been emphasized, the positive predictive value of the codon 245 test is low [1, 2]; ideally, persons with codon 245 polymorphisms should be screened for HLA-B*5701 prior to abacavir use. Instead, the high negative predictive value of the codon 245 test indicates that persons with wild-type RT 245V are at a substantially reduced risk for the abacavir hypersensitivity reaction. Given the ready availability of HIV RT sequence data (collected during routine drug-resistance testing) examining virus variation at codon 245 could be useful in situations in which HLA testing is limited or cost-prohibitive.

HLA-B*5701 allele prevalence is typically highest among white individuals (~5%) [3]. However, the prevalence of HLA-B*5701 in the population tested by Waters et al. [1] was ~10-fold higher (54.7%), which is unprecedented in any unselected population. Waters et al. [1] specifically selected HLA-B*5701–positive individuals, with a random control group of HLA-B*5701–negative individuals for comparison (A. Pozniak, personal communication). Because negative predictive value depends on the characteristics of the population tested [4], the negative predictive value calculated by Waters et al. [1] is accurate only for this highly selected population and is irrelevant for the general population of HIV-infected individuals receiving antiviral drugs. The 2 large, prospective cohorts from which the study subset used in Waters et al. [1] was drawn exhibit a typical HLA-B*5701 allele prevalence of ~7% [5, 6]. With this HLA-B*5701 prevalence, the negative predictive value in their population, using their reported 92.5% sensitivity, would actually be 99%, broadly similar to that given in our original report [2], and with overlapping confidence intervals.

The proportion of HLA-B*5701–negative individuals with codon 245 polymorphisms is substantially higher than the ~29% and ~35% amino acid variability at this codon observed among clade B virus–infected, antiretroviral-naïve individuals

in British Columbia [2, 7] and in the Los Alamos HIV sequence database [8], respectively. This leads to the very low positive predictive value reported by Waters et al. [1]. We have no immediate explanation for their observation, other than the possibility that, for some reason, HLA-B*5702-, HLA-B*5703-, and/or HLA-B*58-expressing individuals could be over-represented in this group.

We are surprised that the sensitivity of screening non-clade B isolates at codon 245 was 100%, but, as we have stated, this observation is limited by the small size of the cohort. This provides a strong argument for further collaborative studies.

It would be interesting to know the duration of infection in the 4 individuals who carried HLA-B*5701 but no codon 245 polymorphisms, because the earliest available plasma sample was genotyped for HIV drug resistance [5]. In the absence of any other information, we would recommend considering the codon 245 polymorphism in the latest available genotyped isolate. Furthermore, maintaining clinical suspicion is still required, regardless of the testing method, because the authors report an abacavir hypersensitivity rate of ~2%, despite HLA-B*5701 screening [5].

Although we agree that indirectly screening for HLA-B*5701 may be less ideal than direct HLA testing, the negative predictive value of the codon 245 test is ~99%, and the approach is cost-free, because codon 245 data are already collected for drug-resistance testing. The examination of sequence variation at RT codon 245 could, thus, be used as a simple screening method to identify individuals who could be safely treated with abacavir or who may benefit from direct HLA typing. The high sensitivity in both clade B and non-clade B isolates is encouraging, and we would advocate further investigation using this and other cohorts, particularly the large PREDICT-1 trial, in which individuals are prospectively screened for HLA-B*5701 [9].

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The Long-Term Outcomes of an Antibiotic Control Program with and without Education

TO THE EDITOR—Controlling antibiotic use and antibiotic resistance is of major importance to all professionals involved in infectious diseases. Strategies to control antibiotic use, including antibiotic restrictions and education, have been reported to have a major impact on antibiotic prescribing behaviors [1–3]. However, these interventional programs are laborious and require long-term commitment from an antibiotic-management team. In addition, the long-term effects of these programs have not been adequately explored. This study provides 2 years of follow-up data from a hospital-wide antibiotic-control program deployed with and without education at the same university-based hospital (Thammasart University Hospital, Pratumthani, Thailand) [1].

From 1 July 2004 through 30 June 2005 (period 1), we introduced obligatory antibiotic order forms as a requirement to procure antibiotic drugs from the pharmacy after bedside discussion among the antibiotic-management team and prescribers (surgical prophylaxis prescriptions were excluded, because they were already standardized) [1]. The antibiotic prescription forms were developed for 6 major classes of antibiotics, including third-generation cephalosporins, β -lactam and β -lactamase inhibitors, glycopeptides, aminoglycosides, fluoroquinolones, and carbapenems. An additional educational intervention included monthly didactic presentations for medical students and for residents in the departments of surgery, obstetrics and gynecology, and internal

Table 1. Patient characteristics, antibiotic prescribing practices, and common bacterial resistance during the study periods.

Characteristic	Period 1 (n = 2830)	Period 2 (n = 2915)	Period 3 (n = 2714)
Age, mean years \pm SD	66 \pm 19	67 \pm 18	65 \pm 18
Male sex	1143 (51)	1399 (48)	1330 (49)
Condition leading to prescription			
Any	1358 (48)	1370 (47)	1303 (48)
Respiratory tract infection	623 (22)	700 (24)	597 (22)
Urinary tract infection	396 (14)	327 (13)	407 (15)
Gastrointestinal tract infection	142 (5)	146 (5)	109 (4)
Fever or suspected bacterial infection	85 (3)	146 (5)	136 (5)
Other ^a	113 (4)	175 (6)	163 (6)
Inappropriate antibiotic use	566 (20)	654 (23)	515 (19) ^b
Reason for inappropriate antibiotic use ^c			
Inappropriate surgical prophylaxis ^d	115 (20)	170 (26) ^e	93 (18) ^b
Use of antibiotic without evidence of infection	200 (35)	235 (36)	175 (34)
Redundant spectrum	50 (9)	52 (8)	46 (9)
Bacterial resistance ^f	91 (16)	98 (15)	77 (15)
Narrow spectrum available ^g	41 (7)	39 (6)	26 (5)
Common antibiotic-resistant microorganisms, ^h % of patients			
Methicillin-resistant <i>Staphylococcus aureus</i>	33.5	30	31
ESBL-producing microorganisms ⁱ	21	22	20
MDR <i>Acinetobacter baumannii</i>	5	4	12 ^{e,b}
Imipenem-resistant <i>Pseudomonas aeruginosa</i>	4	3	2

NOTE. Data are no. (%) of patients, unless otherwise indicated. Period 1 was from 1 July 2004 through 30 June 2005, period 2 was from 1 July 2005 through 30 June 2006, and period 3 was from 1 July 2006 through 30 June 2007. ESBL, extended spectrum β -lactamase; MDR, multidrug-resistant.

^a Includes sepsis, meningitis, endocarditis, or prophylaxis for endocarditis.

^b $P < .05$, compared with period 2.

^c Analyzed using the proportion of each specific reason for inappropriateness divided by the total number of prescriptions associated with inappropriate antibiotic use.

^d Determined on the basis of dose, interval, and duration of treatment before and after surgery.

^e $P < .05$, compared with period 1.

^f Administration of antibiotics for treatment of infection due to microorganisms that are resistant to these antibiotics.

^g Administration of broad-spectrum antibiotics when a narrower-spectrum antibiotic would have been effective and was available.

^h Calculated using the total number of strains.

ⁱ Includes *Escherichia coli* and *Klebsiella pneumoniae*.

medicine. During period 2 (1 July 2005–30 June 2006), we performed similar activities to those in period 1 but without the monthly educational programs; period 3 (1 July 2006–30 June 2007) was similar to both periods 1 and 2, but the monthly educational programs were reintroduced. Data collected included demographic characteristics of the patients, indications for antibiotic prescriptions, appropriateness of antibiotic use, rate and classification of inappropriate antibiotic use, and pattern of common antimicrobial resistance. Categorical variables were compared using χ^2 test or Fisher's exact test, as appropriate. A 2-tailed Student's t test

was performed to compare continuous variables. Trend analysis was performed to evaluate the overall pattern of changes on outcomes of interest over time using interrupted time series analysis.

There were no differences in the patients' demographic characteristics and indications for antibiotic use for each period (table 1). There was a 3% increase in the rate of antibiotic prescriptions in period 2, compared with period 1 (400 prescriptions per 1000 admissions vs. 412 prescriptions per 1000 admissions; $P = .45$). Although the overall incidence of inappropriate antibiotic use was not significantly increased in period 2, compared

with period 1 (20% vs. 23%; $P = .10$), the incidence of inappropriate antibiotic prescriptions for surgical prophylaxis was significantly increased (20% vs. 26%; $P = .02$). There was an 8% decrease in the rate of antibiotic prescriptions in period 3, compared with period 2 (412 prescriptions per 1000 admissions vs. 379 prescriptions per 1000 admissions; $P = .24$). Notably, there was also a significant reduction in the incidence of inappropriate antibiotic prescriptions overall (23% vs. 19%; $P = .04$) and inappropriate antibiotic prescriptions for surgical prophylaxis in period 3, compared with period 2 (26% vs. 18%; $P = .001$). During period 3, a monoclonal outbreak of multidrug-resistant *Acinetobacter baumannii* infection occurred. This outbreak was eliminated with interventions by the infection-control unit using active surveillance, environmental cleaning, and isolation procedures.

Our study has several important implications. Although the overall incidence of inappropriate antibiotic use was not significantly increased in period 2, when the educational intervention was omitted, inappropriate antibiotic prescriptions for surgical prophylaxis were more common. Our data support the recommendation of the Infectious Diseases Society of America and the Society of Healthcare Epidemiology of America [4], suggesting that education is an essential component of any program designed to influence long-term prescribing behavior. Such interventions provide a foundation of knowledge that enhances the acceptance of antibiotic stewardship programs [4]. To sustain or even further improve these results, repeated efforts will be needed. The occurrence of a monoclonal outbreak of multidrug-resistant *A. baumannii* infection, despite a significant reduction in inappropriate antibiotic prescriptions during period 3, emphasized the need to integrate infection-control efforts in the education plan and to establish an antibiotic-control program to help achieve long-term sustained

reductions in the prevalence of antimicrobial-resistant microorganisms [5].

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Living with Tuberculosis: The Myths and the Stigma from the Indian Perspective

TO THE EDITOR—We thank Hamilton et al. [1] for focusing on the global health issue of tuberculosis (TB) and highlighting the importance of funding and research for TB control. However, in India, which bears one-third of the world's TB burden

[2], the myths and the stigma revolving around TB and its treatment have to be targeted to improve TB control. In India, patients with TB often experience rejection and social isolation. Because of the lack of knowledge about the disease and fear of being ostracized, persons with TB often hide their symptoms and fail to receive appropriate treatment—a stumbling block in the control of the disease. A common belief is that TB is incurable and that the drugs for treatment of TB can harm the patient. Many fear that TB can cause impotence and sterility. The public is misinformed about the modes of spread of the disease and believe that TB is hereditary or spread in ways similar to those by which AIDS is spread, such as unsafe sex practices. The belief that TB spreads through handshaking and sharing food with an infected person [3] causes patient to keep their condition a secret for fear of being shunned, even by their own family members. Patients with TB are often economic and social outcasts, with poor emotional quality of life, low self-esteem, and clinical depression, which may even lead to suicide. Men affected by the disease, who usually provide the sole financial support for the family, are forced to quit their jobs and, thus, experience extreme debt and poverty. Other patients have a reduced capacity to work and have to take long leaves of absence from work, with the end result being financial burden [4]. Single women often find it difficult to find life partners and are rejected. Married women are abused by their in-laws and deserted by their husbands. A woman abandoned by her husband is often isolated, and for her to have any social relations is considered to be taboo. The stigma has taken a greater toll on women than on men [5]. Many of the patients who start receiving therapy, frequently in secrecy, stop as soon as they start to develop adverse effects, such as orange discoloration of the skin (seen with rifampin, a first-line drug for TB therapy), which reveals to the community that the patient

has TB. Discontinuation of therapy can lead to emergence of multidrug-resistant TB and extensively drug-resistant TB, which are difficult to treat and can be fatal. Owing to the large psychosocial impact of this debilitating disease, the focus should not just be on early detection and symptomatic and microbiological cure, but should also be on providing psychosocial support to patients and their families. Although the importance of research and clinical trials of TB is unquestionable, health education of the masses by community health programs to dispel the myths and stigma surrounding the disease and its treatment cannot be overemphasized in India's progress toward controlling TB—“the captain of all men of death.”

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Postoperative Central Nervous System Infection after Neurosurgical Procedures: The Bride Is Too Beautiful

TO THE EDITOR—In one of the largest neurosurgical studies to have investigated postoperative CNS infection, McClelland and Hall [1] reported an impressively low incidence of infection (<1%), which was >6 times lower than that reported in recent studies of comparable numerical size [2, 3]. However, their articles raises 2 important questions that they did not address in the discussion. First, in their study, all operations were elective. Because an emergency surgical procedure is an acknowledged risk factor for postoperative infection after various surgical procedures [4], including neurosurgical procedures [3], it is not surprising that the rate of postoperative CNS infection after elective surgery is lower than that reported in previous studies, which included emergency as well as elective procedures. Second, the article does not indicate whether the patients who underwent surgery during the study period underwent any systematic follow-up, and it does not indicate whether any attempts were made to ensure that no complications occurred once the patients were discharged. However, a substantial proportion of postoperative infections are diagnosed after discharge from the hospital [5]; this raises the possibility that some postoperative CNS infections occurred but remained unknown to the investigators in this study. Thus, the authors may have underestimated the true incidence of postoperative CNS infection.

Of course, these limitations do not attenuate the high value of this article, which adds important data on the characteristics of postoperative CNS infection after different types of neurosurgical procedures, identifies some risk factors, and describes the most common offending organisms. However, the authors' conclusion that the true incidence of postoperative CNS infection after neurosurgical procedures may be greatly overestimated in the literature is somewhat excessive.

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Reply to Tattevin et al.

TO THE EDITOR—The letter by Tattevin et al. [1] raises 2 insightful points that pertain to our recent study examining the incidence of infection and associated factors among 2111 consecutive patients who had undergone neurosurgical operations [2]. All surgical procedures were elective; however, not all would be considered to be “clean.” The transsphenoidal resection of pituitary lesions is considered to be a clean-contaminated event, although extensive surgical scrub is performed before the start of the event. The enhanced vas-

cularity of the nasal region is probably responsible for the low rate of infection seen for these events. The authors are correct in stating that the follow-up for these patients is not described in the discussion, although such follow-up did take place. All patients were observed 4–6 weeks after surgery for a routine postoperative evaluation. Because many of the patients had brain tumors and were receiving postoperative adjuvant therapy, they were seen at 8-week intervals if they were receiving chemotherapy; if they had stable, benign tumors, they were evaluated at 3-, 6-, or 12-month intervals. We did not detect an increased incidence of delayed postoperative infection among our patients, although the authors' point is well taken, particularly with regard to those patients in whom indwelling devices, such as CSF shunts, were implanted. The authors are justified in stating that our conclusion that the infections were overestimated in the past may be a bit overzealous, such that the true incidence is most likely somewhere in the middle between our results and the previously reported results [3, 4] mentioned by Tattevin et al. [1].

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Acute Pyelonephritis: Management Steps That Remain Unresolved

TO THE EDITOR—We read with great interest the recent article by Czaja et al. [1], an analysis of a large database of patients with acute pyelonephritis from Seattle, Washington. Although the scale of the project was impressive, we found its clinical utility somewhat limited. The data were obtained >5 years ago (2001), lessening their applicability to current therapy and antimicrobial resistance patterns. In addition, as emphasized in the accompanying editorial [2], resistance data were largely confined to the outpatient setting, because only 40% of inpatient cases were culture confirmed. Whether prior antibiotic therapy was responsible for this low rate is unknown, because data about antibiotic use were not available for inpatients.

Two additional management issues, which remain unresolved in the literature but could have been further addressed by the study of Czaja et al. [1], include the role of blood cultures and renal-tract imaging of adults with acute pyelonephritis. As a consequence of tightening health care resources and the pressures for improved efficiency in many countries, the role of these management issues is escalating. Despite the uncertainty reported in the literature [3–5], national guidelines recommend renal-tract imaging for patients with acute pyelonephritis, to exclude the presence of upper-tract obstruction [6]. To further define these issues, we performed a retrospective review of all patients admitted to the Infectious Diseases Unit at the Alfred Hospital, Melbourne, Australia, between January 2002 and March 2004. Patients were identified as described by Czaja et al. [1]. Seventy-four patients were

included, of whom 92% were female, and the median age was 28 years (range, 17–75 years). Complicated pyelonephritis (defined as having ≥ 1 of the following characteristics: known structural or neurological abnormality of the urinary tract, instrumentation of the urinary tract in the previous month, previous urinary tract infection, male sex, pregnancy, and the presence of a comorbid condition) occurred in 45% of patients. The most common causative organism was *Escherichia coli* (69%), followed by *Staphylococcus saprophyticus* (5%) and other gram-negative rods (4%). Urine cultures yielded negative results or contained fecal contaminants in 16 patients (22%), with 11 (69%) of these having antibiotic exposure within 48 h of culture. Antimicrobial resistance patterns were similar to those described by Czaja et al. [1], with 45%, 29%, and 4% of *E. coli* strains being resistant to ampicillin, trimethoprim, and norfloxacin, respectively.

All patients had a blood culture performed; only 6 cultures (8%) yielded positive results (all for *E. coli*). All patients with positive blood culture results had concordant positive urine culture results, except 1 patient who had prior antibiotic exposure within 48 h of urine culture. The result caused no change in antibiotic therapy. Eighty-seven percent of patients underwent some type of imaging; 58% underwent renal ultrasound, 39% underwent abdominal CT, and 15% underwent abdominal radiography. A total of 26 patients (40%) had an abnormal imaging finding; however, 17 (26%) of these showed changes consistent with pyelonephritis only. Eight (12%) showed anatomical abnormalities of the urinary tract, which may have predisposed the patients to infection, and 1 (1.5%) showed an obstruction at the pelvic-ureteric junction that required acute intervention. Of the 6 male patients, 5 had normal imaging findings, and 1 had changes consistent with pyelonephritis. Renal-tract imaging was less likely to change management or to show a predisposing condition in patients

with uncomplicated pyelonephritis (OR, 0.21; 95% CI, 0.03–1.3; $P = .06$).

These data suggest that blood cultures may have limited clinical utility in the management of acute pyelonephritis and that renal-tract imaging, at least in our institution and especially for patients with uncomplicated pyelonephritis, may be overutilized. Given the size of the database analyzed by Czaja et al. [1], it would be instructive if these questions could be addressed, to optimize investigations in patients with this common infectious disease.

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Reply to Foxman et al. and Peleg et al.

TO THE EDITOR—We appreciate the comments made by Foxman et al. [1] in a previous issue and Peleg et al. [2] in this issue of *Clinical Infectious Diseases* regarding our study [3]. Foxman et al. [1] commented on the low rate of urine-culture confirmation of diagnoses of acute pyelonephritis, as identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes, and suggest some potential biases that may result from excluding outpatient case patients lacking culture confirmation. Peleg et al. [2] commented on the clinical utility of antimicrobial treatment and resistance data collected several years ago.

The primary aim in our analysis was to study trends in the epidemiology of acute pyelonephritis over a 5-year period with use of a large automated database from a well-defined US population. To this end, we chose a case definition of acute pyelonephritis, requiring urine-culture confirmation of outpatients but not of inpatients, that we found to be sensitive and specific on the basis of our earlier experience [4]. Because we applied this case definition consistently throughout, we believe that the secular trends we reported to be informative and representative. In our work, [3] we discussed the limitations of ICD-9-CM diagnoses as measures of disease occurrence, and we noted that these limitations must be considered in the interpretation of our data—as they should be in any such study.

We did not conduct an extensive medical-record review and thus did not further characterize patients who received an ICD-9-CM diagnosis of acute pyelonephritis but who had no positive urine culture results. We did conduct an incidence analysis that included all outpatients with ICD-9-CM pyelonephritis diagnoses and found the incidences to be higher, but we

found the trends with time, age, and sex to be similar (authors' unpublished data). This suggests that outpatients with non-culture-confirmed disease were not substantially different from those with culture-confirmed disease, at least with respect to the available variables.

We highlighted an increase in the rate of fluoroquinolone resistance and a decrease in the rate of trimethoprim-sulfamethoxazole resistance among *Escherichia coli* isolates between 1997 and 2001 that coincided with inverse trends in the use of those antibiotics for the outpatient treatment of acute pyelonephritis. Our methods were similar to those of other published surveys of secular trends that utilize existing data. These observations have important implications for how antibiotic treatment of urinary tract infection may directly impact antimicrobial resistance, and they have not been documented with regard to treatment of acute pyelonephritis. Analysis of data from subsequent years would address whether these trends continue beyond 2001. In the absence of a large, prospective study, we believe these population-based data to be the most representative data available and to be the only such data for a US population.

Foxman et al. [1] and Peleg et al. [2] mentioned several additional issues regarding the epidemiology and management of acute pyelonephritis that merit consideration, including recurrent, health care-associated, and pregnancy-associated diseases; cost-effective treatment; and the use of blood cultures and renal imaging during evaluation. Although these were not the focus of our analyses, we agree that further evaluation of these and other aspects of pyelonephritis would be useful, and we thank Peleg et al. [2] for sharing their findings regarding the use of blood cultures and renal imaging.

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