Information Leaflet and Antibiotic Prescribing Strategies for Acute Lower Respiratory Tract Infection
A Randomized Controlled Trial

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ACUTE LOWER RESPIRATORY tract illness is the most common condition treated in primary care.[1,2] Assuming 75% of patients are prescribed antibiotics[1] and using conservative national morbidity survey estimates,[2] acute cough costs the UK National Health Service at least US $270 million in consultation costs and US $35 million to 70 million antibiotic prescription costs annually. In the United States, excess antibiotic prescribing is mainly for pharyngitis and acute bronchitis, amounting to 55% of prescriptions and costing $726 million per year.[3]

A consensus has been made for limiting antibiotic use in acute lower respiratory tract infection.[4-6] However, recent systematic reviews[7,8] have come to diverse conclusions about the likely effectiveness of antibiotics, and the most recent Cochrane review[7] confirms a moderate effect of antibiotics on illness course; the debate continues unabated about the role of antibiotics be-

Context Acute lower respiratory tract infection is the most common condition treated in primary care. Many physicians still prescribe antibiotics; however, systematic reviews of the use of antibiotics are small and have diverse conclusions.

Objective To estimate the effectiveness of 3 prescribing strategies and an information leaflet for acute lower respiratory tract infection.

Design, Setting, and Patients A randomized controlled trial conducted from August 18, 1998, to July 30, 2003, of 807 patients presenting in a primary care setting with acute uncomplicated lower respiratory tract infection. Patients were assigned to 1 of 6 groups by a factorial design: leaflet or no leaflet and 1 of 3 antibiotic groups (immediate antibiotics, no offer of antibiotics, and delayed antibiotics).

Intervention Three strategies, immediate antibiotics (n = 262), a delayed antibiotic prescription (n = 272), and no offer of antibiotics (n = 273), were prescribed. Approximately half of each group received an information leaflet (129 for immediate antibiotics, 136 for delayed antibiotic prescription, and 140 for no antibiotics).

Main Outcome Measures Symptom duration and severity.

Results A total of 562 patients (70%) returned complete diaries and 78 (10%) provided information about both symptom duration and severity. Cough rated at least "a slight problem" lasted a mean of 11.7 days (25% of patients had a cough lasting ≥17 days). An information leaflet had no effect on the main outcomes. Compared with no offer of antibiotics, other strategies did not alter cough duration (delayed, 0.75 days; 95% confidence intervals [CI], −0.37 to 1.88; immediate, 0.11 days; 95% CI, −1.01 to 1.24) or other primary outcomes. Compared with the immediate antibiotic group, slightly fewer patients in the delayed and control groups used antibiotics (96%, 20%, and 16%, respectively; $P < .001$), fewer patients were "very satisfied" (86%, 77%, and 72%, respectively; $P = .005$), and fewer patients believed in the effectiveness of antibiotics (75%, 40%, and 47%, respectively; $P < .001$). There were lower reattendances within a month with antibiotics (mean attendances for no antibiotics, 0.19; delayed, 0.12; and immediate, 0.11; $P = .04$) and higher attendance with a leaflet (mean attendances for no leaflet, 0.11; and leaflet, 0.17; $P = .02$).

Conclusion No offer or a delayed offer of antibiotics for acute uncomplicated lower respiratory tract infection is acceptable, associated with little difference in symptom resolution, and is likely to considerably reduce antibiotic use and beliefs in the effectiveness of antibiotics.

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cause these reviews are relatively small (9 trials of 750 patients[7]). There are also concerns about complications if antibiotics are not prescribed[9,10] and debate about which clinical characteristics identify those patients at higher risk.[11-14]

Although double-blind placebo-controlled trials are important to assess efficacy, open trials help assess effectiveness and are vital when outcomes include patient perceptions, beliefs, satisfaction, and return rate to the physician's office[15]; only if patients know that they are not getting antibiotics initially can the impact on beliefs, antibiotic use, and behavior of either not prescribing or delayed prescribing be realistically assessed. By using simple-structured support and advice for each group, in effect generating a placebo effect in each group, any placebo effect related to prescribing antibiotics can be minimized.[15]

Prescribing strategies to treat upper respiratory tract illness, which do not involve initial antibiotics (either no antibiotics or offering delayed antibiotics), are effective in 70% to 90% of cases, result in acceptable symptom control, are satisfactory to the patient,[15] and can reduce reconsultation by up to 40%, with the delayed approach having the lowest reattendance rates.[16] It is unclear whether these findings can generalize to lower respiratory tract infection; 1 trial[17] (n=191) compared the delayed prescribing strategy with immediate prescribing, leaving it uncertain whether either approach was preferable to no offer of antibiotic treatment, which has been advocated strongly.[18] A recent Cochrane review[19] of delayed prescribing argued for more evidence and, in particular, better reporting of symptomatic outcomes.

The relative importance of prescribing strategies and information about natural history is also unclear. Preliminary evidence suggests that provision of an information leaflet can affect return rate and antibiotic use in lower respiratory tract infection,[20,21] although the effect on symptomatic management of such a simple leaflet and whether a leaflet provides additional benefit to simple verbal information remains unclear.

Our goals were to assess the effectiveness on symptoms, beliefs, and behavior of 3 different antibiotic prescribing strategies and assess the effectiveness of an information leaflet compared with brief verbal information alone.

METHODS
Inclusion Criteria
We recruited patients aged 3 years or older with uncomplicated acute illness (≤21 days) who presented in primary care with cough as the main symptom and with at least 1 symptom or sign localizing to the lower tract (sputum, chest pain, dyspnea, wheeze). Our criteria used the same criteria as previous large cohorts in England of patients with lower respiratory tract infection.[22,23]

Exclusion Criteria
We excluded patients with a history and physical examination suggestive of pneumonia based on the British Thoracic Society guidelines,[24] which included new focal chest signs (focal crepitations or bronchial breathing) and systemic features (high fever, vomiting, severe diarrhea). Because there is no clear agreement among the clinical prediction rules that have been used to exclude pneumonia[11,12,14,25] and, although C reactive protein (CRP) may help predict pneumonia, most physicians in England rarely use CRP in the assessment of acute infections.[11,12,26] We also excluded patients clinically diagnosed with asthma; other chronic or acute lung diseases, including cystic fibrosis, cardiovascular disease, major current psychiatric diagnosis, mental subnormality, and dementia; or with complications from previous episodes of lower respiratory tract infection (eg, hospital admission for pneumonia).

Sample Size
Using our pilot data,[27] for the immediate antibiotic prescribing strategy to make an SD difference of approximately 0.3 in the severity of symptoms or duration of cough (SD of 0.3 equals 1-2 days), we required at least 162 patients per antibiotic prescribing group, or 486 diary returns (for α=.05, β=.20).

A total of 800 patients allowed us to detect an 11% difference in reconsultation rates.[16] Our study was approved first by the South West Multi Centre Research Ethics Committee (whole region of South West England), and by each local research ethics committee (Southampton, Salisbury, Winchester, Portsmouth, and Bristol).

Randomization
After written informed consent, 807 patients were randomized. Randomization was required within the consultation to make the prescribing strategies feel the most natural to patients. Sealed opaque numbered envelopes containing structured advice for 1 of the 6 groups were prepared several weeks in advance at the study center by the research team by using computer generated random number tables, and block randomization (block size 6) was used to minimize significant group size discrepancies. Recruiters were not told that block randomization was being used, and different recruiters in each practice took individual envelopes from the same source.

Patients were assigned to 1 of 6 groups by a factorial design. The first factor randomized patients to leaflet or no leaflet, and the second factor randomized patients to 1 of 3 antibiotic groups (immediate antibiotics, no offer of antibiotics, and delayed antibiotics). Delayed antibiotics was defined as advice to use a course of antibiotics available on request if symptoms were not resolved after 14 days.

The antibiotics prescribed to the patients were 250 mg of amoxicillin 3 times per day for 10 days (125 mg if aged ≤10 years) or 250 mg of erythromycin 4 times per day if allergic to penicillin. These doses were chosen based on the British National Formulary recommendations for uncomplicated infection and from the evidence of community studies in England before and during the study that indicated no resistance among streptococcal isolates.[22,23]

In the delayed antibiotic group, the prescription was written at the time of

the initial consultation and left in a box at reception. The decision to collect the script was left to the discretion of the patient or parents (if the patient was age <16 years) without requiring a further appointment, which we have shown to be feasible with high compliance.[15] Although patients were advised to wait 14 days, they could request antibiotics earlier.

For each group, a small number of statements were read by the physician, which included advice to take analgesics, the likely natural history of the illness, and supporting the proposed prescribing strategy. This generated a placebo effect in each group.[15] The physician checked a box when each statement was read, documented clinical signs, and mailed the documentation back to the study center.

All patients, irrespective of whether they had the leaflet, were given brief verbal information about the likely range of natural history.[20] The leaflet was simple, only 1 page, and included information about the natural history.[21,28] It also addressed patients' major worries[28] and provided advice about when to seek further help (eg, persistent fever, worsening shortness of breath).

Outcome and Data Collection

Daily Diary and Satisfaction Questionnaire. Patients, or with parents' help if younger than 16 years, completed a validated daily symptom diary (available on request). They also recorded their temperature with single-use disposable thermometers (3M Tempa-DOT, 3M Corporate, St Paul, Minn), where the dots change color and can be read to within 0.1°C.[27] The recorded diary items included antipyretic use and 6 symptoms (cough, dyspnea, sputum production, well-being, sleep disturbance, and activity disturbance). Each of the 6 symptoms were scored (0=no problem, 1=very little problem, 2=slight problem, 3=moderate problem, 4=bad problem, 5=very bad problem, and 6=as bad as it could be). Patients also completed Likert scales of how satisfied or concerned

they were with different aspects of treatment (6-point scale: extremely satisfied, very satisfied, moderately satisfied, slightly satisfied, not very satisfied, and not at all satisfied). These Likert scales have previously been shown to be reliable, have good construct validity, and predict illness duration.[15,29] Patients also rated their belief in antibiotics using a 6-point scale (extremely effective, very effective, moderately effective, slightly effective, not very effective, and not at all effective).

Clinical Symptoms and Signs. The clinical history, symptoms (prior duration, sputum production, sputum color), signs (breath sounds: normal or bronchovesicular), or added sounds (crepitations, wheeze) were documented initially by the physician. Physicians were not provided with any special training, given that the examination of the chest is part of daily routine clinical practice.

Reported Antibiotic Use. Because prescription redemption is not necessarily a guide to prescription use, we asked patients to document whether they used antibiotics and for how many days (giving patients the permission not to comply but not encouraging noncompliance). We have previously shown that reported antibiotic use, documented by a self-completed questionnaire after the diary was completed, is very reliable when validated against prescription collection.[15]

Notes Review. The patients' notes were reviewed by an author (J.K.) who was blind to study group for reconsultation with cough and for complications within 1 month after randomization. The advantage of England's primary care system is that all patients are registered with their primary care physician (private practice is rare), which means that contacts for review of illness will be documented in the note of the registered practice.

Statistical Analysis

We used analysis of variance and logistic regression for a factorial study for continuous and dichotomous out-

comes, respectively. All patient data, where outcomes were available and with no imputation of missing values, were analyzed according to the randomized group in an intention-to-treat analysis. We first tested for interactions between factors. Because no interactions were found, main effects for each factor are presented that mutually control for the effect of each factor. For the number of reattendances with cough in the month after the physician visit, which follows a Poisson distribution, we used Poisson regression for a factorial study. Stata software version 7 (StataCorp LP, College Station, Tex) was used for all statistical analyses. $P \leq .05$ was considered statistically significant.

RESULTS

Recruitment

Thirty-seven physicians in England (mainly around Southampton and Bristol) were recruited during a 5-year period (August 18, 1998, to July 30, 2003) and 807 patients were recruited from the same area (**FIGURE 1**). Although most physicians only approached a few patients (lack of time being the most common reason), the 4 highest recruiting physicians recruited the majority of the patients (540 patients [67%], most of the patients presented to the physician). Recruitment status of patients (from high vs low recruiting physicians) did not predict any outcome. There was no evidence of any significant interaction between recruitment status and the effectiveness of prescribing antibiotics immediately; the estimates of the interaction were small (for the mean diary score, 0.25; 95% confidence interval [CI], –0.20 to 0.71; for mean duration of moderately bad cough, 1 day; 95% CI, –0.76 to 2.76 days; and for mean duration of any moderately bad symptom, 0.55 days; 95% CI, –1.60 to 2.70 days).

Baseline Characteristics

We recruited 136 patients (17%) who were children (<16 years) and 133 older patients (17%) (>60 years). As expected, children presented with

higher temperatures (mean temperature, 36.9°C [SD, 0.7°C]), with 51% having an axillary temperature of at least 37.0°C; for adults, the mean temperature was 36.6°C (SD, 0.7°C).

Baseline clinical characteristics were similar in the intervention groups (TABLE 1). The severity of symptoms was the primary outcome, which was close to being significantly different by group; however, the adjusted estimates for severity of symptoms including all baseline variables in the model were –0.05 for leaflet vs no leaflet (P=.58), –0.02 for delayed vs no anti-biotics (P=.86), and –0.07 for immediate vs no antibiotics (P=.49). This suggests adequate control of confounding by randomization.

Loss to Follow-up for Symptom Resolution

A total of 562 patients (70%) returned complete diaries after 3 weeks and an additional 78 (10%) provided information about both symptom duration and severity. There were no differences in baseline characteristics (eg, fever, sputum, chest signs) comparing those patients followed up to those not followed up. Those patients not followed up had low return rates in the next month (6% vs 15% for those followed up), which suggests they were not likely to have had severe illness.

Symptom Duration and Severity

Main results are shown in TABLE 2 and TABLE 3; descriptive information for cumulative duration of symptoms is shown in FIGURE 2. There was no effect of the leaflet on any primary outcome. Cough that was rated at least "a slight problem" lasted a mean of 11.7 days (25% of patients had a cough lasting ≥17 days), and a moderately bad cough lasted a mean of 6.0 days (25% of patients had a cough lasting ≥8 days). Compared with no offer of antibiotics, other prescribing strategies did not alter the primary outcomes (Table 2). Antibiotics reduced duration of moderately bad symptoms (scoring ≥4 of 6 on any symptom each day) by 1 day overall and reduced moderately bad symptoms for 4 individual diary items, but in all cases making less than 1 day difference for phlegm (mean, –0.96 days; 95% CI, –1.84 to –0.08), sleep disturbance (mean, –0.73 days; 95% CI, –1.46 to 0.00), activity disturbance (mean, –0.93 days; 95% CI, –1.72 to –0.13), and feeling unwell (mean, –0.91 days; 95% CI, –1.71 to –0.11).

Figure 1. Flow of Patients Through Trial
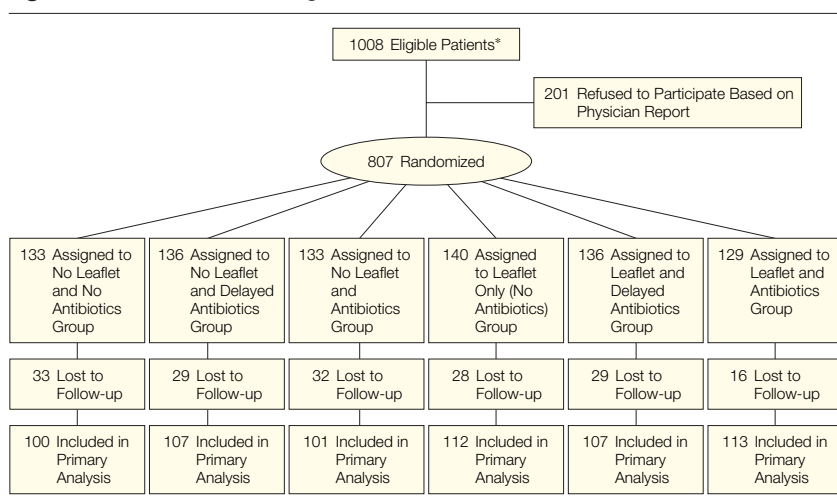
*Eligible patients approached for inclusion in the trial were estimated from physician self-report.

Table 1. Baseline Comparison of Intervention and Control Groups of Each Factor*

	Leaflet	No Leaflet	P Value†	No Antibiotics	Delayed Antibiotics	P Value‡	Immediate Antibiotics	P Value§
Patient age, y	39 (20)	38 (21)	.48	39 (20)	38 (20)	.78	40 (22)	.48
History of								
Fever	250/400 (63)	267/394 (68)	.12	171/269 (64)	178/265 (67)	.38	168/260 (65)	.80
Dark green sputum	176/399 (44)	151/391 (39)	.12	117/266 (44)	101/265 (38)	.17	109/259 (42)	.66
Sore throat	259/400 (65)	269/391 (69)	.23	174/268 (65)	187/266 (70)	.18	167/257 (65)	.99
Coryza	270/398 (68)	274/387 (71)	.37	182/267 (68)	183/263 (70)	.72	179/255 (70)	.61
Coarse crepitations	59/401 (15)	56/390 (14)	.89	38/268 (14)	29/264 (11)	.27	48/259 (19)	.18
Wheeze	60/396 (12)	45/390 (15)	.14	34/268 (13)	33/263 (13)	.96	38/255 (15)	.68
Respiratory rate, breaths/min	16.3 (4.3)	16.2 (4.8)	.79	15.9 (4.2)	16.3 (5.3)	.41	16.4 (4.2)	.18
Prior duration of cough, d	9.6 (7.6)	9.5 (7.1)	.73	9.9 (7.4)	9.4 (6.3)	.33	9.4 (8.3)	.41
Temperature, °C	36.6 (0.75)	36.7 (0.64)	.34	36.7 (0.61)	36.6 (0.84)	.24	36.6 (0.61)	.88

*Data are presented as either No./total No. (%) or mean (SD). Denominators vary due to missing values. Columns relate to the levels within each factor (leaflet and prescribing strategies), not to the 6 individual groups.
†Leaflet vs no leaflet.
‡Delayed antibiotics vs no antibiotics.
§Immediate antibiotics vs no antibiotics.

Satisfaction, Beliefs, and Antibiotic Use

Slightly fewer patients were very satisfied, fewer used antibiotics, and fewer believed in the effectiveness of antibiotics in the delayed and control groups vs the immediate antibiotic group (Table 3).

Reattendance Within 1 Month

Overall, there were fewer reattendances with cough with delayed prescribing and immediate antibiotics in the month after the physician visit (mean attendances for no antibiotics,

0.19; delayed, 0.12; and immediate, 0.11; likelihood ratio [LR] test from Poisson regression, $P = .04$). There was increased attendance with a leaflet (mean attendances for no leaflet, 0.11; and leaflet, 0.17; LR test, $P = .02$). The incidence rate ratio estimates for individual groups were 0.55 (95% CI, 0.33-0.91; $P = .02$) for immediate antibiotics vs no antibiotics (a 45% decrease); 0.65 (95% CI, 0.40-1.04; $P = .08$) for delayed antibiotics vs no antibiotics (a 35% decrease); and 1.63 (95% CI, 1.07-2.49, $P = .02$) for leaflet vs no leaflet (a 63% increase).

Adverse Events

One patient in the no antibiotic group developed pneumonia, was admitted to the hospital, administered antibiotics, and recovered fully. Diarrhea was slightly more common but not significantly in the delayed groups (odds ratio [OR], 1.17; 95% CI, 0.67-2.03; $P = .58$) and the immediate group (OR, 1.22; 95% CI, 0.70-2.12; $P = .48$).

Subgroups

A priori, we defined patients with colored sputum and elderly persons aged at least 60 years as possible subgroups

Table 2. Estimates in Control Group of Each Factor and the Estimated Mean Differences Due to Interventions in Each Factor

	No Leaflet (Control), Mean (SD)	Difference Due to Leaflet (95% CI)*	P Value	No Antibiotic (Control), Mean (SD)	Difference Due to Delayed Antibiotics (95% CI)*	P Value	Difference Due to Immediate Antibiotics (95% CI)*	P Value
Primary symptom outcomes from diary								
Duration of cough until very little problem, d	11.6 (5.8)	0.26 (−0.66 to 1.18)	.58	11.4 (5.8)	0.75 (−0.37 to 1.88)	.19	0.11 (−1.01 to 1.24)	.84
Duration of moderately bad cough, d	5.8 (4.1)	0.20 (−1.60 to 2.00)	.83	5.7 (4.0)	0.13 (−1.70 to 2.00)	.89	0.52 (−1.30 to 2.40)	.58
Severity (mean item score of all 6 diary symptoms on days 2-4 after physician visit)	2.3 (1.1)	−0.03 (−0.20 to 0.15)	.77	2.3 (1.2)	0.06 (−0.15 to 0.27)	.56	−0.10 (−0.31 to 0.11)	.11
Secondary symptom outcomes from diary, d								
Phlegm	9.5 (6.2)	0.39 (−0.64 to 1.43)	.46	10.1 (6.1)	−0.11 (−1.39 to 1.18)	.87	−0.90 (−2.17 to 0.37)	.17
Short of breath	6.3 (5.9)	0.46 (−0.53 to 1.45)	.36	6.3 (6.0)	−0.80 (−0.42 to 2.02)	.20	−0.29 (−1.50 to 0.93)	.64
Sleep disturbance	8.2 (5.7)	−0.23 (−1.16 to 0.70)	.63	7.9 (5.9)	0.67 (−0.48 to 1.82)	.25	−0.20 (−1.34 to 0.94)	.73
Activity disturbance	8.3 (5.7)	−0.09 (−1.01 to 0.88)	.85	8.2 (6.0)	0.75 (−0.44 to 1.94)	.22	−0.57 (−1.75 to 0.62)	.35
Feeling unwell	8.8 (5.4)	0.21 (−0.71 to 1.12)	.66	8.9 (5.8)	0.73 (−0.40 to 1.86)	.20	−0.77 (−1.89 to 0.35)	.18
Duration of any symptoms	12.3 (5.9)	−0.03 (−1.00 to 0.94)	.95	12.1 (5.8)	0.74 (−0.46 to 1.95)	.23	−0.16 (−1.35 to 1.03)	.79
Duration of moderately bad symptoms	7.0 (4.9)	0.15 (−0.67 to 0.96)	.73	7.3 (4.9)	0.14 (−0.87 to 1.14)	.79	−1.08 (−2.1 to −0.09)	.03

Abbreviation: CI, confidence interval.
*The estimates for each intervention are the estimated difference vs control, when controlling for the effects of the other interventions. Leaflet factor: leaflet vs no leaflet (controlling for the effect of antibiotic prescribing strategies); antibiotic factor: delayed and immediate antibiotics vs no offer of antibiotics (controlling for the effect of leaflets). A positive difference means a longer duration (or worse outcome) and a negative difference means a shorter duration (better outcome).

Table 3. Questionnaire Outcomes

|	No./Total No. (%) of Patients		P Value*	No./Total No. (%) of Patients			P Value*
	No Leaflet	Leaflet		No Antibiotics	Delayed Antibiotics	Immediate Antibiotics	
Used antibiotics†	160/281 (57)	159/291 (55)	.58	29/182 (16)	39/197 (20)	185/193 (96)	<.001
Believed in antibiotics‡	122/218 (56)	119/219 (54)	.73	61/131 (47)	57/141 (40)	123/165 (75)	<.001
Very satisfied with overall management§	213/279 (76)	230/286 (78)	.24	130/181 (72)	147/190 (77)	166/194 (86)	.005

*Intervention groups of each factor were compared with control group of each factor. Leaflet factor: leaflet vs no leaflet; antibiotic factor: delayed and immediate antibiotics vs no antibiotics.
†As reported in diary.
‡To simplify presentation, the Likert scale responses were dichotomized as moderately effective or more effective vs other categories.
§To simplify presentation, the Likert scale responses were dichotomized as very satisfied or extremely satisfied vs other categories.

Figure 2. Duration of Cough After Physician Visit Until Patient Is Feeling Better
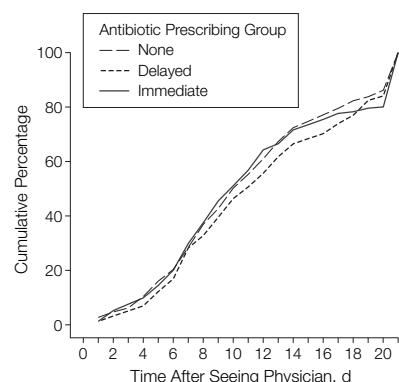
Feeling better was defined as a cough that was rated very little or no problem. The cumulative percentage of patients who are better after the physician visit in the 3 antibiotic-prescribing groups is shown (by day 11, 50% of patients were better and by day 19, 80% were better no matter what prescribing strategy was used).

who might preferentially benefit from the offer of immediate antibiotics.[7,30]

There was no evidence of a significantly different effect for those patients with colored sputum for duration of cough (interaction terms for delayed group, −0.09 days; 95% CI, −3.67 to 3.47; $P = .96$; interaction term for immediate antibiotic group, −1.85 days; 95% CI, −5.51 to 1.81; $P = .32$).

Elderly patients had shorter symptom duration (−2.65 days; 95% CI, −4.78 to −0.62; $P = .01$) and also benefited less from either delayed antibiotics (interaction term, 3.59 days; 95% CI, 0.64-6.53; $P = .02$) or immediate antibiotics (interaction term, 2.84 days; 95% CI, 0.005-5.67; $P = .05$). These results were not affected by controlling for baseline clinical characteristics. There was no evidence for a differential effect in children, either in terms of symptom duration or effect of prescribing strategies on outcome.

Patients with asthma at presentation were excluded, but some patients were given a clinical diagnosis of asthma during follow-up. Excluding 33 (5%) of 691 patients who had a diagnosis of asthma made in the subsequent 12 months did not alter the estimates of effect size on duration of cough for im-

mediate antibiotics (interaction term, 0.14 days; 95% CI, −1.01 to 1.29).

COMMENT

To our knowledge, our trial is the largest randomized trial of antibiotic use for lower respiratory tract infection presenting in primary care and provides important information for management, being a similar size to the data set for the existing Cochrane systematic review,[7] but also suggests a smaller effect of antibiotics.

Our study had several limitations. There is no widely agreed definition of lower respiratory tract infection[7]; therefore, we used the criteria from previous large cohorts[22,23] to define our study population and, in practice, most patients in this cohort had acute cough with sputum.

An open design was essential in our study to allow the observance in practice of the pragmatic uptake and effect of prescribing strategies on such outcomes as beliefs and antibiotic use. The limitation of our design is the possibility of a placebo effect favoring antibiotics. However, any differential placebo effect was minimized by the physician using a structured approach to support each strategy. There was no evidence of a differential placebo effect using the same approach in the previous trial in upper respiratory tract infection.[15] In our study, little evidence of a placebo effect was observed favoring immediate antibiotics for the main outcome measures.

Our study confirms the long natural history of lower respiratory tract infection, in that patients need to be warned that they will on average have an illness lasting 3 weeks in total with 10 days of symptoms before the physician visit and 12 days after the physician visit.

Compared with immediate antibiotics, a strategy of either no offer of antibiotics or delayed prescribing is associated with little difference in duration or severity of symptoms. This is consistent with recent existing systematic reviews and suggests that for most patients, antibiotics probably provide modest symptomatic relief.[7,8] The

estimates from our study suggest that the likely effect sizes of prescribing immediate antibiotics in routine practice are likely to be rather more modest than documented in the Cochrane review.[7]

A secondary finding from our study was that immediate antibiotics may possibly reduce the duration of moderately bad symptoms. This must be interpreted with caution as it is a secondary finding. Even if this finding is not due to type I error, it represents benefit of only 1 day in an illness with a relatively long natural history. It is difficult to justify widespread antibiotic prescribing for uncomplicated lower respiratory tract infection on this basis given the dangers of antibiotic resistance.[31,32]

Other important findings of our study were that although 10% fewer of our patients were very satisfied, not offering antibiotics or using delayed prescribing are both very acceptable to most patients, which supports previous evidence about the modest differences in satisfaction when antibiotics are prescribed[33]; and there are likely to be reductions in both belief in antibiotics and antibiotic use, with delayed prescribing performing almost as well as no initial offer of antibiotic use. The low prescription use for the collection approach to delayed prescribing used in our study is similar to the finding in upper respiratory tract infection,[15] but may well be lower than rates of delayed prescription use in which the patient is given the prescription to take away.[34] Our study suggests that one advantage of immediate or delayed antibiotics is fewer reattendances with cough in the month after the physician visit.

The lack of effect of an information leaflet does not mean that leaflets are unhelpful because previous evidence suggests that they are helpful,[20,21] but that there is no reinforcing effect of a leaflet beyond providing verbal information, which all patients in our study were given. The 14% decrease in antibiotic use with a leaflet among those patients who received a delayed antibiotic prescription reported previously[20] occurred when the delayed prescription was given to the

patient and antibiotic use was high (49%-63%). In contrast with our study in which patients were asked to collect their prescription if they wished to use it, antibiotic use was much lower, which may have limited the power of our study to detect an information-leaflet effect. The finding of increased attendance during the following month probably reflects patients responding to advice in the leaflet to reattend for particular circumstances, such as ongoing fever or shortness of breath.

In conclusion, in our patients from primary care who presented with acute uncomplicated lower respiratory tract infection, the use of delayed antibiotics or no antibiotics was acceptable, resulted in little difference in duration or severity of symptoms compared with immediate treatment with antibiotics, and considerably reduced both antibiotic use and belief in antibiotics. These findings suggest that adopting these strategies would help limit the vicious circle of the medicalization of self-limiting illness when antibiotics are prescribed. Immediate antibiotic prescribing is likely to limit the number of patients who return for cough within the next month but only by a little more than delayed antibiotic prescription. The challenge now is for clinicians and researchers to determine which groups are at risk of adverse outcomes and identify those patients who might selectively benefit from immediate antibiotic prescription.

Author Contributions: Dr Little had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Little, Rumsby, Watson, Moore, Warner, Fahey, Williamson.
Acquisition of data: Little, Rumsby, Kelly, Watson, Moore, Warner, Fahey, Williamson.
Analysis and interpretation of data: Little, Moore, Fahey, Williamson.
Drafting of the manuscript: Little.
Critical revision of the manuscript for important intellectual content: Little, Rumsby, Kelly, Watson, Moore, Warner, Fahey, Williamson.
Statistical analysis: Little.
Obtained funding: Little.
Administrative, technical, or material support: Little, Rumsby, Kelly, Watson, Moore, Warner, Fahey, Williamson.
Study supervision: Little, Rumsby, Watson, Moore, Warner, Fahey, Williamson.
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