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Impact of acute otitis media clinical practice guidelines on antibiotic and analgesic prescriptions: a systematic review

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ABSTRACT

Background Clinical practice guidelines focusing on judicious use of antibiotics for childhood acute otitis media (AOM) have been introduced in many countries around the world.

Objective To systematically review the effects of these guidelines on the prescription of antibiotics and analgesics for children with AOM.

Methods Systematic searches of PubMed, Embase and Cochrane Library from inception to 6 June 2017 using broad search terms. Studies specifically aimed at evaluating the effects of introduction of national AOM practice guidelines on type of antibiotic and/or analgesic prescriptions were included, irrespective of design, setting or language. The Risk Of Bias In Non-randomized Studies of Interventions tool was used to assess risk of bias.

Results Of 411 unique records retrieved, seven studies conducted in six different countries (France, Italy, Spain, Sweden, UK and USA (twice)) compared data before and after guideline introduction. All studies had an observational design, using longitudinal data of children aged under 15 years (n=200–4.6 million) from either routine care, insurance databases or electronic surveys. Risk of bias of all studies was judged serious to critical. Of the five studies reporting on antibiotic prescription rates, three showed a decline of 5%–12% up to 3 years after guideline introduction and two found no or negligible effect. In one US study, the initial 9% decline decreased to 5% after 4–6 years. The recommended first choice antibiotic was prescribed more frequently (9%–58% increase) after guideline introduction in four out of five studies reporting on this outcome. Analgesic prescription rates for AOM were reported in one US study and increased from 14% to 24% after guideline introduction.

Conclusion Based upon what is published, the effects of introduction of national clinical practice guidelines on antibiotic and analgesic prescribing for children with AOM seem modest at the most.

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INTRODUCTION

With emerging antimicrobial resistance posing a serious threat to global public health, promoting judicious use of antibiotics has become a top priority for governments worldwide. As a consequence, clinical practice guidelines for common infectious diseases, including acute otitis media (AOM), have been introduced and updated in many countries over the past decades.[1] Although AOM guidelines vary regarding specific recommendations across countries, they generally emphasise the importance of accurate diagnosis and adequate analgesia as well as advocating selective antibiotic prescribing.[1]

It has been suggested that guideline adherence for AOM may be suboptimal[2] due to a variety of factors, such as fear of serious complications and parental pressure to prescribe antibiotics.[3] In daily practice, antibiotics are commonly prescribed to children with AOM, ranging from around 50% in the Netherlands[4] to 80% in the USA,[5] whereas analgesics are only recommended in a minority of cases.[6]

However, the true impact of introducing AOM guidelines on prescription of antibiotics and analgesics for children with AOM in daily practice has not been reviewed systematically. We aim to do so and provide an overview of current available studies that compare prescription data before and after national AOM clinical practice guideline introduction.

METHODS

Search strategy and study selection

We performed systematic searches of the PubMed, Embase and Cochrane Library databases from inception to 6 June 2017 using database-specific syntaxes of keywords relevant to 'acute otitis media' and 'guidelines' (see online supplementary for full search strategies). After removing duplicates (RefWorks), two reviewers (YD and RTvU) independently screened titles and abstracts for inclusion. Discussion with a third and fourth reviewer (MLAdH and RPV) resolved any discrepancies. We screened reference lists of included studies for additional studies.

We included all original studies, irrespective of design, setting or language, evaluating the effects of the introduction of national clinical practice guidelines on prescription of antibiotics (rate and type) and/or analgesics for children (up to the age of 16 years) with AOM by comparing data before and after guideline introduction. We only included studies in which the time between data collection before and after guideline introduction was less than 5 years; this was to minimise the impact of other factors that may affect AOM epidemiology and subsequent prescription rates, for example, the introduction of pneumococcal conjugate vaccines and anti-smoking campaigns.

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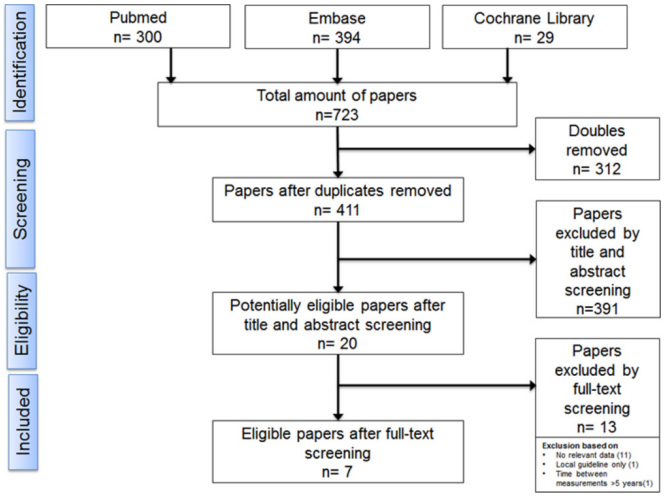

Figure 1 Flow chart.

Data extraction and synthesis

The primary outcome of interest was the overall antibiotic prescription rate for AOM. Secondary outcomes included type of antibiotic prescribed and analgesic prescription rate.

Two review authors (YD and RTvU) independently extracted the following data from the included studies: characteristics of study (year, country, design, setting and data source), study population (number and age of children with AOM), guideline details (date of introduction, method of dissemination and management recommendations) and data on our predefined outcomes. Discussion with a third and fourth reviewer (MLAdH and RPV) resolved any discrepancies. To obtain further information on guideline dissemination strategies, we contacted authors of the original publications as well as clinical scientists involved in guideline development in countries subject to this review.

Methodological quality of the included studies was assessed by three reviewers independently (YD, RTvU and RPV) using 'The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool',[7] and any discrepancies were resolved by discussion.

Antibiotic prescription rates, type of antibiotic and analgesic prescription rates before and after introduction of the AOM clinical practice guideline were presented for each study individually. Where before and after guideline introduction data were reported for individual years or subgroups, (such as age), we aimed to calculate averages.

RESULTS

Search results and study characteristics

Figure 1 shows the search results; 20 of the 411 unique records were considered potentially relevant. Of these, seven studies[8–14] were suitable for inclusion in this review. For detailed information of the included studies (see table 1); the seven studies were conducted in six countries: France, Italy, Spain, Sweden, UK and USA (two studies). All were observational studies using longitudinal data of children aged under 15 years; they differed substantially in terms of setting (primary vs secondary care), number of patients (n=200–4.6 million), study duration (6 months–10 years longitudinal data) and data source (routine care, insurance databases or electronic surveys).

Table 2 summarises the key guideline recommendations of the included studies. Detailed information on guideline dissemination strategies was obtained for Italy, Sweden, UK and USA (table 3). The method of dissemination varied considerably

Table 1 Baseline characteristics of included studies

Study ID	Country	Study design	Participants: Study population	Participants: Setting	Participants: Age	Data source	Time: Guideline introduction	Time: Years of follow-up	Outcomes reported
Tyrstrup *et al*[14]	Sweden	Observational	N=1 245 599*	PC	1–12 Y	Routine care	2010	Pre: 2008 Post: 2013	Antibiotic prescription rate Type of antibiotic
Palma *et al*[11]	Italy	Observational	N=4559 N_{pre}=2692 N_{post}=1867	SC	0–14 Y	Routine care	2010	Pre: 2007–2010 Post: 2011–2013	Antibiotic prescription rate Type of antibiotic
Levy *et al*[9]	France	Observational	N=14 661	SC	6 M–2 Y	Routine care	2011	Pre1: November 2009–October 2010 Pre2: November 2010–October 2011 Post: November 2011–October 2012	Type of antibiotic
McGrath *et al*[10]	USA	Observational	N=4 629 460	SC	3 M–12 Y	Insurance databases	2004	Pre: 2000–2003 Post1: 2005–2007 Post2: 2008–2011	Antibiotic prescription rate
Coco *et al*[8]	USA	Observational	N=1114 N_{pre}=584 N_{post}=530	PC+SC	6 M–12 Y	Electronic surveys	2004	Pre: January 2002–June 2004 Post: July 2004–December 2006	Antibiotic prescription rate Type of antibiotic Analgesic prescription rate
Thompson *et al*[13]	UK	Observational	N=464 845†	PC	3 M–15 Y	Routine care	2003 2004	Pre: 1999–2001 Post: 2005–2006	Antibiotic prescription rate
Rios *et al*[12]	Spain	Observational	N=200 N_{pre}=102 N_{post}=98	PC	2–15 Y	Routine care	2001	Pre: January–March 2000 Post: January–March 2002	Type of antibiotic

*Number of patient years.
†Number included in total study period of 17 consecutive years, no specific information on number of children over 1999–2001 and 2005–2006 periods.
M, months; N, number of patients; N/A, not available; PC, primary care setting; SC, secondary care setting; Y, years.

Table 2 Guideline recommendations in included studies

Study ID	Country	Year	Condition	Guideline recommendation (summary)	
Tyrstrup *et al*[14]	Sweden	2010	Children 1–12 years with uncomplicated AOM	First line	Wait-and-see for 3 days
				Second line	Penicillin V (first choice antibiotic)
Palma *et al*[11]	Italy	2010	Children >2 years with uncomplicated, non-severe AOM	First line	Analgesics, wait-and-see for 3 days
				Second line	First choice: high-dose amoxicillin (80–90 mg per kg per day) Second choice: cephalosporin
			Children 6 months–2 years with uncomplicated AOM Children >2 years with severe AOM*	First line	First choice: high-dose amoxicillin (80–90 mg per kg per day) Second choice: cephalosporin
Levy *et al*[9]	France	2011	Children >2 years with uncomplicated AOM	First line	Wait-and-see, reassessment after 48–72 hours
				Second line	High-dose amoxicillin (80–90 mg per kg per day)
			Children <2 years with uncomplicated AOM Children >2 years with severe AOM*	First line	High-dose amoxicillin (80–90 mg per kg per day)
				Second line	Amoxicillin/clavulanic-acid or cefpodoxime in case of treatment failure
McGrath *et al*[10]	USA	2004	Children >2 years with uncomplicated, non-severe AOM	First line	Analgesics, wait-and-see for 3 days
				Second line	First choice: high-dose amoxicillin (80–90 mg per kg per day) Second choice: cephalosporin
			Children 6 months–2 years with uncomplicated AOM Children >2 years with severe AOM*	First line	First choice: high-dose amoxicillin (80–90 mg per kg per day) Second choice: cephalosporin
Coco *et al*[8]	USA	2004	Children >2 years with uncomplicated, non-severe AOM	First line	Analgesics, wait-and-see for 3 days
				Second line	First choice: high-dose amoxicillin (80–90 mg per kg per day) Second choice: cephalosporin
			Children 6 months–2 years with uncomplicated AOM Children >2 years with severe AOM*	First line	First choice: high-dose amoxicillin (80–90 mg per kg per day) Second choice: cephalosporin
Thompson *et al*[13]	UK	2003 2004	Children >2 years with uncomplicated, non-severe AOM	First line	Analgesics, wait-and-see for 24–72 hours
				Second line	Amoxicillin thrice daily 125–250 mg, for 5 days Second choice: erythromycin, azithromycin or clarithromycin
			Children <2 years or severe AOM or recurrent infections	First line	Amoxicillin thrice daily 125–250 mg, for 5 days
Rios, *et al*[12]	Spain	2001	Children >6 months with uncomplicated AOM	First line	High-dose amoxicillin for a minimum of 5 days
				Second line	Amoxicillin/clavulanic-acid or ceftriaxone if no response within 48–72 hours
			Children <6 months with uncomplicated AOM Children >6 months with severe AOM	First line	Amoxicillin/clavulanic-acid or ceftriaxone
				Second line	Tympanocentesis and treatment according to results of Gram staining and antibiotic sensitivity

*Severe AOM is defined as moderate to severe otalgia with fever >39°C.
AOM, acute otitis media; N/A, not available.

across countries, ranging from passive dissemination through online publication or paper copies targeted at individual physicians only to extensive (public) media attention, interactive workshops and joint antibiotic stewardship campaigns.

Risk of bias assessment and study findings

Risk of bias was judged serious in six studies and critical in one; see figure 2. The primary and secondary outcome data are illustrated in figures 3 and 4. Two of the five studies reporting antibiotic prescription rates before and after guideline introduction showed no or a negligible effect. Three studies showed a decline of 5%–12% up to 3 years after guideline introduction.

One US study reported both the short- and long-term impact of guideline introduction; the decline of 9% in the first 3 years decreased to 5% after four to 6 years.

In four out of five studies reporting on the type of antibiotic prescribed, prescription of the recommended first choice antibiotic, either amoxicillin or penicillin V, increased by 9%–58% after guideline introduction, with inverse trends for amoxicillin/clavulanic acid which decreased by 7%–36%.

Only one US study reported on analgesic prescription rates; this increased from 14% before to 24% after guideline introduction.

DISCUSSION

The introduction of national AOM clinical practice guidelines seems to have at best a modest impact on antibiotic and analgesic prescribing; antibiotic prescription rates decrease by a maximum of 12% and analgesic rates increase by 10%. Its effect on the type of antibiotic is more substantial with an increase of up to 58% for the recommended first choice antibiotic.

In line with available literature,[15 16] results from the study of Tyrstrup *et al*[14] suggest that tailored guideline dissemination may have a larger impact on antibiotic prescription rates than passive dissemination only. Our findings also indicate that physicians find it easier to substitute rather than refrain from antibiotic prescribing. Reasons include their concerns about the risk of the child falling seriously ill when not prescribing antibiotics, or missing a diagnosis which would have been adequately treated with antibiotics.[17] This is especially the case when dealing with young children, or in consultations in which physicians perceive parental pressure to prescribe antibiotics.[17] Apparently, many physicians are either not convinced of, or unfamiliar with, the literature that refutes the risks of restrictive prescribing[18] and parental expectations of antibiotics.[3 17 19]

Table 3 Guideline dissemination efforts in included studies

Study ID	Country	Year	Online publication	Online self-care advice to the public	Hard copy dissemination	Public media campaigns	Newspapers	Workshops or lectures for physicians	Debates or round tables for physicians	Antibiotic stewardship campaigns*	Patient leaflet
Tyrstrup *et al*[14]	Sweden	2010	✓	✓		✓	✓	✓	✓	✓	✓
Palma *et al*[11]	Italy	2010	✓		✓			✓	✓		
Levy *et al*[9]†	France	2011	✓								
McGrath *et al*[10]	USA	2004	✓	✓			✓				
Coco *et al*[8]	USA	2004	✓	✓			✓				
Thompson *et al*[13]	UK	2003 2004	✓		✓						
Rios *et al*[12]†	Spain	2001	✓								

*Antibiotic stewardship campaigns specifically set up with the aim to promote guideline awareness, through various methods (eg, lectures, educational outreach visits).
†Guideline dissemination methods solely based on article, authors not available for correspondence.

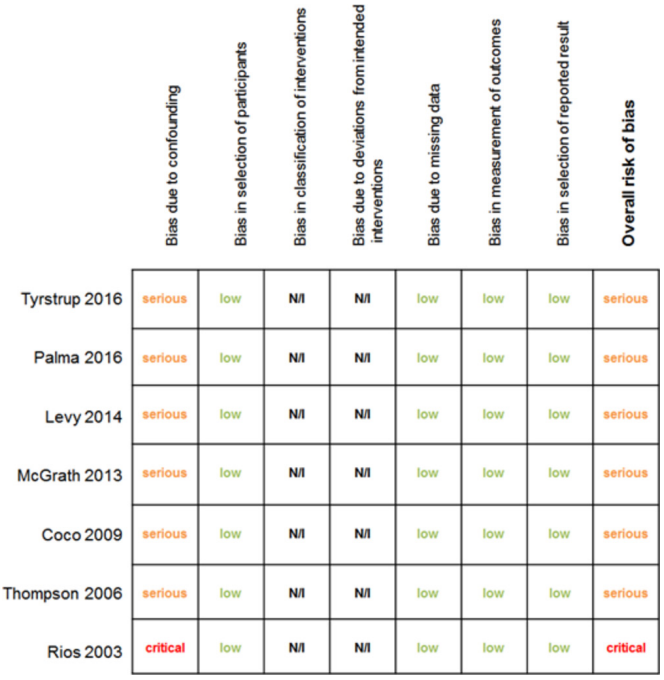

Figure 2 Risk of bias assessment.

Our findings should be interpreted with some caution. Despite our efforts to minimise the impact of external factors affecting childhood AOM epidemiology and prescribing patterns, such as anti-smoking campaigns, pneumococcal conjugate vaccination and strategies to promote breast-feeding,[20 21] we cannot rule out this has influenced our results. Also, we were not able to account for ongoing prescribing trends prior to the introduction of the guideline; none of the studies applied interrupted time-series analysis.[22] Importantly, dissemination of the guideline to the general audience suggesting that parents can manage milder cases of AOM themselves can lead to fewer overall AOM consultations and subsequent antibiotic prescriptions.[23] Nevertheless, only two out of the seven studies reported on annual fluctuations in AOM consultation rates and none of them accounted for this in their analyses.[13 14] Besides, when parents do self-manage these milder cases of AOM, physicians may be faced with more severe AOM and thus prescribe antibiotics more frequently (leading to a relative increase over time). These aforementioned trends are not captured in the studies. Neither are the phenomena that, with explicit diagnostic guidance, physicians may diagnose AOM more accurately,

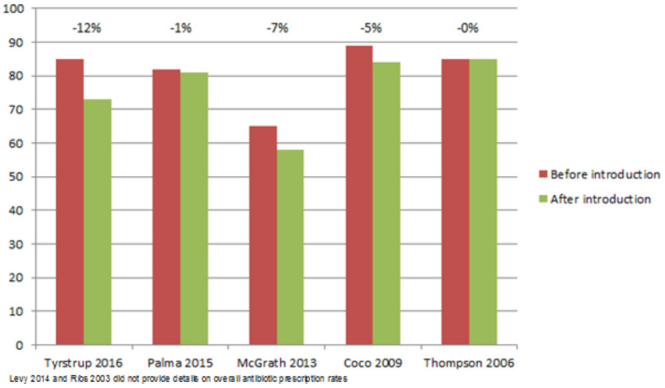

Figure 3 Antibiotics prescription rates.

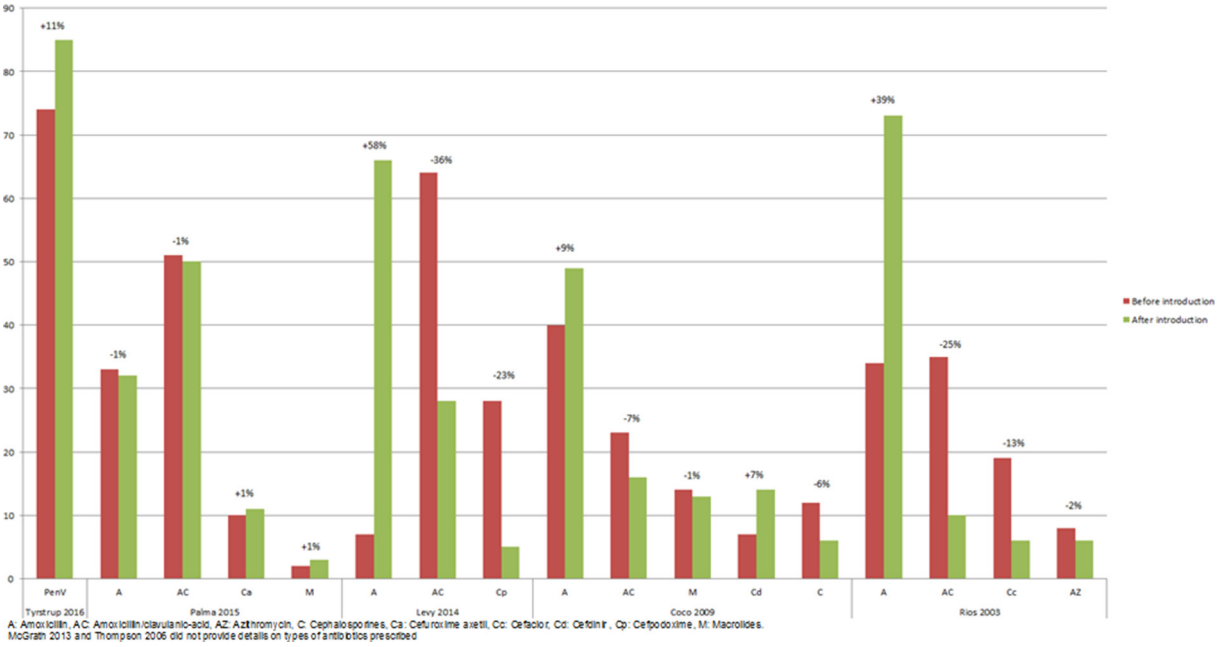

Figure 4 Types of antibiotics prescribed.

leading to fewer overall diagnoses and antibiotic prescriptions, but at the same time a higher prescription rate per diagnosis.

Finally, the vast majority of analgesics for AOM are obtained over-the-counter rather than prescribed. This implies that our results regarding analgesic prescriptions for AOM are incomplete and preclude strong conclusions.

CONCLUSION

Based on what is published, the introduction of national AOM clinical practice guidelines seems to have at best a modest impact on antibiotics and analgesics prescription rates for childhood AOM. Future studies evaluating the impact of clinical guidelines using longitudinal observational data should use a quasi-experimental approach, and take fluctuations in AOM consultation rates into account, to provide more meaningful estimates on the impact on antibiotic and analgesic prescribing.

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REFERENCES

1 Ovnat Tamir S, Shemesh S, Oron Y, *et al*. Acute otitis media guidelines in selected developed and developing countries: uniformity and diversity. *Arch Dis Child* 2017;102:450–7.
2 Haggard M. Poor adherence to antibiotic prescribing guidelines in acute otitis media--obstacles, implications, and possible solutions. *Eur J Pediatr* 2011;170:323–32.
3 Lucas PJ, Cabral C, Hay AD, *et al*. A systematic review of parent and clinician views and perceptions that influence prescribing decisions in relation to acute childhood infections in primary care. *Scand J Prim Health Care* 2015;33:11–20.
4 van den Broek d'Obrenan J, Verheij TJ, Numans ME, *et al*. Antibiotic use in Dutch primary care: relation between diagnosis, consultation and treatment. *J Antimicrob Chemother* 2014;69:1701–7.
5 Grijalva CG, Nuorti JP, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. *JAMA* 2009;302:758–66.
6 Pulkki J, Huikko S, Rautakorpi UM, *et al*. Management of pain in acute otitis media in Finnish primary care. *Scand J Infect Dis* 2006;38:265–7.
7 Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
8 Coco A, Vernacchio L, Horst M, *et al*. Management of acute otitis media after publication of the 2004 AAP and AAFP clinical practice guideline. *Pediatrics* 2010;125:214–20.
9 Levy C, Pereira M, Guedj R, *et al*. Impact of 2011 French guidelines on antibiotic prescription for acute otitis media in infants. *Med Mal Infect* 2014;44:102–6.
10 McGrath LJ, Becker-Dreps S, Pate V, *et al*. Trends in antibiotic treatment of acute otitis media and treatment failure in children, 2000-2011. *PLoS One* 2013;8:e81210.
11 Palma S, Rosafio C, Del Giovane C, *et al*. The impact of the Italian guidelines on antibiotic prescription practices for acute otitis media in a paediatric emergency setting. *Ital J Pediatr* 2015;41:37.
12 Ríos L, Mallafré M, González-Hidalgo RM, *et al*. Aplicación de una pauta terapéutica revisada de otitis media en una consulta pediátrica. *Revista de Calidad Asistencial* 2003;18:5–8.
13 Thompson PL, Gilbert RE, Long PF, *et al*. Has UK guidance affected general practitioner antibiotic prescribing for otitis media in children? *J Public Health* 2008;30:479–86.
14 Tyrstrup M, Beckman A, Mölstad S, *et al*. Reduction in antibiotic prescribing for respiratory tract infections in Swedish primary care- a retrospective study of electronic patient records. *BMC Infect Dis* 2016;16:709.
15 Davis DA, Thomson MA, Oxman AD, *et al*. Changing physician performance. A systematic review of the effect of continuing medical education strategies. *JAMA* 1995;274:700–5.
16 Grimshaw JM, Thomas RE, MacLennan G, *et al*. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004;8:1–72.
17 Cabral C, Lucas PJ, Ingram J, *et al*. "It's safer to …" parent consulting and clinician antibiotic prescribing decisions for children with respiratory tract infections: An analysis across four qualitative studies. *Soc Sci Med* 2015;136-137:156–64.

18 Van Zuijlen DA, Schilder AG, Van Balen FA, *et al*. National differences in incidence of acute mastoiditis: relationship to prescribing patterns of antibiotics for acute otitis media? *Pediatr Infect Dis J* 2001;20:140–4.
19 Butler CC, Rollnick S, Pill R, *et al*. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *BMJ* 1998;317:637–42.
20 Yilmaz G, Hizli S, Karacan C, *et al*. Effect of passive smoking on growth and infection rates of breast-fed and non-breast-fed infants. *Pediatr Int* 2009;51:352–8.
21 Fortanier AC, Venekamp RP, Boonacker CW, *et al*. Pneumococcal conjugate vaccines for preventing otitis media. *Cochrane Database Syst Rev* 2014:CD001480.
22 Kontopantelis E, Doran T, Springate DA, *et al*. Interrupted time-series analysis: a regression based quasi-experimental approach for when randomisation is not an option. *BMJ* 2015;350:h2750.
23 McWilliams DB, Jacobson RM, Van Houten HK, *et al*. A program of anticipatory guidance for the prevention of emergency department visits for ear pain. *Arch Pediatr Adolesc Med* 2008;162:151–6.

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