MAJOR ARTICLE

Effect of Changes in Antibiotic Prescribing on Patient Outcomes in a Community Setting: A Natural Experiment in Australia

Justin Beilby, John Marley, Don Walker, Nicole Chamberlain, and Michelle Burke for the FIESTA Study Group[a]

Department of General Practice, University of Adelaide, North Tce, Adelaide, Australia

This study examined whether a significant change in antibiotic use caused by an Australian government directive targeted at amoxicillin with clavulanic acid (AC) was associated with changes in prescription share, health care costs, and patient outcomes. We used an integrated database of computerized general practice medical records, which included data regarding 34,242 patients and 318,234 recorded patient visits. There were 15,303 antibiotic prescriptions provided to 9921 patients during a 4-year period, with AC prescribed for 1453 (14.6%) of these patients. A total of 5125 patient outcomes were identified. There was a shift away from best-practice antibiotic prescribing, and a significant association was identified between the rate and cost of process-of-care and patient outcomes and the decrease in AC-prescription share. This policy initiative created unintended changes in prescribing behavior, increased costs to the government, and a trend toward poorer patient outcomes. Detailed analyses are required before instigating initiatives aimed at changing clinicians' prescribing behavior.

There have been few published studies to have examined the interaction between antibiotic prescribing and patient outcomes, particularly from a community perspective. A small number of studies have attempted to define appropriate therapy in terms of patient outcomes, but those studies have been limited to hospitals [1–3]. In contrast, the majority of antibiotics are prescribed in outpatient and community practices. This study examines complete longitudinal computerized clinical records from 4 Australian general practices involving 22 general practitioners (GPs) from July 1994 through June 1998.

During this period, a significant change in the prescribing of antibiotics in Australia occurred. This change was prompted by a letter sent in February–March 1996 by the Commonwealth Government's Health Insurance Commission (HIC), which subsidizes medication use, to the top 2000 prescribers of amoxicillin with clavulanic acid (AC). The letter contained a number of statements, including the following comments: AC should be used only to manage infections in which resistance to amoxicillin is suspected or proven; that hepatic problems could be complications from the use of AC, particularly in elderly recipients; and that there would be a follow-up audit, aimed at GPs, to assess compliance with the recommendation (HIC; Canberra, Australia; unpublished letter). No recommendation was provided regarding which antibiotic to use in place of AC. The message contained within this letter was widely disseminated in the medical press and pharmaceutic marketing literature, so that the change in prescribing was not limited to those who directly received a letter. As a result, there was a significant decrease in the national number of prescrip-

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[a] Members of the study group are listed after the text.

Reprints or correspondence: Dr. Justin Beilby, Dept. of General Practice, University of Adelaide, North Tce, Adelaide 5005, Australia (justin.beilby@adelaide.edu.au).

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tions for AC, with an increase in the prescription of other antibiotics (as recorded by the Commonwealth Government Drug Utilisation Subcommittee). There was a particular increase in the prescribing of macrolides and, to a lesser extent, the cephalosporins (P. McManus, personal communication).

Streptococcus pneumoniae is the principal causative agent for sinusitis, otitis media (OM), and lower respiratory infection, and the most recent Australian study to have analyzed isolates obtained from multiple centers documented the following rates of resistance in 1997 [4]: for AC and amoxicillin, 0.1% of isolates were resistant and 0.2% had intermediate resistance; for cefaclor, the rates were 4.0% and 17.4%, respectively; for erythromycin, 15.6% and 0.7%, respectively; for tetracyclines, 15.7% and 0.2%, respectively; for cotrimoxazole, 33.4% and 12.4%, respectively.

On the basis of these resistance patterns, it seemed logical to assess whether the therapeutic shift to cefaclor and the macrolides produced poorer patient outcomes. The hypothesis was that the targeted change in AC-prescribing behavior was associated with changes in the number and rates of patient outcomes and process-of-care outcomes. A time-series design [5, 6] was used to identify the temporal relationship between the effect of the Commonwealth Government letter on prescription share and patient outcomes. Inherent in the use of time series alone is the possibility of ecologic bias [7]—that is, implying causal relationships from associations between grouped data. To clarify whether ecologic bias was present, individual patient-level data were examined, adjusting for the antibiotic prescribed, patient age, and case mix.

METHODS

Creation and analysis of the overall database. The study database consisted of computerized records from 4 general practices based in 3 states in Australia. Of the 22 GPs who contributed information to the study database, 10 (45%) were aged <44 years, 13 (59%) were men, and 12 (55%) were in full-time practice. Four (18%) of the 22 GPs remembered having received the actual letter from the HIC.

The database contained information about 34,242 patients who had generated 318,234 recorded patient visits. The visit notes included encounter information, pathologic and diagnostic-imaging reports, and clinical summary and allergy data. The participating GPs used free text to enter all consultation information, and the pathologic and diagnostic information was scanned into the notes. The fields in the notes did not change throughout the complete study period; the GPs had been using this method to collect this information for >10 years. The following 4 specific study conditions, which are commonly treated in general practice [8, 9], were chosen to answer the study hypothesis: OM; acute sinusitis; and lower respiratory tract infection, including bronchitis and pneumonia (LRTI) and acute exacerbation of chronic bronchitis (AECB). Acute OM and OM with effusion were considered together.

We used complex searches to identify all patient visits that involved the conditions of interest. To do this, the database was enhanced by the development of a full data dictionary of key terms, which enabled comprehensive searching. These key terms included all possible phrases that could identify mentions of drugs, problems, and conditions. These visits were then separated from the database and individually checked. To achieve this, trained data-entry staff read each note of interest and mapped its relevant concepts to a controlled vocabulary of terms that included diagnoses, tests, radiology, drugs, and appropriate patient characteristics. All patient-identifying material had been removed before this checking process began. The intra- and interreliability of the data-entry staff, as measured by κ [10], was >0.85 for both.

Completeness of the database. External validation for completeness of the database included comparison of the consultation numbers for the study database with those held by the HIC for the period of 1994–1997. In Australia, the HIC has all recorded information regarding community consultation for GPs.

Age and sex profile in the patient database. To assess the representativeness of the patients to the Australian population, the age and sex profiles of the database patient sample were compared with the national Australian general practice attendees [11] for the middle year of the study, 1997.

Patient numbers and case-mix profile. Patient numbers were added together for each antibiotic both before and after the letter was distributed. The total patient numbers and case mix for each antibiotic were compared before and after the letter. The case-mix profile was compared by means of a 12-category classification system developed by Weiner et al. [12]. Differences in the time periods before and after the letter are accounted for by using rates of episode of care (EOC; see the "EOC" subsection below) [13].

Antibiotic use according to prescription share. Patterns of antibiotic use for the study GPs were examined by means of prescription shares. "Prescription share" refers to the percentage of the antibiotic ordered when compared with other antibiotics in connection with an episode of sinusitis, OM, LRTI, or AECB. The study prescription shares for AC and other antibiotics were compared with the national antibiotic prescription shares to ensure that the database changes corresponded with national trends (P. McManus, personal communication). Prescription share was the preferred measure of antibiotic prescribing because it accounted for seasonal variation. Changes in prescription shares were reviewed against changes in total use of antibiotics during the same period to ensure prescription share changes were not driven by an increase or decrease in antibiotic use.

Outcomes were separated into "patient outcomes" and "pro-

cess-of-care outcomes" within an episode of sinusitis, OM, LRTI, or AECB. The patient outcomes included uninitiated return visits to the GP within 2 weeks of receiving the antibiotic, hospitalization, and referral to a specialist. The process-of-care measures included the following: CT scan of sinus and chest, chest radiography, any pathology tests (e.g., complete blood picture, sputum, erythrocyte sedimentation rate), and spirometry, bronchoscopy, and sinoscopy.

Initially, all outcomes were collectively analyzed by simple sum of events divided by the total number of GP encounters. Costs were then attached to each outcome; then, outcomes were analyzed by weighting each type of event by median cost; finally, they were summed and divided by the total number of GP encounters. Median costs were taken from the national HIC schedule [14] for pathologic and diagnostic-imaging services and the tertiary-hospital case-mix table (P. Widdas, personal communication). The values (in Australian dollars) used in the weighted analysis for patient outcomes were $56 for referral to a specialist, $21.30 for return visits, and $2095 for hospitalizations; for process measures, costs (in Australian dollars) were $16 for a pathology test, $133 for radiology, and $115 for all other tests.

EOC. The data were defined by EOC, which describes the period surrounding all care related to a specific clinical problem presented [13]. A new EOC for a condition was begun if there had been a month between visits for the same problem. Therefore, an outcome was considered to be related to a specific antibiotic if it occurred within the EOC in which the antibiotic was prescribed.

Statistical analysis. For the intervention time point, segmented regression lines were fitted to the time-series data to determine where the significant changes occurred in both study and national prescription share (P. Widdas, personal communication) [15]. All main antibiotic groups were examined. Both 1- and 2-breakpoint models were tried. For models with 2 breakpoints, it was assumed that there existed 3 distinct and separate linear relationships over time separated by 2 time points. The residual sum of squares for each combination of breakpoints during the length of the time series was examined, and the time points at which this quantity was minimized were chosen [15, 16]. To test whether a change had occurred in the series and whether the 3-segment regression may have been a better representation of the data than was the simple linear regression and 2-segment regression, a likelihood ratio test was performed. Splines [17] were used to define, in greater detail, the change in AC and all antibiotics prescription share across the study database. All analyses were completed by use of SAS/ETS, version 6.0 (SAS Institute) [18].

For time-series analyses, we used intervention analysis to determine the effect of the letter on the level of the AC-prescription share and outcome series [19, 20]. Autoregressive integrated moving average (ARIMA) models were used to model the noise in the series. In all cases, the form of the intervention was a step shift. A step intervention was used to determine whether the letter changed the level of the series in all months after the event. The effect of the intervention was investigated for all antibiotic prescriptions, antibiotic prescription share, sum of all patient and process outcomes, and sum of patient and process-of-care outcomes weighted by median costs. Rates of outcomes were calculated as (1) sum of all patient and process outcomes divided by total number of notes for indicator conditions (i.e., sinusitis, OM, LRTI, AECB), and (2) sum of patient and process-of-care outcomes weighted by median costs divided by total number of notes for indicator conditions. The relationships between the outcome series (rate and sum) and antibiotic prescription shares were determined by use of a distributed lag transfer function model. The effect of antibiotic prescribing was modeled such that the impact on the outcome time series was distributed over past lags (months) of antibiotic prescribing. This type of model describes the level of outcomes as a linear function of the current level of AC-prescription share and of the previous 3 months. This is sensible for the conditions of interest; in particular, the outcomes of interest are indicators of treatment failure, which will not present at the time of the prescription, but, rather, at some time after the treatment has begun.

For detailed analyses of EOC, EOCs were examined to determine the antibiotic prescribed in the first instance and the relationship with outcomes. Patient outcomes were measured on the first visit and on any subsequent visit within 2 weeks of the prescription for a new and active condition. The frequency of patient and process-of-care outcomes that occurred on the first visit were compared between the periods before and after the letter for all antibiotics and for each antibiotic separately. Comparisons were also made between the periods before and after the letter in the proportion of EOCs with an outcome after the first visit.

Multivariate regression models. These models were used to ascertain the affect of the intervention on outcomes for each antibiotic. Adjustments were made for the possible confounding effects of condition, patient age, and case mix on patient outcomes. Analyses were completed by use of SAS/ETS, version 6.0 (SAS Institute), and SCA (Scientific Computing Associates) [21]. Ethical approval was obtained from the Adelaide University Institutional Ethics committee.

RESULTS

Completeness of the database. Abstracted data from the database were consistent with national consultation claims data from the HIC. In the study, there were ~332,288 consultations recorded within the database and 317,819 identified by the HIC. This gives an agreement between the study database and the HIC of 104%, implying that the study database completely

Table 1. Comparison of profile of national general practice attendees (from [11]) with study database attendees.

Age group, years	Percentage of patients			
	National profile		Study database profile	
	Male	Female	Male	Female
0–4	3.9	3.6	4.7	4.3
5–14	6.9	6.5	7.0	6.7
15–24	6.6	7.3	6.3	8.4
25–44	13.9	16.3	14.6	17.9
45–64	10.3	10.9	9.8	9.9
65–74	3.7	4.1	3.1	3.4
⩾75	2.3	3.7	1.7	2.2
Total	47.5	52.5	47.2	52.8

captured all information from the practices during the study period.

Age and sex profiles of the patient database. The age and sex profiles of the overall patient sample that visited the study general practices are presented in table 1; they were found to be similar to those reported by the national Australian general practice attendees [11].

Description of patients, chosen conditions, and case mix. The number of EOCs for the chosen conditions were as follows: (1) For all specified problems, there were 11,378 EOCs. A total of 1329 patients were treated with AC alone, and 9811 received other antibiotics. Two hundred thirty-eight patients received a mixture of AC and other antibiotics within the same EOC. (2) For OM, there were 3826 EOCs. A total of 419 patients were treated with AC alone, and 3313 received other antibiotics. Ninety-four received a mixture of AC and other antibiotics. (3) For sinusitis, there were 2841 EOCs. A total of 428 patients were treated with AC alone, and 2354 received other antibiotics. Fifty-nine received a mixture of AC and other antibiotics. (4) For LRTI, there were 4962 EOCs. A total of 515 patients were treated with AC alone, and 4324 received other antibiotics. One hundred twenty-three received a mixture of AC and other antibiotics. (5) For AECB, there were 189 EOCs. A total of 34 patients were treated with AC alone, and 150 received other antibiotics. Five received a mixture of AC and other antibiotics.

No antibiotics were given for 157 cases of OM, 236 cases of sinusitis, 416 cases of LRTI, and 108 cases of AECB. It is important to note that the EOC for both AC and other antibiotic groups do not add to the sum of the overall specified problems because there may have been EOCs for which ⩾1 condition existed.

The numbers of patients who were given AC at least once were 738 (before the letter) and 810 (after the letter). The most common choices of antibiotics in Australia were selected for comparison. Additional patient numbers for the other antibiotics are summarized in table 2—for example, the numbers of patients provided amoxicillin at least once were 1284 (before the letter) and 1521 (after the letter); for cefaclor, the numbers were 1141 (before the letter) and 1866 (after the letter). Overall,

Table 2. Overall patient numbers, antibiotics prescribed, and adverse patient outcomes.

Parameter	Rate per month	
	Before the letter[a]	After the letter[b]
Patients who received an antibiotic prescription,[c] no. (%)		
AC	738 (39)	810 (28)
Amoxicillin	1284 (68)	1521 (52)
Macrolides[d]	765 (40)	1511 (52)
Cefaclor	1141 (60)	1866 (64)
Cephalexin	376 (20)	600 (21)
Tetracyclines	647 (34)	1050 (36)
Trimethoprim-sulfamethoxazole	107 (6)	114 (4)
Antibiotic prescriptions,[e] no. (%)		
AC	860 (45)	986 (34)
Amoxicillin	1543 (81)	1782 (61)
Macrolides[d]	882 (46)	1857 (55)
Cefaclor	1480 (78)	2539 (88)
Cephalexin	431 (23)	687 (24)
Tetracyclines	758 (40)	1233 (43)
Trimethoprim-sulfamethoxazole	122 (6)	143 (5)
Total	6076 (320)	9227 (318)
Outcomes, no. (%)		
All adverse outcomes	584 (30.7)	1289 (44.4)
Hospitalizations	27 (1.4)	99 (3.4)
Referrals	123 (6.5)	228 (7.9)
Radiology	250 (13.2)	544 (18.8)
Pathology	174 (9.2)	387 (13.3)
Other tests	10 (0.5)	31 (1.1)
Return visits	1270 (66.8)	1982 (68.3)
Rate of adverse outcomes[f]		
AC	7.9	11.3
Amoxicillin	3.8	3.8
Macrolides[d]	9.3	11.5
Cefaclor	6.9	7.1
Cephalexin	9.0	9.6
Tetracyclines	2.6	4.2
All other antibiotics, excluding AC	7.1	9.5

NOTE. AC, amoxicillin with clavulanic acid.

[a] Nineteen-month period.

[b] Twenty-nine–month period.

[c] The number of patients who had ⩾1 prescription of each antibiotic. Some patients are recorded twice because they received >1 type of antibiotic. Overall, 9921 people had 1 of the conditions during the study period, with AC prescribed for 1453 people in this group.

[d] Roxithromycin and erythromycin.

[e] The number of prescriptions written for each antibiotic.

[f] Rate of adverse patient outcomes per 100 episodes of care with ⩾1 type of antibiotic prescribed.

9921 persons had 1 of the conditions during the study period, and AC was prescribed for 1453 persons in this group.

Before the letter, the case-mix profiles of the patients who had ⩾1 of the specified conditions and who received AC alone did not significantly differ from those of patients who received other antibiotics ($P = .237$). In contrast, after the letter, the case-mix profile of the patients who received AC was significantly different from that of the patients who received other antibiotics. After the letter, there was a significant case-mix difference: 218 (32.8%) of the 665 patients who received AC were identified as having acute major conditions, and 1499 (28.3%) of the 5295 patients who received other antibiotics were identified with this case mix ($P = .0164$; table 3).

Antibiotic use, including prescription shares. The total amount of antibiotic prescribing remained relatively stable during the study period, both before the letter (319 prescriptions per month; 19 months from June 1994–January 1996, with 6076 total prescriptions; table 2) and after the letter (318 prescriptions per month; 29 months, with 9227 total prescriptions).

The study prescription shares for all antibiotics were summarized by use of splines (figure 1). The decrease in AC- and amoxicillin-prescription shares appears to be mirrored by an increase in cephalosporin- and macrolide-prescription shares. Segmented regression analyses for all antibiotics revealed 2 significant intervention time points for the AC-prescription share series. These were identified in May 1996 and August 1997. The AC-prescription share was stable in the years preceding the intervention and was estimated to be 13.8%. During the year of the intervention, the AC-prescription share decreased and then stabilized at 8.6%. The amoxicillin-prescription share showed a steady decrease from 1994 until early 1997, with no excess decrease in the amoxicillin-prescription share at the time of the intervention. The cephalosporin- and macrolide-prescription shares showed steady increase during the study period. Closer examination of specific prescribing rates (table 2) reveals further evidence that macrolides and cefaclor were substituted for amoxicillin and AC—that is, the rate of prescription ordering per month for the macrolides before the letter was 46, and after the letter, it was 66 prescriptions per month; for cefaclor, the figures were 78 and 91, respectively; for amoxicillin, 81 and 64, respectively; and for AC, 45 and 35, respectively. Time-series analysis that used an intervention model with a prespecified breakpoint at January 1996 indicated that the AC market share was stable between July 1994 and December 1995, but the share dropped ~0.2% per month between January 1996 and June 1998 ($P = .029$).

When all specific conditions are separately examined, AC-prescription share changed significantly for sinusitis alone and not for the other conditions.

Patient and process outcomes. The total number of out-

Table 3. Patient numbers for the case-mix categories before and after a letter regarding prescription of amoxicillin with clavulanic acid (AC) was sent to general practitioners.

	No. (%) of patients			
	Before the letter		After the letter	
Case mix	Received AC	Received other antibiotics	Received AC	Received other antibiotics
Acute major conditions	169 (26.9)	1033 (29)	218 (32.8)	1499 (28.3)[a]
Acute minor conditions	30 (4.8)	129 (3.6)	36 (5.4)	232 (4.4)
Conditions that are likely to recur	48 (7.6)	280 (7.8)	61 (9.2)	514 (9.7)
Asthma	107 (17.0)	587 (16.5)	128 (19.2)	871 (16.4)
Chronic unstable medical conditions	23 (3.7)	193 (5.4)	28 (4.2)	276 (5.2)
Chronic stable medical conditions	69 (11)	415 (11.6)	97 (14.6)	744 (14.1)
Chronic stable specialty conditions	22 (3.5)	149 (4.2)	28 (4.2)	218 (4.1)
Eye or dental conditions	—	1 (0.03)	—	2 (0.0)
Chronic unstable specialty conditions	—	3 (0.1)	—	5 (0.1)
Psychological or psychophysiological conditions	25 (4)	46 (1.3)	43 (6.5)	304 (5.7)
Preventive or administrative	—	—	—	—
Pregnancy	6 (1)	36 (1)	6 (1)	53 (1)
All patients	629	3568	665	5295

NOTE. "All patients" indicates patients with ⩾1 episode of care (EOC) that involved the specified antibiotic. Individual patients may be counted more than once if they were identified as having >1 case mix. The percentage values are calculated as all patients of given a specific antibiotic (e.g., AC with an acute major condition within an EOC divided by all patients given the specified antibiotic—in this case, AC). It is important to note that the percentages do not add to 100 because there were patients who received a specified antibiotic but who were without a case-mix category. The patient numbers are taken from the EOCs in which there was either an AC prescription or a prescription of ⩾1 other antibiotic alone.

[a] $P < .05$.

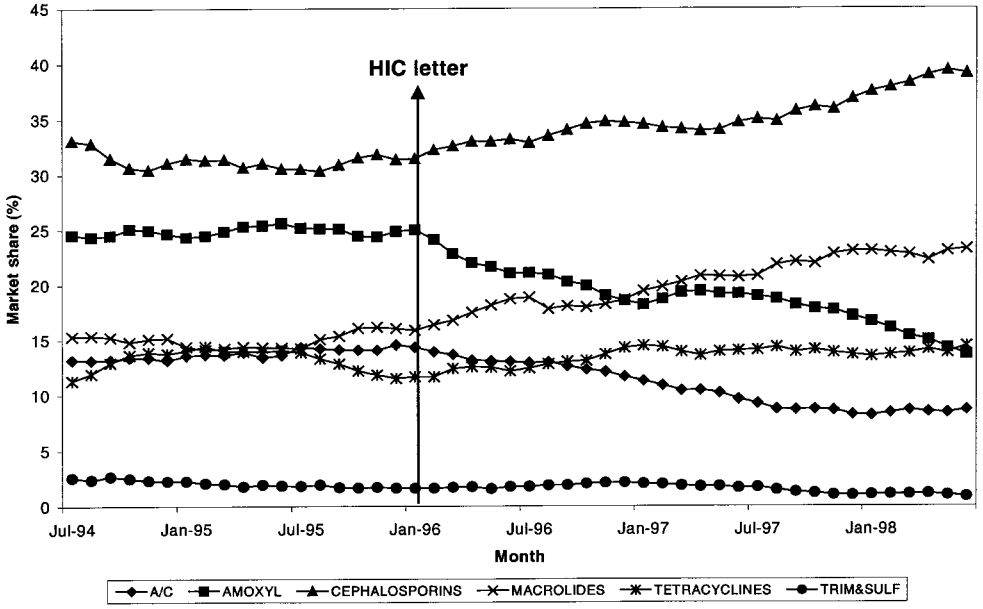

Figure 1. The prescription share for amoxicillin with clavulanic acid (A/C) compared with the prescription shares for all antibiotics for the 4 general practices involved (June 1994–July 1998). "Prescription share" refers to the prescribing percentage of an antibiotic as part of all antibiotics prescribing among the study of general practitioners. The splines technique was used to smooth the prescription share lines. The cephalosporins include cefaclor and cephalexin. AMOXYL, amoxicillin; HIC, Health Insurance Commission; Jan, January; Jul, July; TRIM&SULF, trimethoprim-sulfamethoxazole.

comes were 5125, comprising 126 hospitalizations, 351 referrals, 3252 return visits, 794 radiologic investigations, 561 pathology tests, and 41 other investigations (which included spirometry, bronchoscopy, and sinoscopy). There were 1854 adverse outcomes in the period before the letter and 3271 in the period after the letter (table 2).

When the rate of patient and process-of-care outcomes per 100 EOCs was calculated before and after the letter, it was found that the rate for amoxicillin remained the same, at 3.8. For macrolides, the rate changed from 9.3 to 11.5; for cefaclor, 6.9 to 7.1; for cephalexin, 9.0 to 9.6; and for AC, 7.9 to 11.3. Overall, for all antibiotics (excluding AC), the mean rates were 7.1 before the letter and 9.5 after the letter (table 2).

Before the letter, there was a single EOC in which AC was prescribed and a hospitalization was reported. After the letter, there were 14 EOCs in which AC was prescribed and a hospitalization was reported. Of all EOCs that involved AC before the letter, 0.14 per 100 EOCs had a hospitalization, whereas of all EOCs that involved AC after the letter—1.84 per 100 EOCs—had a hospitalization ($P = .0011$). This was the only significant increase after the letter for the EOC that involved AC. This suggests that the GPs may have been prescribing AC to patients who had more severe illness. Conversely, more patients after the letter may have been exposed to AC-resistant bacteria or to such organisms as *Mycoplasma* or *Legionella* species, for which AC is not the appropriate antibiotic. The information regarding the causative organisms was not available in the database. For the EOCs in which the macrolides cefaclor, cephalexin, and amoxicillin were given alone, there were no significant changes in the rate of each outcome group. However, when we analyzed all EOCs for which >1 of these antibiotics were given as a total group, there were significant increases in the rate of adverse outcomes per 100 other antibiotic-related EOCs for the following: hospitalizations (0.44 before the letter and 0.86 after the letter; $P = .0054$), radiologic investigations (3.27 before the letter and 4.87 after the letter; $P = .00001$), and pathologic investigations (2.73 before the letter and 3.62 after the letter; $P = .005489$).

Time-series analysis of the relationship of the antibiotic-prescription share and outcomes. Overall, there was a significant association between the increase in the rate per month for all outcomes and the decrease in AC-prescription share ($P = .011$), with a 3-month lag. There was also a significant association between AC-prescription share and overall outcome rate weighted by relative cost ($P = .0024$; table 4). The rate of outcomes per month from July 1994 to June 1998 is displayed graphically in figures 2 and 3, in which it is further separated into process-of-care outcomes and patient outcomes, with and without return visits. The rate of patient outcomes, including return visits, was not significantly associated with AC-prescription share (table 4). However, when return visits were excluded, there was a significant association ($P = .0365$) and marginal association at the 3-month lag ($P = .0689$). The rate of process-of-care outcomes was significantly associated with AC-prescription share also at the 3-month lag ($P = .006$). When the rates of patient outcomes with and without return visits series were weighted by cost, there was a significant association with AC-

Table 4. Intervention shift parameters for amoxicillin with clavulanic acid–prescription share and overall patient and process-of-care outcome time series, including costs.

Variable	Transfer function model	Noise model	*P*	*P* for 3-month lag
Rate of overall outcomes	Distributed lag	MA (2)	—	.011
Rate of overall outcome cost	Simple linear regression	White noise	.0024	NS
Patient outcome rate				
Including return visits	Simple linear regression	White noise	NS	—
Excluding return visits	Simple linear regression	White noise	.0365	.0689
Process-of-care outcome rate	Distributed lag	AR (1)	—	.006
Patient outcome rate cost				
Including return visits	Simple linear regression	White noise	.0081	NS
Excluding return visits	Simple linear regression	White noise	.0114	NS
Process-of-care rate cost	Simple linear regression	White noise	—	.0242

NOTE. AR (1), autoregressive model order 1; MA (2), moving average model order 2.

prescription share ($P = .0114$ and $P = .0081$, respectively). There was a significant association between process-of-care outcomes weighted by relative cost and AC-prescription share ($P = .0242$) at the 3-month lag.

Detailed analysis of the EOCs. All EOCs that involved new and active conditions were sought, and the antibiotic prescribed at the first visit was determined. Occurrences of patient or process-of-care outcomes within 2 weeks after the prescription (but not on the day that the prescription was written) were identified. Initially, the univariate model examined outcomes after the first visit. There was no significant increase in the proportion of EOCs with a patient outcome before and after the letter ($P = .1776$). There was a significant increase in the proportion of EOCs with a process-of-care outcome after the letter ($P < .0001$). When broken down according to antibiotic, there was a significant increase in the proportion of EOCs in which tetracyclines were prescribed, and process-of-care outcomes were analyzed after the letter, as compared with before the letter ($P = .0304$)

EOCs in which patient outcomes occurred on the first visit (during which an antibiotic was prescribed) were then examined. There was a significant increase in the proportion of EOCs that involved a patient outcome before and after the letter (2.3% before the letter and 6.1% after the letter; $P < .0001$). There was also a significant increase in the proportion of EOCs with a process-of-care outcome after the letter (4.3% before the letter and 10.2% after the letter; $P < .0001$). These trends are consistent for all antibiotics.

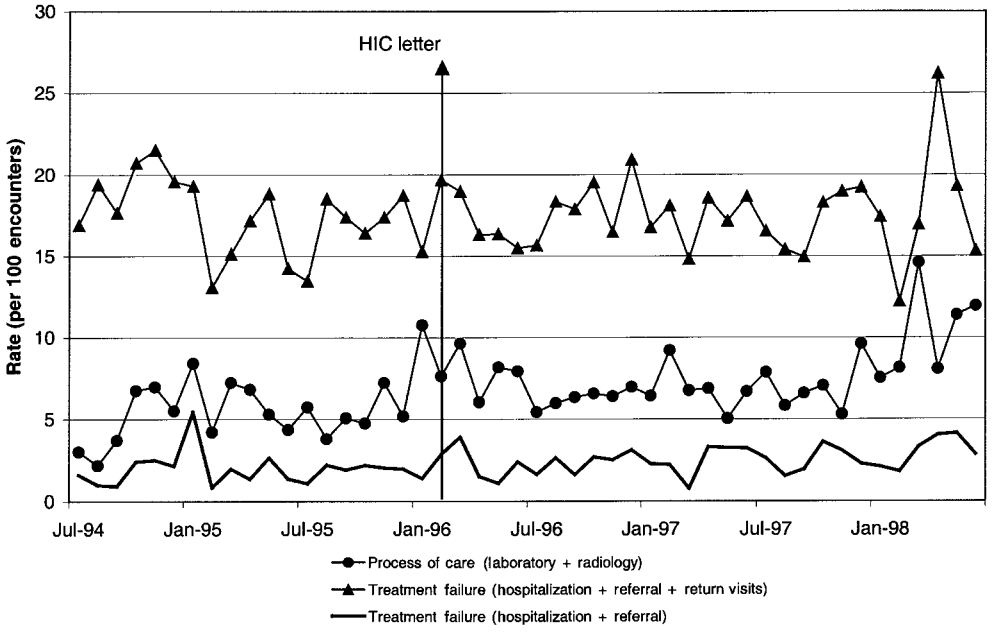

Figure 2. Rate of patient outcomes per 100 encounters. HIC, Health Insurance Commission; Jan, January; Jul, July.

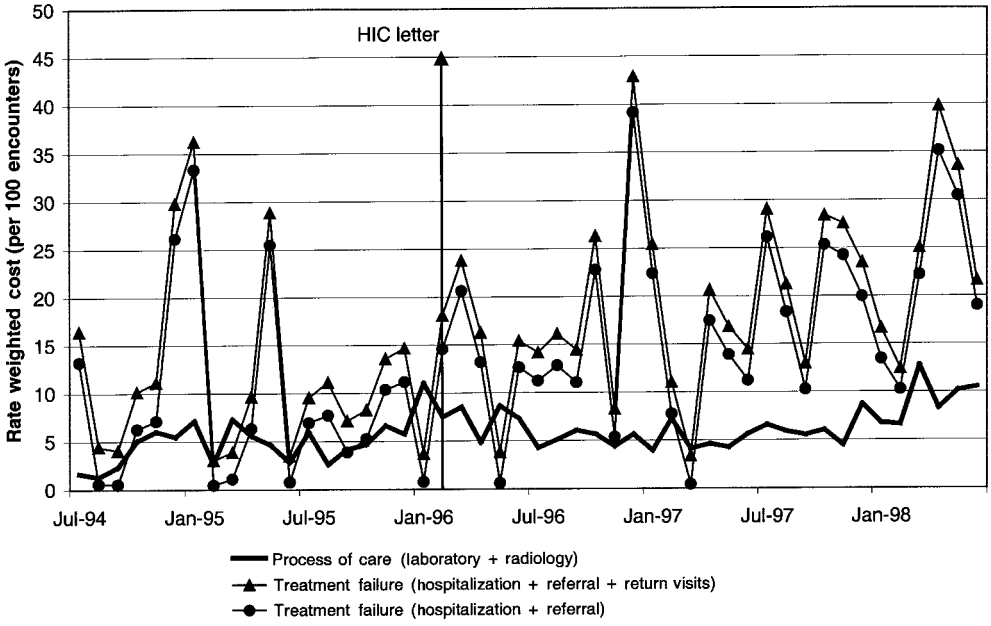

Figure 3. Rate of adverse patient outcomes (weighed by relative costs) per encounter. HIC, Health Insurance Commission; Jan, January; Jul, July.

Multivariate regression models. In the multivariate model, which adjusts for age, sex, and case mix, EOCs in which an antibiotic was prescribed were no more likely to have a patient outcome after the first visit in the period after the letter than they were in the period before the letter. Similarly, EOCs in which an antibiotic was prescribed were no more likely to have process-of-care outcomes after the first visit in the period after the letter than they were during the period before the letter.

Overall, there was a significant increase in the number of EOCs in which there were patient and process-of-care outcomes identified on the initial visit in the period after the letter (compared with the period before the letter: RR, 2.6; $P < .0001$; and RR, 2.3; $P < .0001$, respectively; table 5). EOCs in patients who were prescribed AC showed a significantly greater risk of a patient outcome during the initial visit after the letter when compared with the period before the letter (RR, 3.6; $P = .0025$). EOCs in patients who were prescribed AC showed a significantly greater risk of a process-of-care outcome on the initial visit in the period after the letter compared with the period before the letter (RR, 2.26; $P = .0061$). This may again reflect the fact that the GPs were prescribing AC to patients with more severe illness.

DISCUSSION

Before commenting on the results, it is important to examine the validity of the findings. All chosen outcomes were sought from the EOC (in which the conditions of interest were found) by trained staff, and all used defined criteria. The GPs involved in the study enter all of their data regarding patient medical records into the computer, and they have been gathering information in this manner for >10 years. As such, there was complete capture of study data, including prescribing behavior and outcomes [22]. Furthermore, the comparison with the HIC revealed total coverage of all encounter data. Because the medical records were obtained from well-established general practices, there is no suggestion that selection bias or a change in patient behavior could explain the study findings. Despite the fact that patients were not formally linked to a specific GP in Australia, there is evidence that patients are loyal to individual practices [23]. Finally, there is no information that, during the winters of 1996 and 1997, other situations, such as an influenza epidemic [24], may have caused the increase in outcomes.

Individual and ecologic measures were integrated into the study analyses because this is the best way to deal with the possibility of ecologic bias [7]. Within the study database, there was no available information on bacterial resistance, and as such, it was not possible to adjust for this confounding variable at the individual level. An alternative explanation for the findings may be that bacterial resistance had increased during this time. In Australia, there is some evidence that this was occurring, with the rates of penicillin-resistant *Streptococcus pneumoniae* increasing from 1% of isolates in 1989, to 7% in 1994, and to >25% in 1997 [4]. Although altered microbiology and bacterial resistance could explain the overall increase in patient outcomes, process-of-care outcomes would not have been influenced by this variable.

In an examination of the relationship between prescription shares, the monthly antibiotic prescribing rate before the letter was similar to that after the letter. This provided evidence

Table 5. The outcomes of multivariate regression analyses, according to visit per episode of care.

Parameter	RR	*P*
Patient outcome after initial visit	1.2	.1608
AC	1.9	.1331
Amoxicillin	0.73	.4166
Cephalosporins	0.8	.5375
Macrolides	1.49	.4858
Tetracyclines	2.1	.1772
Patient outcome on the initial visit	2.6	<.0001
AC	3.6	.0025
Amoxicillin	1.69	.4018
Cephalosporins	1.53	.4112
Macrolides	1.8	.3772
Tetracyclines	2.4	.0176
Process-of-care outcome after the initial visit	1.15	.0813
AC	0.987	.9546
Amoxicillin	0.86	.6353
Cephalosporins	1.03	.8702
Macrolides	1.6	.0845
Tetracyclines	1.9	.0506
Process-of-care outcome on the initial visit	2.28	<.0001
AC	2.26	.0061
Amoxicillin	1.92	.0624
Cephalosporins	1.38	.2799
Macrolides	1.38	.2975
Tetracyclines	2.8	<.0001

NOTE. RR is the risk of outcome after the letter divided by the risk of an outcome before the letter, after adjusting for age, sex, and case mix. An RR of >1 implies that the probability of an outcome is greater in the period after intervention compared with the period before intervention. AC, amoxicillin with clavulanic acid.

that the AC-prescription share did not decrease in the GP database because of an increase in the prescribing volume. In the time-series analyses, patient outcomes (excluding return visits) showed a significant association ($P = .0365$) with the decrease in AC-prescription share. In this study population, the main patient outcomes in which increases have occurred are hospitalizations and referrals to specialists, but not uninitiated return visits. The process-of-care outcomes were significantly associated with AC-prescription share at the 3-month lag. Detailed examination of the EOCs revealed increases in process-of-care outcomes and patient outcomes at the first visits for all antibiotic groups. In the regression model that involved age, sex, and case mix, all outcomes increased at the first visit, with a trend to increases in process-of-care outcomes after the initial visit. Clinically, the letter seems to have had a delayed effect on the process-of-care outcomes.

The study examined information from 9921 patients of 22 GPs throughout Australia; the patients experienced 11,378 EOCs for the conditions of interest. A total of 15,303 antibiotic prescriptions were written during the 4-year study period, with a total of 3729 patient outcomes and 1396 process-of-care outcomes identified. The letter had a substantial effect on the pattern of antibiotic use among these GPs. A cascade of events occurred. There seems to have been a shift away from best-practice antibiotic prescribing (as outlined in the contemporary Australian antibiotic guidelines) among these GPs. For example, for OM and sinusitis, the guidelines available at that time recommend amoxicillin as first-line therapy; AC is recommended as second-line therapy for situations in which "poor response may suggest infection with resistant organisms" [25]. The cephalosporins and macrolides are not recommended first- or second-line therapy, with the exception of cefaclor, which is provided to persons who are allergic to penicillin.

There have been changes in management by the GPs in the 4 practices whose medical records were gathered. After the letter, AC appeared to be used for sicker patients, some of whom required hospitalization. This was, in fact, one of the desired effects of the letter. The GPs seemed to have ordered more investigations after the letter, with a resultant increase in the cost to society. The reason for this change is unclear, but after the distribution of the letter, GPs seem to have shifted to a more conservative model of practice.

The effect on patient outcomes is less clear, although some trends are worth noting. Patient outcomes, particularly hospitalizations and referrals, did increase after the letter. Within the time-series analyses, there was a significant association between the increase in patient outcomes and the decrease in AC prescriptions. Calculation of the rate of outcomes per EOC in which macrolides, cefaclor, cephalexin, and amoxicillin were given revealed an overall increase (before and after the letter) in the rates of hospitalization. The rate of outcomes per EOC in which AC was prescribed increased because the GPs seemed to be prescribing AC for sicker patients, many of whom ended up in the hospital. Detailed analyses of the EOCs and the multivariate analyses indicated that some of the increase in patient outcomes was because sicker patients presented at the first visit—particularly patients who received AC and the tetracyclines.

Although the link between microbiologic in vitro resistance and patient outcomes is uncertain [26], there is evidence that both the morbidity and length and possibility of hospitalization for persons infected with drug-susceptible organisms are double those for persons infected with drug-resistant bacteria [27]. The value of observational databases (such as the one used in this study to document the link between antibiotic resistance and patient outcomes) deserves more exploration, particularly when it is known that very large sample sizes are required to document differences in outcomes for these common infectious diseases [28].

The study successfully measured the effectiveness of prescribing for common conditions among GPs during a time when a policy-driven letter influenced GP behavior. The letter was sent by a government agency and did not provide information re-

garding drug-substitution choices [29]. Complex changes occurred that seem to have resulted in more conservative GP behavior, increased cost to government, and a general trend toward poorer patient outcomes. National policies aimed at changing the prescribing behavior of GPs need to carefully analyze the likely effect on clinicians, patients, and the health system before being initiated.

STUDY GROUP MEMBERS

The FIESTA study group consisted of the following GPs from 4 practices: Michael Aird, Angelo Carbone, Marc Cesana, Elizabeth Cusby, Deborah Daniell, James Farrent, Oliver Frank, Mary Gerardine Healy, Rhys Henning, Paul Hyam, Laureen Lawlor-Smith, Lynette Lawlor-Smith, Graham Lovell, Ann Matthews, Edward Quay, Amanda Northridge, Nick Richardson, George Vlahos, Kerry Vlahos, Shanton Wenceslaus, Lou Zaninovich, and Johanna Zimmermann.

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