Predictors of poor outcome and benefits from antibiotics in children with acute otitis media: pragmatic randomised trial

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Abstract

Objectives To identify which children with acute otitis media are at risk of poor outcome and to assess benefit from antibiotics in these children.
Design Secondary analysis of randomised controlled trial cohort.
Setting Primary care.
Participants 315 children aged 6 months to 10 years.
Intervention Immediate or delayed (taken after 72 hours if necessary) antibiotics.
Main outcome measure Predictors of short term outcome: an episode of distress or night disturbance three days after child saw doctor.
Results Distress by day three was more likely in children with high temperature (adjusted odds ratio 4.5, 95% confidence interval 2.3 to 9.0), vomiting (2.6,1.3 to 5.0), and cough (2.0, 1.1 to 3.8) on day one. Night disturbance by day three was more likely with high temperature 2.4 (1.2 to 4.8), vomiting (2.1,1.1 to 4.0), cough (2.3,1.3 to 4.2), and ear discharge (2.1, 1.2 to 3.9). Among the children with high temperature or vomiting, distress by day three was less likely with immediate antibiotics (32% for immediate *v* 53% for delayed, $\chi^2 = 4.0$; P=0.045, number needed to treat 5) as was night disturbance (26% *v* 59%, $\chi^2 = 9.3$; P=0.002; number needed to treat 3). In children without higher temperature or vomiting, immediate antibiotics made little difference to distress by day three (15% *v* 19%, $\chi^2 = 0.74$; P=0.39) or night disturbance (20% *v* 27%, $\chi^2 = 1.6$; P=0.20). Addition of cough did not significantly improve prediction of benefit.
Conclusion In children with otitis media but without fever and vomiting antibiotic treatment has little benefit and a poor outcome is unlikely.

Introduction

Although otitis media is one of the most common acute respiratory conditions managed in primary care, its treatment is controversial.[1–3] Most children will be prescribed antibiotics, but systematic review suggests that there is only marginal benefit.[4] An estimated 18 children have to be treated for one child to benefit from resolution of symptoms during the next week. The effect of prescribing antibiotics on beliefs and expectations for antibiotics is also important as prescribing for all children is likely to encourage attendance in future episodes, increase pressure on doctors to prescribe, increase antibiotic use,[5–8] and increase antibiotic resistance.[3 9]

If antibiotics are not to be prescribed initially then what alternatives exist? Evidence from a cohort of 5000 children aged 2-12 years from the Netherlands shows that waiting for 72 hours with just treatment for symptoms is safe, but a blanket approach may have dangers. In the Dutch study the only child to develop mastoiditis was not given antibiotics after 72 hours despite remaining unwell.[10] A recent trial that compared immediate with delayed antibiotics showed that for most children the benefit with immediate antibiotics was only marginal with no significant difference in pain or distress scores.[11] Another study has shown that parents find the approach of delayed use acceptable.[12] We still do not know, however, whether there are children particularly at risk of poor short term outcome and whether they would benefit from treatment.

We determined the predictors of outcome from a randomised trial in primary care and assessed whether these predictors identify those children who are likely to benefit from immediate antibiotics.

Methods

This study was part of a pragmatic randomised controlled trial of two prescribing strategies for acute otitis media, the methods of which have previously been reported in full.[11]

Sample

The participants were children aged 6 months to 10 years who were brought to their general practitioner with acute otalgia and otoscopic evidence of acute inflammation (dullness, cloudiness, erythema or bulging, perforation). When children were too young for otalgia to be documented from the history (under 3 years old) otoscopic evidence only was sufficient. Coloured photographs were provided to guide general practitioners in diagnosis.

Exclusion criteria were otoscopic appearance consistent with crying or fever alone (pink drum); appearance and history more suggestive of otitis media with effusion and chronic suppurative otitis media; serious

chronic disease (for example, cystic fibrosis, valvular heart disease); use of antibiotics for ear infections within the previous two weeks; previous complications (septic complications, hearing impairment); child too unwell to be left to wait and see (very unwell systemically with high fever, floppy, drowsy, not responding to antipyretics).

We calculated the sample size for 80% power and 95% confidence using the Nquery sample size program. To detect a risk factor with an odds ratio of 2.5 for poor outcome where a minority of children suffer poor outcome (25%) and where between 33% and 66% of children have the risk factor required data from 280 children.

Intervention

Children were randomised when the doctor opened a sealed numbered opaque envelope containing an advice sheet for one of two groups. The groups were immediate antibiotics (amoxicillin or erythromycin for those allergic to penicillin) or delayed antibiotics. In the delayed antibiotics group parents were asked to wait for 72 hours after seeing the doctors before considering using the prescription. They were advised to use antibiotics if their child had severe otalgia or fever after 72 hours or if discharge lasted for 10 days or more. We used standardised advice sheets to maximise the support and placebo effect for each strategy and to ensure some consistency between groups, despite the personal prescribing preference of the doctor.[5 6 11]

Outcome measurement

The general practitioners recorded days of illness, physical signs, and antibiotic prescription. Parents used daily diaries to record the children's symptoms (earache, unwell, sleep disturbance), perceived severity of pain (from 1 (no pain) to 10 (extreme pain)), number of episodes of distress, number of 5 ml doses of paracetamol used, and temperature (using a single use thermometer (TempaDot)[13]) and presence of cough, vomiting, rash, and diarrhoea. We have shown the diary outcomes to be both reliable and valid.[11]

Analysis

We assessed predictors of poor outcome using logistic regression. We then entered variables that were significant in univariate analysis at the 5% level by forward selection, starting with the most significant first, and retained those that remained significant at the 5% level. We then used variables that predicted poor outcome to identify clinical subgroups, estimated the effect of antibiotic in those subgroups (by χ^2), and summarised the effect by the number needed to treat.

Results

Symptom duration was documented in 285 children (90%). Parents returned diaries for 219 (70%) children. We obtained information by phone about duration of symptoms on a further 66 (20%) children. There were no differences in clinical characteristics between non-responders and responders.[11]

Table 1 Predictors of poor outcome (earache lasting more than three days after seeing doctor) in children with acute otitis media. Figures are numbers (percentage) of children*

	Earache	No earache	Crude odds ratio (95% CI)	Adjusted odds ratio† (95% CI)‡	P value‡
Symptoms and signs					
High temperature	22 (23)	23 (12)	2.10 (1.10 to 4.01)	1.23 (0.57 to 2.59)	0.61
Vomiting	21 (22)	33 (18)	1.30 (0.70 to 2.39)	0.92 (0.45 to 1.85)	0.81
Cough	60 (62)	115 (61)	1.02 (0.62 to 1.70)	0.92 (0.52 to 1.63)	0.78
Ear discharge	35 (36)	38 (20)	2.23 (1.29 to 3.85)	2.55 (1.38 to 4.69)	0.003
Red drum	77 (80)	148 (80)	1.04 (0.56 to 1.93)	1.06 (0.53 to 2.16)	0.86
Bulging drum	48 (51)	85 (46)	1.23 (0.75 to 2.01)	1.27 (0.73 to 2.23)	0.39
Clinical features					
Age ⩽3 years	31 (32)	82 (44)	0.60 (0.36 to 1.01)	0.57 (0.32 to 1.03)	0.062
Previous epiodes of respiratory tract infection:					
0	21 (25)	26 (16)	1	1	0.63
1	23 (27)	29 (18)	0.98 (0.44 to 2.17)	1.02 (0.44 to 2.41)	
2	14 (16)	38 (23)	0.46 (0.20 to 1.06)	0.60 (0.24 to 1.53)	
⩾3	27 (32)	72 (44)	0.46 (0.22 to 0.96)	0.72 (0.26 to 2.00)	
Prescription for antibiotics in previous year:					
0	43 (51)	61 (37)	1	1	0.001
1	26 (31)	46 (28)	0.80 (0.43 to 1.49)	0.76 (0.40 to 1.45)	<0.001§
2	11 (13)	29 (18)	0.54 (0.24 to 1.19)	0.48 (0.21 to 1.11)	
⩾3	5 (6)	29 (18)	0.24 (0.09 to 0.68)	0.15 (0.05 to 0.46)	
Satisfaction and communication					
Satisfied:					
Extremely	29 (30)	65 (36)	1	1	0.04
Very	49 (52)	95 (52)	1.16 (0.66 to 2.02)	1.57 (0.83 to 2.96)	0.015§
Moderately	19 (20)	12 (12)	1.85 (0.88 to 3.92)	2.98 (1.25 to 7.13)	
Worries dealt with:					
Extremely well	31 (32)	66 (36)	1	1	0.75
Very well	52 (54)	100 (55)	1.11 (0.64 to 1.90)	0.74 (0.33 to 1.64)	
Moderately	14 (14)	17 (9)	1.75 (0.77 to 4.00)	0.75 (0.18 to 3.05)	

*Denominators vary due to missing values.
†Adjusted for other significant predictors of outcome.
‡Based on likelihood ratio test.
§Trend, z test.

Table 2 Predictors of episodes of distress by day three in children with acute otitis media. Figures are numbers (percentage) of children*

	Distressed	Not distressed	Crude odds ratio (95% CI)	Adjusted odds ratio† (95% CI)‡	P value‡
Symptoms and signs					
High temperature on day 1 (>37.5°C)	24 (33)	21 (10)	4.56 (2.34 to 8.85)	4.54 (2.28 to 9.03)	>0.001
Vomiting	23 (32)	31 (15)	2.74 (1.47 to 5.12)	2.56 (1.32 to 4.95)	0.006
Cough	54 (75)	120 (57)	2.30 (1.26 to 4.19)	2.02 (1.07 to 3.80)	0.025
Ear discharge	22 (31)	51 (24)	1.39 (0.77 to 2.51)	1.24 (0.65 to 2.40)	0.52
Red drum	55 (76)	169 (81)	0.77 (0.40 to 1.46)	0.82 (0.41 to 1.65)	0.58
Bulging drum	36 (50)	97 (46)	1.15 (0.68 to 1.97)	1.14 (0.64 to 2.03)	0.66
Clinical features					
Previous episodes of respiratory tract infection:					
0	10 (16)	36 (19)	1	1	0.95
1	16 (26)	36 (19)	1.60 (0.64 to 4.00)	1.32 (0.49 to 3.54)	
2	12 (19)	40 (21)	1.08 (0.42 to 2.80)	1.19 (0.43 to 3.30)	
3	24 (39)	75 (40)	1.15 (0.50 to 2.66)	1.07 (0.44 to 2.61)	
Age ≤3 years	26 (36)	87 (42)	0.79 (0.46 to 1.38)	0.59 (0.32 to 1.08)	0.084
Communication and satisfaction					
Worries dealt with:					
Extremely well	21 (29)	76 (37)	1	1	0.16
Very well	39 (54)	112 (54)	1.26 (0.69 to 2.31)	1.23 (0.64 to 2.35)	0.08§
Moderately well	12 (17)	19 (9)	2.29 (0.96 to 5.45)	2.53 (0.99 to 6.46)	
Satisfied:					
Extremely	22 (31)	72 (35)	1	1	0.56
Very	35 (49)	108 (52)	1.06 (0.58 to 1.95)	1.05 (0.55 to 2.01)	0.37§
Moderately	15 (21)	27 (13)	1.82 (0.82 to 4.01)	1.57 (0.66 to 3.75)	

*Denominators vary due to missing values.
†Adjusted for other significant predictors of outcome.
‡Likelihood ratio test.
§Trend, z test.

Tables 1, 2, and 3 show predictors of poor outcome (prolonged duration of symptoms). Predictors of earache lasting for more than three days were ear discharge, previous antibiotic treatment, and satisfaction with the consultation. However for children whose symptoms lasted over 72 hours earache was mostly mild (mean score 2.6), and interviews with parents suggested the outcomes that matter more to them are night time disturbance and episodes of distress. Distress by day three was predicted by higher temperature (>37.5°C) recorded by parents on day one, parental reporting of vomiting, and cough (table 2). Although prescription of antibiotics may confound these associations, this is unlikely as we have shown

Table 3 Predictors of disturbed nights by day three in children with acute otitis media. Figures are numbers (percentage) of children*

	Disturbed nights	Nights not disturbed	Crude odds ratio (95% CI)	Adjusted odds ratio† (95% CI)‡	P value‡
Symptoms and signs					
High temperature on day 1 (>37.5°C)	22 (26)	23 (12)	2.63 (1.37 to 5.04)	2.43 (1.23 to 4.81)	0.01
Vomiting	26 (30)	28 (14)	2.65 (1.44 to 4.87)	2.09 (1.09 to 3.99)	0.027
Cough	64 (74)	111 (56)	2.31 (1.32 to 4.04)	2.29 (1.26 to 4.15)	0.005
Ear discharge	31 (36)	42 (21)	2.11 (1.21 to 3.68)	2.13 (1.17 to 3.90)	0.014
Red drum	69 (80)	156 (80)	1.04 (0.55 to 1.96)	1.06 (0.55 to 2.08)	0.85
Bulging drum	39 (45)	94 (48)	0.90 (0.54 to 1.50)	0.87 (0.51 to 1.59)	0.61
Clinical features					
Previous episodes of respiratory tract infection:					
0	8 (11)	39 (22)	1	1	0.073
1	22 (29)	30 (17)	3.58 (1.40 to 9.14)	3.60 (1.34 to 9.65)	
2	14 (18)	38 (22)	1.80 (0.68 to 4.77)	1.94 (0.70 to 5.40)	
3	32 (42)	67 (39)	2.33 (0.98 to 5.55)	2.06 (0.83 to 5.13)	
Age ≤3 years	41 (48)	72 (37)	1.57 (0.94 to 2.62)	1.35 (0.78 to 2.33)	0.28
Communication and satisfaction					
Worries dealt with:					
Extremely well	27 (31)	70 (36)	1	1	0.52
Very well	47 (55)	105 (54)	1.16 (0.66 to 2.04)	1.14 (0.63 to 2.07)	
Moderately	12 (14)	19 (10)	1.64 (0.70 to 3.82)	1.70 (0.69 to 4.17)	
Satisfied:					
Extremely	24 (28)	70 (36)	1	1	0.25
Very	44 (51)	100 (52)	1.28 (0.72 to 2.30)	1.26 (0.68 to 2.34)	
Moderately	18 (21)	24 (12)	2.19 (1.02 to 4.71)	2.00 (0.89 to 4.53)	

*Denominators vary due to missing values.
†Adjusted for other significant predictors of outcome.
‡Based on likelihood ratio test.

that randomisation group did not predict distress.[11] Furthermore when we added randomisation group to the logistic model predicting distress, the estimates of all the predictive variables changed by less than 10% (odds ratios were 4.9 for temperature, 2.3 for vomiting, 2.1 for cough)—that is, they were not significantly confounded by parental perceptions resulting from being prescribed immediate antibiotics. Night disturbance by day three was predicted by higher temperature recorded on day one, vomiting, cough, and ear discharge (table 3).

We found that the predictive ability of not recording temperature and low recording of temperature were equivalent: not recording temperature (odds ratio 1.0) had the same risk of predicting distress as low temperature (odds ratio 1.0) and use of the three level variable (higher recorded temperature, lower temperature, temperature not recorded) did not alter the estimates either of the effect of higher temperature (odds ratio 4.5) nor the estimates for the other variables (vomiting 2.6; cough 2.0)—that is, identical to using the two level variable shown in table 2. Thus for simplicity and to maximise power to assess the predictive value of other variables (that is, by not excluding parents who did not record temperature) we used a two level variable (parents recorded higher temperature; no recording of higher temperature).

Children with a high temperature or vomiting were more likely to have poor outcomes by day three (table 4). These children represent the simplest way to target antibiotics for clinicians and are a small minority. Immediate antibiotics resulted in less distress, fewer disturbed nights, and fewer days of crying. Children without higher temperature or vomiting on day one showed less benefit from immediate antibiotics (table 5). Cough also predicted distress and night disturbance by day three. Thus a simple alternative to targeting those with high temperature or vomiting could be to target children with two of the three symptoms: high temperature, vomiting, and cough. However, addition of cough to the symptom count made little difference to the ability to predict benefit from immediate antibiotics.

Discussion

Using data from a randomised controlled trial we found that children with a raised temperature and vomiting were more likely to be distressed or have disturbed nights three days after seeing the doctor and more likely to benefit from immediate antibiotic prescription.

Table 4 Outcome by day three children with otitis media in according to immediate or delayed treatment with antibiotics. Figures are numbers (percentage) of children

	Immediate	Delayed	P value	NNTB (95% CI)
Children with high temperature or vomiting*				
Distress	21 (32)	27 (53)	0.045	5 (2 to 83)
Disturbed nights	10 (26)	30 (59)	0.002	3 (2 to 8)
Children without high temperature or vomiting*				
Distress	14 (15)	19 (19)	0.39	22 (7 to ∞ to NNTH 17)
Disturbed nights	19 (20)	20 (27)	0.20	13 (5 to ∞ to NNTH 24)
Children with two of three symptoms† on day 1				
Distress	11 (39)	22 (55)	0.20	6 (3 to ∞ to NNTH 12)
Disturbed nights	9 (32)	26 (65)	0.008	3 (2 to 10)

NNTB=number needed to treat to benefit; NNTH=number needed to treat to harm.
*Temperature as measured on day 1, vomiting on any day.
†High temperature, vomiting, cough.

Study limitations

General practitioners who did not recruit many participants were more unsure about recruiting younger children and those with perforation.[11] However, the impact on the results is likely to be minimal as neither age nor perforation predicted the main outcomes of interest (night disturbance and distress by day three). There was no evidence of significant differences in the characteristics of those who did not provide information compared with those who did.

We chose an open trial design and minimally intrusive outcomes (for example, no intrusive measures of compliance or investigation) to assess realistic outcomes after pragmatic prescribing strategies in everyday practice. However, this has the disadvantage of a potential placebo effect. Although a structured advice sheet approach has been shown to reduce the placebo effect,[5] a component of this effect may contribute to the apparent benefits from antibiotics. Any effect, however, was probably small: parental satisfaction with management did not predict distress and night disturbance, and adjustment for satisfaction or randomisation group did not did not confound the estimates nor alter the inferences. Furthermore the estimates from this study (for example, night disturbance, consumption of paracetamol)[11] were similar to those in the previous largest placebo controlled trial in primary care in a similar study population.[14]

Predictors of poor outcome and benefit

Parents are most concerned about symptoms such as distress and night disturbance, both of which were predicted by systemic features (high temperature, vomiting) and cough.

The simplest method to target the minority of children at higher risk of poor outcome is to select those children with systemic features—that is, either high

Table 5 Outcome in children with otitis media in week after seeing doctor according to immediate or delayed use of antibiotics. Figures are means (SE)

	Immediate	Delayed	Difference (95% CI)	P value	
				t test	Mann-Whitney
Children with high temperature or vomiting on day 1					
Days of crying	1.58 (0.15)	2.82 (0.24)	1.24 (0.68 to 1.81)	<0.001	<0.001
Disturbed nights	1.95 (0.23)	2.98 (0.26)	1.03 (0.35 to 1.72)	0.004	0.005
Episodes of distress*	0.94 (0.12)	1.34 (0.22)	0.40 (–0.10 to 0.90)	0.11	0.71
Children without high temperature or vomiting on day 1					
Days of crying	1.53 (0.13)	1.93 (0.21)	0.40 (–0.09 to 0.89)	0.11	0.47
Disturbed nights	1.52 (0.15)	2.03 (0.21)	0.51 (0.05 to 1.02)	0.05	0.10
Episodes of distress*	0.61 (0.08)	0.55 (0.07)	–0.06 (–0.27 to 0.15)	0.59	0.50

*Average per day.

temperature or vomiting. This identifies children who are likely to benefit (number need to treat of 3-6 compared with 13 to 22 in children without such features). Although cough also predicted poor outcome, addition of cough to the clinical score did not improve the ability to predict benefit from antibiotics. Thus children without systemic features are unlikely to benefit from antibiotics. Whether it is worth treating children with systemic features immediately is debatable as many such children (about half) will still settle within 72 hours. Nevertheless, the results support doctors discussing the likely benefit of antibiotics in systemically unwell children and possibly shortening the delay period from 72 hours to 48 or 24 hours.

Conclusion

As these data are based on secondary analysis they require cautious interpretation. However, they indicate that children without systemic features (higher temperature or vomiting) are unlikely to have poor short term outcome. Immediate use of antibiotics is unlikely to make a difference to outcomes in such children.

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1 Bain J. Childhood otalgia: acute otitis media. 2. Justification for antibiotic use in general practice. *BMJ* 1990;300:1006-7.
2 Browning G. Childhood otalgia: acute otitis media. 1. Antibiotics not necessary in most cases. *BMJ* 1990;300:1005-6.
3 Froom J, Culpepper L, Jacobs M, DeMelker RA, Green LA, van Buchem L, et al. Antimicrobials for acute otitis media? A review from the international primary care network. *BMJ* 1997;315:98-102.
4 Glasziou P, Del Mar C, Sanders S, Hayem M. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* 2002;(1):CD000219.

What is already known on this topic

Most children with otitis media will not benefit symptomatically from immediate use of antibiotics

It is unclear which children are more likely to benefit from antibiotics and which features predict poor outcome

What this study adds

Children with high temperature or vomiting were more likely to be distressed or have night disturbance three days after seeing the doctor

Children with high temperature or vomiting were more likely to benefit from antibiotics, although it is still reasonable to wait 24-48 hours as many children will settle anyway

Children without high temperature or vomiting were unlikely to have poor outcome and unlikely to benefit from immediate antibiotics

5 Little PS, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat. *BMJ* 1997;314:722-7.
6 Little PS, Gould C, Williamson I, Warner G, Gantley M, Kinmonth AL. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ* 1997;315:350-2.
7 Britten N, Ukoumunne O. The influence of patients' hopes of receiving a prescription on doctors' perceptions and the decision to prescribe: a questionnaire survey. *BMJ* 1997;315:1506-10.
8 MacFarlane J, Holmes W, MacFarlane R, Britten N. Influence of patients' expectations on antibiotics management of acute lower respiratory illness in general practice: questionnaire study. *BMJ* 1997;315:1211-4.
9 Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. *BMJ* 1996;313:387-91.
10 van Buchem FL, Peeters MF, Van't Hof MA. Acute otitis media a new treatment strategy. *BMJ* 1985;290:1033-7.
11 Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for acute otitis media. *BMJ* 2001;322:336-42.
12 Pitts J. Shared decision-making in the informed treatment of acute otitis media. *Practitioner* 1987;231:1232-3.
13 Rogers M. A viable alternative to the glass/mercury thermometer. *Paediatr Nurs* 1992;4:8-11.
14 Burke P, Bain J, Robinson D, Dunleavey J. Acute red ear in children: controlled trial of non-antibiotic treatment in general practice. *BMJ* 1991;303:558-62.

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Commentary: research directions for treatment for acute otitis media

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Some children are greatly troubled with acute otitis media; others are hardly inconvenienced. This useful subgroup analysis predicts which children benefit most from antibiotics for acute otitis media (mostly those with a temperature >37.5°C or vomiting; about one in five affected children) and the size of the benefit (the number of children we need to treat to shorten the illness is as high as three to six). So we still need to weigh potential benefits against costs, case by case, mixing parental preference and other relevant clinical and psychosocial information into the clinical decision.

General practitioners may worry about withholding antibiotics because of past indoctrination with deductive pathophysiology ("the pain of otitis media is caused by infection in the middle ear, the causative agents are susceptible to the following antibiotics..."). The empirical evidence, however, is that antibiotics make little difference. They may also worry about the risk of dangerous suppurative complications. Should another study be undertaken to address this? There are so few cases of acute mastoiditis, the most common complication, that such an analysis would require huge numbers. Data from a large observational study of 4860 cases of acute otitis media showed that initially withholding antibiotics from those without severe symptoms led to no extra cases of mastoiditis.[1]

Could this study be the end of the story? We don't think so. Firstly, there remain problems with the outcomes measured. We are interested in two vectors of illness in spontaneously remitting illness: the duration of illness (which Little et al measured) and its severity. Severity is harder to measure. Together severity and duration give a measure of "severity days" that more accurately describes the impact of the illness. Measuring changes on just one axis will considerably underestimate the effect of an intervention on the burden of illness. Future research should collect serial data on severity to estimate changes in "total illness."[2]

Secondly, for trials of a new intervention the control is usually nothing (placebo). But for trials of antibiotics for acute respiratory infections the established treatment is already antibiotics. These then are trials of "no antibiotics" (the "new" intervention) against "antibiotics." Therefore patients recruited are likely to be the least ill. Re-examining the trials in a Cochrane review[3] we could extract this "non-recruitment because the child was too ill" out of the total recruited from only two of the seven trials (52/232 and 27/240). We need a greater understanding of how selection of patients for trials may affect the interpretation and application of results.

We also have surprisingly little information about alternative treatments. With spontaneously remitting illnesses such as acute otitis media, killing bacteria ("cure") has no advantage over palliating the symptoms.[2] We know that antihistamines and decongestants contribute modest, if any, benefit.[4] But which is the best analgesic? Is anything else helpful? Innovative emerging treatments, such as using benign commensals to overwhelm pathological bacteria, may ultimately prove the most effective treatment for acute otitis media[5] and make the current debate over antibiotic use redundant.

1 van Buchem FL, Peeters MF, van't Hof MA. Acute otitis media: a new treatment strategy. *BMJ* 1985;290:1033-7.
2 Del Mar C. Spontaneously remitting disease. Principles of management. *Med J Aust* 1992;157:101-7.
3 Glasziou PP, Del Mar CB, Hayem M, Sanders SL. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* 2002;(1):CD000219.
4 Flynn CA, Griffin G, Tudiver F. Decongestants and antihistamines for acute otitis media in children. *Cochrane Database Syst Rev* 2002;(1):CD001727.
5 Roos K, Håkansson EG. Holm S. Effect of recolonisation with"interfering"alpha streptococci on recurrences of acute and secretory otitis media in children: randomised placebo controlled trial. *BMJ* 2001;322:1-4.

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