

Primary care

Penicillin for acute sore throat in children: randomised, double blind trial

Sjoerd Zwart, Maroeska M Rovers, Ruut A de Melker, Arno W Hoes

Abstract

Objective To assess the effectiveness of penicillin for three days and treatment for seven days compared with placebo in resolving symptoms in children with sore throat.

Design Randomised, double blind, placebo controlled trial.

Setting 43 family practices in the Netherlands.

Participants 156 children aged 4-15 who had a sore throat for less than seven days and at least two of the four Centor criteria (history of fever, absence of cough, swollen tender anterior cervical lymph nodes, and tonsillar exudate).

Interventions Patients were randomly assigned to penicillin for seven days, penicillin for three days followed by placebo for four days, or placebo for seven days.

Main outcome measures Duration of symptoms, mean consumption of analgesics, number of days of absence from school, occurrence of streptococcal sequelae, eradication of the initial pathogen, and recurrences of sore throat after six months.

Results Penicillin treatment was not more beneficial than placebo in resolving symptoms of sore throat, neither in the total group nor in the 96 children with group A streptococci. In the groups randomised to seven days of penicillin, three days of penicillin, or placebo, one, two, and eight children, respectively, experienced a streptococcal sequela.

Conclusion Penicillin treatment had no beneficial effect in children with sore throat on the average duration of symptoms. Penicillin may, however, reduce streptococcal sequelae.

Introduction

Acute sore throat is one of the most common complaints for which children visit doctors. Roughly 15-30% of all cases with pharyngitis presented to a doctor are caused by group A streptococci.¹

We previously reported that penicillin treatment for seven days was superior to treatment for three days or placebo in resolving symptoms of sore throat in adult patients with group A streptococcal pharyngitis.² Empirical evidence for children is, however, scarce.³

Simultaneously with our trial in adults we performed a double blind, randomised trial in children aged 4-15 presenting with sore throat, comparing the effectiveness of penicillin V for seven days, penicillin V for three days (followed by placebo for four days), and placebo for seven days.

Participants and methods

We described the methods in detail in our earlier report.² Overall 308 children aged 4-15 contacted their general practitioner

because of an acute sore throat. We excluded 45 children because of medical reasons, such as an imminent quinsy (n=28), (suspected) scarlet fever (n=9), an intercurrent disease requiring antibiotics (n=6), and intolerance to penicillin (n=2).⁴ The participating general practitioners were experienced users of these so called Centor criteria, which were developed to trace patients with streptococcal tonsillitis.⁵ Of the 262 eligible children 156 were randomly assigned to one of three treatment groups: penicillin V for seven days (n=46), penicillin V for three days followed by placebo for four days (n=54), or placebo for seven days (n=56). The dosage was one 250 mg capsule three times daily for children aged 4-10 and two 250 mg capsules three times daily for children aged 10 and older.

The patients were randomly assigned according to a computer generated list that was blinded to both patients and doctors. The figure shows the flow of patients through the trial. An independent pharmacist filled and numbered the medication trays. Each general practitioner received medication trays from the study coordinator, to be used in the numbered order. After six months of follow up the parents of the children were informed by telephone about the treatment received.

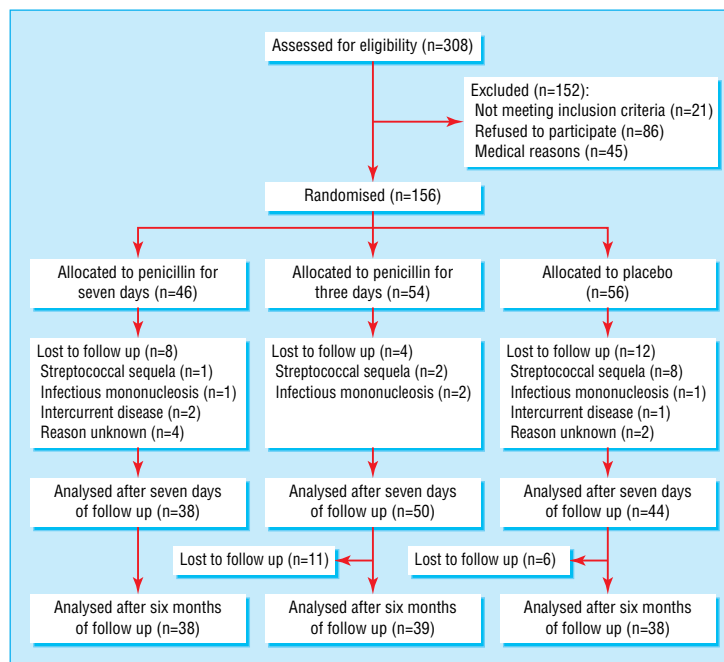
Throat swabs were taken after randomisation and again after two weeks, and a diary was given to the parents. During the study they recorded the children's attendance at school and possible side effects of penicillin.

The primary outcome variable was the duration of symptoms, defined as the number of days of symptoms after randomisation until the pain had resolved permanently. Secondary outcome variables included mean consumption of analgesics (in days), absence from school, development of streptococcal sequelae such as an (imminent) quinsy, eradication of the initial pathogen after two weeks, and recurrent episodes of sore throat during the six month follow up period. Imminent quinsy was defined as a unilateral, peritonsillar or tonsillar swelling with oedema and exudate, pushing aside the uvula. Informed consent was obtained from the child's parent or carer.

With at least 52 children in each of the three groups a difference of one day of duration of symptoms could be detected at a 5% level of significance with 90% power. For subgroup analysis a total of 20 children per group would be needed to detect a difference of 1.5 days of duration of symptoms. We performed all analyses on an intention to treat basis.

Results

The mean age of the included children was 10, half (78) were boys, and the mean duration of complaints before inclusion in the study was three days. We observed no relevant baseline differences between the three treatment groups (table 1).



Flow of participants through the trial of penicillin for acute sore throat in children

The mean duration of sore throat was the same in children taking penicillin for seven days (mean 3.8 days, 95% confidence interval 3.2 to 4.4) and in children taking placebo (3.8 days, 3.3 to 4.3); the difference was 0 days (-0.9 to 0.9). The number of days with a sore throat did not differ between children who took penicillin for three days (mean 4.6 days, 4.0 to 5.2) and children taking placebo (difference 0.8 days, -0.1 to 1.7; table 2). The number of days missed at school and the incidence of recurrent episodes of sore throat were also similar in all treatment groups (tables 3 and 4).

In children with group A streptococci (n=96) who were treated with penicillin for seven days the sore throat resolved permanently 0.5 (-0.6 to 1.5) days sooner than in children who took placebo, whereas in those who took penicillin for three days the sore throat resolved permanently 1.3 (0.2 to 2.4) days later

Table 1 Baseline characteristics of patients in the three treatment groups. Values are numbers (percentages) of children unless otherwise indicated

	Duration of penicillin treatment per group		
	Seven days (n=46)	Three days (n=54)	Placebo group (n=56)
Mean age in years (SD)	9.9 (3.8)	10.5 (3.8)	10.1 (3.9)
Male	20 (44)	20 (37)	30 (54)
Healthcare insurance	32 (70)	34 (63)	36 (64)
Resident in cities >30 000 inhabitants	21 (46)	22 (41)	28 (50)
Presented to general practitioner in October-March	28 (61)	42 (78)	37 (66)
Sore throat >3 days	30 (65)	29 (54)	33 (59)
Fever (reported)	43 (94)	49 (91)	47 (84)
Absence of cough	34 (74)	37 (69)	40 (71)
Absence from school	28 (72)	37 (69)	40 (74)
Tonsillar exudate	35 (76)	43 (79)	42 (75)
Cervical lymph nodes	43 (94)	53 (97)	54 (96)
All four Centor criteria present	19 (41)	24 (44)	25 (45)
History of tonsillectomy	2 (4)	3 (6)	2 (4)
Throat culture:			
Positive for group A streptococci	28 (70)	26 (48)	43 (77)

Table 2 Mean duration of sore throat (in days, with 95% confidence intervals) in the three treatment groups

Culture	No of patients	Duration of penicillin treatment per group		
		Seven days	Three days	Placebo group
All	156	3.8 (3.2 to 4.4)	4.6 (4.0 to 5.2)	3.8 (3.3 to 4.3)
Positive for group A streptococci	96	3.0 (2.4 to 3.6)	4.8 (4.0 to 5.6)	3.5 (2.9 to 4.1)
Other or negative	60	4.9 (4.1 to 5.7)	4.4 (3.6 to 5.4)	4.7 (3.5 to 5.9)

than in the placebo group (table 5). We found no differences in mean consumption of analgesics (table 6).

Penicillin treatment for seven days was more effective than treatment for three days and placebo in eradicating group A

Table 3 Mean duration of absence from school in days (with 95% confidence intervals) in the three treatment groups

Treatment group	Duration of penicillin treatment		
	0 days	3 days	7 days
All (n=156)	2.4 (1.8 to 3.0)	2.3 (1.7 to 2.9)	2.8 (2.2 to 3.5)
Children with group A streptococci (n=96)	2.2 (1.6 to 2.8)	2.2 (1.3 to 3.0)	2.5 (1.8 to 3.1)
Children without group A streptococci (n=60)	3.2 (1.6 to 4.7)	2.4 (1.6 to 3.3)	3.3 (2.0 to 4.6)

Table 4 Episodes of upper respiratory tract infection and sore throat reported by the parent or carer during the 6 month follow up period. Values are numbers (percentages) of patients with at least one episode per given period per treatment group

	Duration of penicillin treatment			P value (χ ² test)
	7 days	3 days	0 days	
Upper respiratory tract infection:				
Day 8-15	8/39 (20)	8/39 (20)	7/40 (18)	0.9
Day 16-180	32/39 (82)	31/39 (80)	30/40 (75)	0.6
Sore throat:				
Day 8-15	4/39 (10)	6/39 (15)	4/40 (10)	0.8
Day 16-180	24/39 (62)	18/39 (46)	18/40 (45)	0.2

Table 5 Difference in mean duration of sore throat (in days, with 95% confidence intervals) of seven days of penicillin treatment versus placebo, and three days of penicillin treatment versus placebo

Throat cultures	No of patients	Penicillin versus placebo	
		Seven days	Three days
All	156	0.0 (−0.9 to 0.9)	0.8 (−0.1 to 1.7)
Positive for group A streptococci	96	−0.5 (−1.5 to 0.6)	1.3 (0.2 to 2.4)
Other or negative	60	−0.2 (−2.0 to 1.6)	0.3 (−1.4 to 1.9)

Table 6 Mean consumption of analgesics (in days, with 95% confidence intervals) in the three randomised groups

Culture	No of patients	Duration of penicillin treatment per group		
		Seven days	Three days	Placebo group
All	156	1.1 (0.7 to 1.6)	1.4 (1.0 to 1.9)	1.4 (1.0 to 1.8)
Positive for group A streptococci	96	0.8 (0.3 to 1.3)	1.3 (0.7 to 1.9)	1.2 (0.8 to 1.6)
Other or negative	60	1.6 (0.7 to 2.5)	1.6 (0.9 to 2.3)	2.0 (1.1 to 2.9)

streptococci. The eradication rates were 68%, 35%, and 28% in children who took penicillin for seven days, three days, or placebo, respectively ($P=0.003$).

Eleven children developed a streptococcal sequela: nine had an imminent quinsy, one scarlet fever, and one impetigo. In the group taking penicillin for seven days one child (0.02%) experienced a streptococcal sequela, compared with two (0.04%) in the group taking penicillin for three days, and eight (0.1%) in the placebo group. The incidence rate ratio of seven days of penicillin versus placebo was 0.15 (95% confidence interval 0.02 to 1.2); the incidence rate ratio of three days of penicillin versus placebo was 0.26 (0.06 to 1.2). After breaking the treatment code all 11 children received new, prolonged, or alternative antibiotic treatment. They recovered uneventfully, without referral to a hospital. The occurrence of possible side effects, such as abdominal pain (38%), diarrhoea (26%), and vomiting (30%) did not differ between the three treatment groups.

Discussion

No rationale exists for treatment with antibiotics in most children with sore throat, irrespective of the presence of streptococci. This finding is in agreement with the Dutch and Scottish guidelines on the management of sore throat.^{5 6}

Resolution of symptoms and group A streptococci

In the total group of children and the children who were positive for group A streptococci treatment with penicillin for seven days failed to shorten the duration of sore throat, reduce non-attendance at school, or reduce recurrence of sore throat in the following six months. In our previous study, however, adult patients experienced an accelerated recovery of two days when treated with penicillin, most notably patients from whom group A streptococci were cultured.² This discrepancy between children and adults is probably attributable to the high carrier rate of group A streptococci in asymptomatic children in our region (30% compared with 7% of adults).⁷ The 30% yield of group A streptococci in asymptomatic children is relatively high. Previous population based studies reported prevalences between 6% and 16%.^{8 9} As serotyping and genotyping of the group A streptococci did not show a predominant strain the existence of a local epidemic during the time of our study is unlikely.^{7 10}

The preparatory training of the general practitioners to take throat swabs for culture, the use of two swabs instead of one per

patient, and updated laboratory techniques¹¹ are likely to have contributed to the high yield of streptococci in this study. In this way group A streptococci, possibly those in cultures with a low colony count, were detected that would have been missed by the techniques applied in previous studies. Cultures with a low colony count have been assumed to be more prevalent among carriers of group A streptococci who do not have an infection than among those having true streptococcal disease.^{7 9 12} Therefore we believe that the prevalence of streptococcal infections in our study is unlikely to differ from clinical practice or earlier studies. We probably included many carriers of group A streptococci in our group A positive children, which may have diluted the effect of penicillin.

Effects of penicillin for three days

The finding that the three day penicillin group had a slower recovery than the placebo group is in accordance with our finding in adult patients.² The increased recurrence rate of sore throat at the end of the first week is probably due to the three days' exposure to penicillin, reducing the natural immune response without eradicating the pathogenic streptococci.

Generalisability

To our knowledge our study is the first large, randomised, double blind, placebo controlled trial in children. A recent systematic review on the management of sore throat reported important methodological limitations in all of the few available studies in children.³

As we expected, not all children with acute sore throat were included by the participating doctors. The inclusion rate, however, is in line with other randomised trials on the effects of antibiotics in upper respiratory tract infections in primary care. Possible reasons for a lower inclusion rate are that, firstly, doctors did not include all eligible patients, notably during busy office hours and during holiday periods, and secondly, patients may have visited other doctors who were not participating in the study—for example, because their own general practitioner was on leave or because they did not present during office hours. Since this selection is expected to be independent of patients' characteristics, it will not influence the generalisability.

We decided to use only two out of the four Centor criteria as an inclusion criterion in children because we considered them to be less useful than in adults. Nevertheless, we were concerned to include too many children with an unspecified upper respiratory tract infection if we did not use any criterion apart from "acute sore throat."

We excluded severely ill children. In clinical practice this small subgroup might benefit more from penicillin than the children included in our trial. In the future such a subgroup might be identifiable by new diagnostic tools, such as genetic techniques, which help doctors to detect harmless colonisers as well as virulent invaders among the group A streptococci.¹³

Risk of streptococcal sequelae

The results of our study showed that streptococcal sequelae seem to occur more often in the placebo group than in the penicillin groups, but the power of our study, like all other individual trials, was too limited to draw firm conclusions. On the other hand, the observed trend is in concordance with a Cochrane review of trials in adults and children with sore throat.³ In this review the incidence of suppurative sequelae, such as acute otitis media and sinusitis in patients treated with antibiotics, was 50-75% lower than in the placebo group. Furthermore, these sequelae can safely be treated at the moment of occurrence, and their preven-

What is already known on this topic

Complications of sore throat that presented a serious problem in the past, such as acute rheumatic fever and post-streptococcal glomerulonephritis, have become extremely rare in affluent Western communities

Evidence is lacking whether penicillin treatment is needed for children with an acute sore throat who test positive for streptococci, and the advice given in national guidelines diverges

What this study adds

Penicillin V does not reduce the duration of symptoms or the use of analgesics, nor does it affect school attendance or recurrences of sore throat, irrespective the presence of group A streptococci

Penicillin V may reduce the development of streptococcal sequelae, such as quinsy, scarlet fever, or impetigo

Once a sequela is diagnosed, sufficient time is left to start antibiotic treatment

Nearly all children with a sore throat in Western communities can be treated safely without penicillin

tion is not a specific indication for antibiotic treatment in sore throat.

Conclusion

In view of the extremely low incidence of potentially severe post-streptococcal sequelae such as rheumatic fever in affluent Western communities, rising antibiotic resistance rates, and the high carrier rate of group A streptococci in children, we advocate prudent prescription behaviour with respect to penicillin. General practitioners are recommended to treat children having an acute sore throat only when they are severely ill (unable to drink, an imminent quinsy) or at high risk (history of rheumatic fever, having an anatomical or immunological disorder, high incidence of streptococcal infections in the community).

Contributors: SZ initiated the research, designed the protocol, and collected the data. MMR analysed the data. RAAdM was involved in the study design and the interpretation of data. AWH was involved in the study design and

data analyses. All authors participated in writing the report. SZ will act as guarantor for the paper.

Funding: This study was funded by Groene Land Achmea Health Insurances and the Stichting Gezondheidszorgonderzoek Ysselmond in Zwolle.

Competing interests: None declared.

Ethical approval: The study protocol was approved by the medical ethics committee of the Isala Clinics, Zwolle.

- 1 Bisno AL, Gerber MA, Gwaltney JM Jr, Kaplan EL, Schwartz RH, Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Clin Infect Dis* 2002;35:113-25.
- 2 Zwart S, Sachs APE, Ruijs GJHM, Gubbels JW, Hoes AW, de Melker RA. Penicillin for acute sore throat: randomised double blind trial of seven days versus three days treatment or placebo in adults. *BMJ* 2000;320:150-4.
- 3 Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *Cochrane Database Syst Rev* 2000;(4):CD000023.
- 4 Centor RM, Whitherspoon JM, Dalton HP, Brody ChE, Link K. The diagnosis of strep throat in adults in the emergency room. *Med Decis Making* 1981;1:239-46.
- 5 Dagnelie CF, Zwart S, Balder FA, Romeijnders ACM, Geijer RMM. *NHG Standard "Acute sore throat"*. Utrecht: Dutch College of General Practitioners, 2002. <http://nhg.artsennet.nl/guidelines2/E11.htm> (accessed 21 Nov 2003).
- 6 Scottish Intercollegiate Guidelines Network. *Guideline 34: management of sore throat and indications for tonsillectomy*. Edinburgh: Royal College of Physicians, 2001. www.sign.ac.uk/guidelines/fulltext/34/summary.html (accessed 17 Nov 2003).
- 7 Zwart S, Ruijs GJHM, Sachs APE, van Leeuwen WJ, Gubbels JW, de Melker RA. Beta-haemolytic streptococci isolated from acute sore-throat patients: cause or coincidence? A case-control study in general practice. *Scand J Infect Dis* 2000;32:377-84.
- 8 Begovac J, Bobinac E, Benic B, Desnica BB, Maretic T, Basnec A, et al. Asymptomatic pharyngeal carriage of beta-hemolytic streptococci and streptococcal pharyngitis among patients at an urban hospital in Croatia. *Eur J Epidemiol* 1993;9:405-10.
- 9 Gunnarsson RK, Holm SE, Söderström M. The prevalence of beta-hemolytic streptococci in throat specimens from healthy children and adults. Implications for the clinical value of throat cultures. *Scand J Prim Health Care* 1997;15:149-55.
- 10 Zwart S, Ruijs GJHM, Sachs APE, Schellekens JFP, de Melker RA. Potentially virulent strains and high colony counts of group A beta-haemolytic streptococci in pharyngitis patients having a delayed recovery or a complication. *J Antimicrob Chemother* 2001;47:689-91.
- 11 Ruoff KL, Whitley RA, Beighton D. Streptococcus. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Tenover RH, eds. *Manual of clinical microbiology*. 7th ed. Washington: ASM Press, 1999:283-96.
- 12 Kaplan EL, Couser R, Ballard Huwe B, McKay C, Wannamaker LW. Significance of quantitative salivary cultures for group A and non-group A beta-hemolytic streptococci in patients with pharyngitis and in their family contacts. *Pediatrics* 1979;64:904-12.
- 13 Musumeci R, Bue CL, Milazzo I, Nicoletti G, Serra A, Speciale A, Blandino G. Internalization-associated proteins among *Streptococcus pyogenes* isolated from asymptomatic carriers and children with pharyngitis. *Clin Infect Dis* 2003;37:173-9.

(Accepted 21 October 2003)

bmj.com 2003;327:1324

Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Stratenum 6.131, PO Box 85060, 3508 AB Utrecht, Netherlands
 Sjoerd Zwart *general practitioner*
 Maroeska M Rovers *clinical epidemiologist*
 Ruut A de Melker *emeritus professor of general practice*
 Arno W Hoes *professor of clinical epidemiology*
 Correspondence to: S Zwart
 S.Zwart@med.uu.nl

Commentary: More valid criteria may be needed

Paul Little

Zwart et al¹ provide a welcome addition to the efficacy literature since a systematic review reports data from only three double blind studies among children and few from typical primary care settings.² The study shows that—among a selected group of more unwell children (with two of the Centor criteria: absence of cough, history of fever, cervical nodes, and purulent pharynx)—antibiotics do not help symptomatically but may reduce imminent quinsy, impetigo, or scarlet fever.

There are several reasons to support the authors' reluctance to advocate immediate antibiotics, even in this more unwell subgroup. The study was not powered a priori to detect

deterioration of illness, hence secondary findings must be treated with some caution. Furthermore antibiotics did not prevent true major complications (such as rheumatic fever, quinsy) but the worsening illness (mainly "imminent quinsy"), and all cases resolved with further antibiotics and without admission. Finally efficacy trials with close follow up probably improve compliance and effect sizes compared with routine practice, where half of the medication is not taken. If the study findings can be generalised to everyday practice it means that seven children with two out of four of the Centor criteria would have to be treated to prevent one case of worsening of illness, with the asso-

ciated disadvantages of side effects, reduced local and systemic immunity, and the cycle of recurrence.³⁻⁶

What evidence do we need to move practice forward? The study highlights two key questions around the targeting of antibiotics.

Firstly, are the Centor criteria valid? They were developed to predict the presence of streptococci, but with high asymptomatic carriage rates (particularly in children) this study highlights that predicting the presence of bacteria is not enough, particularly for infections of the upper respiratory tract.⁷ We therefore need to develop criteria based on immunological evidence of infection.⁷ It is also unclear what cut-off point should be used—in adults three out of the four criteria are normally used, but in this study only two were used.

Secondly, do the criteria predict benefit from treatment? The next step is—either with the Centor criteria or with more valid criteria—to assess benefit among subgroups in a large, adequately powered trial. We therefore need to show whether antibiotics selectively predict benefit, either symptomatically or for complications, among people who meet the Centor criteria, and what cut-off in the criteria should be used.

Until such evidence is available, what should clinicians do? It would be reasonable to share the results of this study—that seven children with the Centor criteria need to be treated to prevent worsening illness in one child—with parents. If parents were keen to have antibiotics the case would still be very strong for offering

delayed antibiotics for children with two out of the four Centor criteria, since in unwell children a delayed prescribing strategy (waiting for 48 hours, rather than the normal five days) in three placebo controlled trials for patients with streptococcal pharyngitis did not result in complications.⁴⁻⁶

Competing interests: PL has received consultancy fees for two half day meetings in the past two years on the role of antibiotics in preventing complications of lower respiratory tract infections that were funded by Abbott Pharmaceuticals.

- 1 Zwart S, Roevers MM, de Melker RA, Hoes AW. Penicillin for acute sore throat in children: randomised, double blind trial. *BMJ* 2003;327:1324-7.
- 2 Del Mar C, Glaziou P, Spinks A. Antibiotics for sore throat. *Cochrane Database Syst Rev* 2000;(2):CD000023. Update in: *Cochrane Database Syst Rev* 2000;(4):CD000023.
- 3 Roos K, Holm S, Grahn-Hakansson E, Lagergren L. Recolonization with selected alpha streptococci for prophylaxis of recurrent streptococcal pharyngotonsillitis. *Scand J Infect Dis* 1996;28:459-62.
- 4 Gerber M, Randolph M, DeMeo K, Kaplan E. Lack of impact of early antibiotic therapy for streptococcal pharyngitis on recurrence rates. *J Pediatr* 1990;117:853-8.
- 5 Pichichero ME, Disney F, Talpey W, Green J, Francis A, Roghmann K, et al. Adverse and beneficial effects of immediate treatment of group A beta haemolytic streptococcal pharyngitis. *Ped Inf Dis J* 1987;6:635-43.
- 6 El-Daher N, Hijazi S, Rawashdeh N, Al-Kalil I, Abu-Ektaish F, Abdel-Latif D. Immediate versus delayed treatment of Group A beta-haemolytic streptococcal pharyngitis with penicillin V. *Ped Inf Dis J* 1991;10:126-30.
- 7 Del Mar C. Managing sore throat: a literature review I: Making the diagnosis. *Med J Austr* 1992;156:572-5.

University of Southampton, Aldermoor Health Centre, Southampton SO16 55T
Paul Little *professor of primary care research*
ps13@soton.ac.uk