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Published in:
Cochrane Database of Systematic Reviews

DOI:
10.1002/14651858.CD011360.pub2

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Recommended citation(APA):
O'Sullivan, J. W., Harvey, R. T., Glasziou, P. P., & Mccullough, A. (2016). Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care. *Cochrane Database of Systematic Reviews*, *2016*(11), Article CD011360. https://doi.org/10.1002/14651858.CD011360.pub2

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Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care (Review)

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DOI: 10.1002/14651858.CD011360.pub2.

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[Intervention Review]

Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New, published in Issue 11, 2016.
Review content assessed as up-to-date: 6 July 2016.

Citation: O'Sullivan JW, Harvey RT, Glasziou PP, McCullough A. Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD011360. DOI: 10.1002/14651858.CD011360.pub2.

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ABSTRACT

Background

Acute upper respiratory tract infections (URTIs) are frequently managed in primary care settings. Although many are viral, and there is an increasing problem with antibiotic resistance, antibiotics continue to be prescribed for URTIs. Written patient information may be a simple way to reduce antibiotic use for acute URTIs.

Objectives

To assess if written information for patients (or parents of child patients) reduces the use of antibiotics for acute URTIs in primary care.

Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL, LILACS, Web of Science, clinical trials.gov, and the World Health Organization (WHO) trials registry up to July 2016 without language or publication restrictions.

Selection criteria

We included randomised controlled trials (RCTs) involving patients (or parents of child patients) with acute URTIs, that compared written patient information delivered immediately before or during prescribing, with no information. RCTs needed to have measured our primary outcome (antibiotic use) to be included.

Data collection and analysis

Two review authors screened studies, extracted data, and assessed study quality. We could not meta-analyse included studies due to significant methodological and statistical heterogeneity; we summarised the data narratively.

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Main results

Two RCTs met our inclusion criteria, involving a total of 827 participants. Both studies only recruited children with acute URTIs (adults were not involved in either study): 558 children from 61 general practices in England and Wales; and 269 primary care doctors who provided data on 33,792 patient-doctor consultations in Kentucky, USA. The UK study had a high risk of bias due to lack of blinding and the US cluster-randomised study had a high risk of bias because the methods to allocate participants to treatment groups was not clear, and there was evidence of baseline imbalance.

In both studies, clinicians provided written information to parents of child patients during primary care consultations: one trained general practitioners (GPs) to discuss an eight-page booklet with parents; the other conducted a factorial trial with two comparison groups (written information compared to usual care and written information plus prescribing feedback to clinicians compared to prescribing feedback alone). Doctors in the written information arms received 25 copies of two-page government-sponsored pamphlets to distribute to parents.

Compared to usual care, we found moderate quality evidence (one study) that written information significantly reduced the number of antibiotics used by patients (RR 0.53, 95% CI 0.35 to 0.80; absolute risk reduction (ARR) 20% (22% versus 42%)) and had no significant effect on reconsultation rates (RR 0.79, 95% CI 0.47 to 1.32), or parent satisfaction with consultation (RR 0.95, 95% CI 0.87 to 1.03). Low quality evidence (two studies) demonstrated that written information also reduced antibiotics prescribed by clinicians (RR 0.47, 95% CI 0.28 to 0.78; ARR 21% (20% versus 41%); and RR 0.84, 95% CI 0.81 to 0.86; 9% ARR (45% versus 54%)). Neither study measured resolution of symptoms, patient knowledge about antibiotics for acute URTIs, or complications for this comparison.

Compared to prescribing feedback, we found low quality evidence that written information plus prescribing feedback significantly increased the number of antibiotics prescribed by clinicians (RR 1.13, 95% CI 1.09 to 1.17; absolute risk increase 6% (50% versus 44%)). Neither study measured reconsultation rate, resolution of symptoms, patient knowledge about antibiotics for acute URTIs, patient satisfaction with consultation or complications for this comparison.

Authors' conclusions

Compared to usual care, moderate quality evidence from one study showed that trained GPs providing written information to parents of children with acute URTIs in primary care can reduce the number of antibiotics used by patients without any negative impact on reconsultation rates or parental satisfaction with consultation. Low quality evidence from two studies shows that, compared to usual care, GPs prescribe fewer antibiotics for acute URTIs but prescribe more antibiotics when written information is provided alongside prescribing feedback (compared to prescribing feedback alone). There was no evidence addressing resolution of patients' symptoms, patient knowledge about antibiotics for acute URTIs, or frequency of complications.

To fill evidence gaps, future studies should consider testing written information on antibiotic use for adults with acute URTIs in high- and low-income settings provided without clinician training and presented in different formats (such as electronic). Future study designs should endeavour to ensure blinded outcome assessors. Study aims should include measurement of the effect of written information on the number of antibiotics used by patients and prescribed by clinicians, patient satisfaction, reconsultation, patients' knowledge about antibiotics, resolution of symptoms, and complications.

PLAIN LANGUAGE SUMMARY

Does written information reduce antibiotic use for upper airway infections among people treated in primary care settings?

Review question

We wanted to find out if written information reduces antibiotic use for acute upper airway infections (colds, sore throats, cough, or earaches).

Background

Most colds, sore throats, coughs and earaches are caused by viruses. Although antibiotics do not work against viruses, they are sometimes prescribed. We wanted to find out if giving written information about antibiotics immediately before or during doctor visits, together with usual care, changed antibiotic use compared with the doctor's usual practice or something else. We also wanted to know if: patients would be more likely to return to their doctor; symptoms would improve sooner; patients' knowledge about antibiotics would improve; patients were satisfied with their doctor's care; and if complications occurred.

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Search date

We searched the literature up to July 2016.

Study characteristics

We found two studies that included children with upper airway infections: one involved 558 children who were recruited from 61 general practices in England and Wales; and another of 269 doctors who provided data on 33,792 patient-doctor consultations in Kentucky, USA. Participants were children accompanied by an adult. One study trained general practitioners (GPs) to discuss written information with parents, and in the other, doctors distributed copies of government-sponsored pamphlets to parents.

Study funding sources

Both studies were funded by government bodies and one was also funded by Pfizer (a pharmaceutical company).

Key results

Providing a booklet and explanation by a specially-trained doctor reduced the number of antibiotics children consumed by 20% (from 42% to 22%) without affecting parent satisfaction with consultation or numbers of return visits for the same illness. Compared to the doctor's usual practice, two studies showed that providing a booklet reduced the proportion of children prescribed an antibiotic by 9% to 21%. When doctors were also given feedback on their antibiotic prescribing along with providing a booklet to parents, the proportion of children prescribed an antibiotic increased by 6% (from 44% to 50%). None of the included studies assessed if people were better informed, how long symptoms lasted, or if people had complications.

Quality of evidence

Evidence quality was moderate to low. Doctors and parents knew when written information had been used. One study had a high risk of bias because study groups were not comparable at baseline, so we can be less confident of its findings.

Studies were set in the UK and USA, so results are not applicable to lower-income countries, nor for different primary healthcare services, including settings where prescriptions are unnecessary to obtain antibiotics.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Written information for patients (or parents of child patients) compared with usual care to reduce the use of antibiotics for acute upper respiratory tract infections in primary care

Patient or population: patients (or parents of child patients) with acute upper respiratory tract infections
Setting: primary care
Intervention: written information on antibiotics
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Usual care	Written information			
Antibiotics used by patients	420 per 1000	222 per 1000 (147 to 336)	RR 0.53 (0.35 to 0.80)	220[1] (1 RCT)	⊕⊕⊕◯ **moderate**[2,3]
Antibiotics prescribed by clinicians	407 per 1000	190 per 1000 (114 to 317)	RR 0.47 (0.28 to 0.78)	18,813[1] (2 RCTs)	⊕⊕◯◯ **low**[4,5,6,7]
	539 per 1000	453 per 1000 (437 to 464)	RR 0.84 (0.81 to 0.86)		
Reconsultation rates	164 per 1000	129 per 1000 (77 to 216)	RR 0.79 (0.47 to 1.32)	347[1] (1 RCT)	⊕⊕⊕◯ **moderate**[2,3]
Patient satisfaction with consultation	938 per 1000	891 per 1000 (816 to 966)	RR 0.95 (0.87 to 1.03)	220[1] (1 RCT)	⊕⊕⊕◯ **moderate**[2,3]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Sample size for Francis 2009 was 558. This sample size was adjusted for clustering: intraclass correlation coefficient (ICC) 0.15 for antibiotics used by patients and patient satisfaction, 0.24 for antibiotics prescribed by clinicians, 0.06 for reconsultation. Sample size for Mainous 2000 was 33,792 patient-doctor consultations.

[2] Downgraded due to risk of bias. High risk of bias for performance and detection bias - participants and personnel were unblinded, and outcome was measured by self-report.

[3]Downgraded due to indirectness. Study only included children with acute URTIs, and general practitioners (GPs) were trained to explain the intervention to parents. The effect of using written information with adults or delivering it without an explanation is not known.

[4] Downgraded due to imprecision. Francis 2009 was a small study with wide confidence intervals. Mainous 2000 was a larger study with narrow confidence intervals.

[5] Downgraded due to indirectness. Both studies included children with acute URTIs and provided either training or a letter to clinicians. The effect of using written information with adults and delivering it without additional training or a letter to clinicians is not known.

[6] Downgraded due to inconsistency. Significant heterogeneity between studies that precluded pooling of data.

[7] Downgraded due to risk of bias. High risk of bias across studies for all domains of risk of bias.

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BACKGROUND

Description of the condition

Respiratory infections are a heterogeneous group of diseases that are traditionally divided into upper respiratory tract infections (URTIs) or lower respiratory tract infections (LRTIs). These infections are typically defined as above or below the vocal folds, respectively. URTIs can include acute rhinitis (common cold), acute otitis media (AOM), sore throat, acute cough, and influenza. They are commonly caused by viruses and usually present with nasal stuffiness and discharge, sneezing, sore throat, and cough. Other symptoms include hoarseness, headache, malaise, and lethargy (Heikkinen 2003). Viral transmission is via contact with bodily secretions or, less commonly, air transmission (via particle aerosols) (Heikkinen 2003). On average, children are subject to six to eight URTIs per year; and two to four per year among adults (Heikkinen 2003). In the USA, more than 70% of outpatients with an URTI will receive an antibiotic (Lee 2014). Growing evidence suggests that antibiotics have little or no effect on URTIs: common cold (Kenealy 2013), AOM (Venekamp 2015), pharyngitis (Spinks 2013), and acute laryngitis (Reveiz 2015). They may also cause rash, abdominal pain, diarrhoea, and vomiting. On a global and individual level, antibiotic use is associated with the development of antibiotic resistance (Costelloe 2010; Goossens 2005). But antibiotic resistance could be reversed - resistance in commensals decreases rapidly to near pre-antibiotic levels within 12 months of last antibiotic use (Costelloe 2010).

Description of the intervention

Written information on the use of antibiotics potentially offers a cheap and practical method of reducing antibiotic use for people with acute URTIs. This approach can be used either in isolation, or combined with other interventions, such as delayed prescribing (where patients are asked to wait a few days before using antibiotics) (Spurling 2013), shared decision-making (Légaré 2012), and behavioural interventions (Meeker 2014).

How the intervention might work

Knowledge of illness and treatment, beliefs about the benefits or harms of taking a treatment, and expectations of treatment outcome are known to influence medication-taking behaviour (Jackson 2014; Michie 2011). Patients consistently overestimate the benefits of treatment and underestimate their harms (Hoffmann 2014). Written information about antibiotics for acute URTIs may target these determinants of antibiotic-taking behaviour and thereby, change patients' antibiotic use. In the case of children, written information may change parents' decisions to use antibiotics for their children. Patients who receive antibiotics to treat acute URTIs are more likely to attend repeat consultations with the same illness (Moore 2009). Providing written information may also change clinician behaviour, by providing a tool that clinicians can use to initiate discussions about the benefits and harms of antibiotics for URTI. If written information was able to prevent patients taking antibiotics, this would potentially interrupt this cycle, reduce repeat consultation rates, and subsequent antibiotic use.

Why it is important to do this review

Antibiotic resistance is a major global health problem that is predicted to cause 10 million deaths annually and cost USD 100 trillion by 2050 (Review on Antimicrobial Resistance 2014). Global antibiotic use continues to grow (Van Boeckel 2014), despite most clinicians being aware of the growing antibiotic resistance problem (McCullough 2015). Many different approaches to reducing antibiotic use in primary care have been tested (Arnold 2005), and several have been shown to be effective (Plejdrup Hansen 2015), including: delayed prescribing (Spurling 2013); shared decision-making (Légaré 2012); and behavioural interventions (Meeker 2014). However, many of these interventions require significant changes in clinician and patient behaviour. This is particularly challenging because many clinicians do not believe their prescribing patterns contribute to the development of resistance (McCullough 2015). Simple and effective interventions that target patients' knowledge and beliefs about antibiotics may overcome some of these barriers. Identifying whether written information about antibiotics is effective is particularly important because it has the potential to be implemented in primary care settings globally.

OBJECTIVES

To assess if written information for patients (or parents of child patients) reduces the use of antibiotics for acute upper respiratory tract infections (URTIs) in primary care.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs that compared information about antibiotics for acute upper respiratory tract infections (URTIs) with no information. We also included studies that included information as an add-on intervention.

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Types of participants

Patients of all ages defined as having an acute URTI presenting to primary care were included. When children were involved, the intervention may have been directed to the parent/guardian. We excluded patients with lower respiratory tract infections (LRTIs) and those with chronic lung conditions, such as chronic obstructive pulmonary disease. Primary care was defined as general practice, emergency department (accident and emergency), and other primary care settings.

Types of interventions

1. Written information versus no written information.
2. Written information plus intervention-X versus no written information plus intervention-X (for example, where Intervention-X was delayed prescribing or another intervention).

Any written information, in both paper (e.g. handout, booklet, poster) or electronic (e.g. video) format, given to a patient with the aim of informing them about antibiotics for acute URTIs, either as the main or as an add-on intervention. This information must have been given at the time of prescribing, that is, immediately before or during a consultation where an antibiotic may be prescribed. Studies were eligible if patients were or were not about to receive an antibiotic prescription. Information must have included details about antibiotics for acute URTIs, but did not have to be exclusive. We excluded studies that offered information after prescribing, for example, pharmacists providing education via package inserts. We excluded interventions where only verbal information was given.

Types of outcome measures

We extracted outcome data at the end of treatment and end of follow-up. We excluded studies that did not measure our primary outcome.

Primary outcomes

1. Antibiotic use (measured as antibiotics used by patients or antibiotics prescribed by clinicians)

Secondary outcomes

1. Reconsultation rates.
2. Resolution of symptoms.
3. Patient knowledge about antibiotics for acute URTIs.
4. Patient satisfaction with consultation.
5. Complications
   i) Adverse drug reaction due to the prescribed antibiotics.
   ii) Disease complications (for example, pneumonia or mastoiditis).

If future studies were to report time to resolution data we would add this as a secondary outcome.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (6 July 2016; Issue 6, June 2016), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1946 to 6 July 2016), Embase (2010 to 6 July 2016), CINAHL (1981 to 6 July 2016), LILACS (1982 to 6 July 2016), and Web of Science (1955 to 6 July 2016).

We used the search strategy described in Appendix 1 to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE (Lefebvre 2011). We adapted the search strategy to search Embase (Appendix 2), CINAHL (Appendix 3), LILACS (Appendix 4), and Web of Science (Appendix 5). We did not use any language or publication restrictions.

Searching other resources

We searched the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en; Appendix 6), and ClinicalTrials.gov (www.clinicaltrials.gov; Appendix 7), for completed and ongoing studies. We reviewed the reference lists of retrieved articles.

Data collection and analysis

Selection of studies

Two review authors (JOS, RH or AMcC) independently assessed abstracts for eligibility and selected studies for full-text review. We resolved disagreements by discussion with a third review author (AMcC or PG).

Data extraction and management

Two review authors (JOS, RH) independently extracted data using a standardised Cochrane data collection form. We extracted the following information.

1. Age and gender of participants.
2. Number of participants.
3. Literacy level of participants (measured by highest level of education or other methods employed by authors).
4. Description of intervention content, mode of delivery and fidelity to intervention, where available.
5. Antibiotic use.
6. Reconsultation rates.
7. Symptom resolution.
8. Complications such as adverse drug reactions and disease complications.

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One of the included studies provided a copy of their patient information online, free of charge (www.whenshouldiworry.com) (Francis 2009). We contacted the other study authors, but they were unable to provide any of the original data files (Mainous 2000).

Assessment of risk of bias in included studies

Two review authors (JOS or RH) independently assessed the risk of bias of included studies using the Cochrane 'Risk of bias' tool (Higgins 2011). Any disagreements were resolved by consensus. We assessed the following domains.

Selection bias

The method used to generate allocation sequencing and whether this method was adequate to produce comparable groups was assessed independently by two review authors.
Two review authors independently assessed the method used to conceal the allocation sequence to determine whether intervention allocations could have been foreseen in advance of or during enrolment.

Performance bias

Two review authors independently assessed the measures used to blind study participants and personnel from knowledge of which intervention a participant received. Two review authors assessed if the intended blinding was effective.

Detection bias

Two review authors independently assessed the measures used to blind outcome assessors from knowledge of which intervention a participant received. Two review authors assessed if the intended blinding was effective.

Attrition bias

Two review authors independently assessed the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Two review authors determined whether attrition and exclusions were reported, the numbers in each intervention group (compared to total randomised participants), reasons for attrition/exclusions (if reported), and any re-inclusions in analyses (if performed).

Reporting bias

Two review authors independently assessed whether the possibility of selective outcome reporting was examined by study authors, and elaborated on what was found.

Other bias

Two review authors independently assessed whether authors stated any important concerns about bias not addressed. Authors noted any significant information about sources of funding that may introduce bias. Two review authors assessed the quality of included studies.
All review authors resolved any disagreements by consensus. If required, we were prepared to reconstruct an intention-to-treat analysis.

Measures of treatment effect

We used Review Manager 5 for data analyses (RevMan 2014). For dichotomous primary and secondary outcomes, we used risk ratios (RRs) as the main measure of effect. If studies can be meta-analysed when updating this review, we will calculate and report the number needed to treat to benefit (NNTB) for any statistically significant outcomes.

Unit of analysis issues

Units of randomisation were: general practices (Francis 2009); and primary care clinicians (Mainous 2000). Units of analysis were: parents of patients (Francis 2009); and episodes of care (defined as one patient-clinician consultation with acute URTI as the diagnosis) (Mainous 2000). The same parent and child may have contributed to more than one episode of care if they attended their physician with an URTI more than once during the data collection period. We adjusted for within-cluster correlations by calculating the design effect of included studies using the formula 1 + (M - 1)*ICC. Where M equals average cluster size and ICC equals intraclass correlation coefficient. Francis 2009 included a specific ICC for two outcomes: antibiotics prescribed by clinicians (ICC 0.24) and reconsultation (ICC 0.06). They did not report a specific ICC for antibiotics used by patients or satisfaction. For these two outcomes, we calculated the mean ICC from the reported outcomes, that is, 0.24 + 0.06/2 = 0.15. Cluster sizes (M) averaged 9.5 in the intervention group and 10 in the usual care group. We divided the sample size for each outcome by the design effect to calculate the effective sample size. Mainous 2000 did not report any information on cluster size or ICC so we could not adjust for clustering in that study.

Dealing with missing data

The included studies had minimal missing data. We emailed the authors of seven studies to request further or stratified data (Alder 2005; Bauchner 2001; Mainous 2000; Schnellinger 2010; Sustersic 2012; Taylor 2003; Taylor 2005). The study authors either did not reply or no longer had the data available. If eligible studies are identified in future updates, we will contact study authors for clarification of any missing data. If a study outcome has

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more than 20% missing data, we will exclude it from the primary analysis but include it in a sensitivity analysis.

Assessment of heterogeneity

We assessed the presence of heterogeneity by comparing populations, settings, interventions, and outcomes before deciding whether it was appropriate to pool study data using a fixed-effect analysis, a random-effects analysis, or to not pool data. If appropriate, when updating the review, we will assess statistical heterogeneity by means of the I^2 statistic (Higgins 2011). We will interpret heterogeneity as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011): 0% to 40% - might not be important; 30% to 60% - may represent moderate heterogeneity; 50% to 90% - may represent substantial heterogeneity; 75% to 100% - considerable heterogeneity.

Assessment of reporting biases

We searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform for unpublished studies (www.clinicaltrials.gov; www.who.int/ictrp/en). When updating this review, we will contact study authors to request any unreported outcomes.

Data synthesis

We attempted to meta-analyse data for antibiotics prescribed by clinicians but concluded that heterogeneity between the included studies was too great (I^2 statistic = 80%). Data are presented as a narrative synthesis. If appropriate when updating this review, we will analyse differences in antibiotic use using a risk ratio (RR) with 95% CI calculated by the Mantel-Haenszel method using a fixed-effect model (where appropriate, based on Assessment of heterogeneity).

GRADE and 'Summary of findings' table

We created two 'Summary of findings' tables that present data for both comparisons (Summary of findings for the main comparison; Summary of findings 2). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess evidence quality for the prespecified outcomes (GRADE Working Group 2004). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and GRADEpro GDT software (GRADEpro GDT 2014). We justified all decisions to down- or upgrade the quality of studies using footnotes, and made comments to aid readers' understanding of the review, where necessary.

Subgroup analysis and investigation of heterogeneity

When updating the review, we will conduct subgroup analysis of the impact of patient information based on whether or not delayed prescribing was also used. Factorial studies (2 x 2 of delayed prescription x handout) will contribute to both groups. This principle would also be used for other potential co-interventions within studies.

Sensitivity analysis

When updating this review, if a study outcome has more than 20% missing data, we will exclude it from the primary analysis but include it in a sensitivity analysis (see Dealing with missing data). We plan to conduct sensitivity analyses to determine the robustness of results to intervention intensity and fidelity.

RESULTS

Description of studies

Results of the search

We retrieved 600 studies for title and abstract screening from six electronic databases and 127 from reviewing the reference lists of retrieved studies. After removal of duplicates, we screened 517 titles and abstracts, identified 54 records for full-text review, and included two studies in the qualitative synthesis (Francis 2009; Mainous 2000) (Figure 1).

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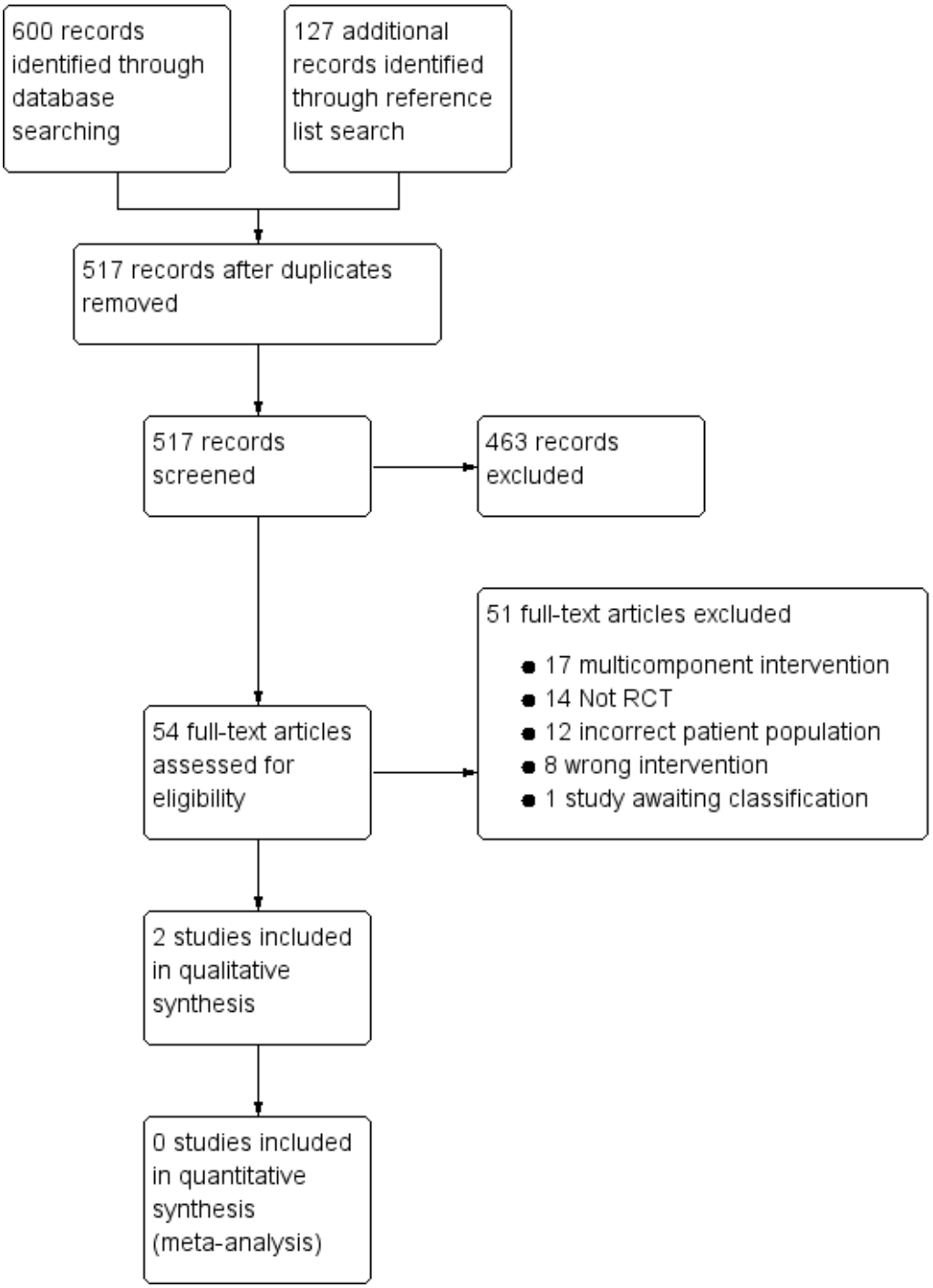
Figure 1. Study flow diagram



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Included studies

We included two studies that investigated two different written information interventions (both delivered to parents of child patients during primary care consultation). Francis 2009 recruited 558 children from 61 general practices in England and Wales, and Mainous 2000 recruited 269 primary care doctors who provided data on 33,792 patient-doctor consultations in Kentucky, USA. See Characteristics of included studies.

Study design

Francis 2009 conducted a two-arm pragmatic cluster-RCT of written information compared to usual care. Mainous 2000 conducted a four-arm factorial cluster-RCT and we extracted data on two comparisons from this study: written information compared to usual care and written information plus prescribing feedback to clinicians compared to prescribing feedback to clinicians alone.

Characteristics of settings and participants

Francis 2009 was conducted in 61 general practices (n = 558 patients) in the United Kingdom; and Mainous 2000 was conducted in the United States with 269 primary care clinicians (family practice, paediatricians or 'other primary care'). Both included children with acute upper respiratory tract infections (URTIs). Mainous 2000 reported baseline differences in the number of acute URTI episodes and the geographical location of the clinicians targeted (see Characteristics of included studies).

Characteristics of interventions and comparisons

The written information intervention was different in both studies. Francis 2009 trained general practitioners (GPs) to discuss an eight-page booklet on acute URTIs during a consultation with parents. Parents of children in the intervention group received the booklet during consultation with their GP (When should I worry). Fidelity to the intervention was not assessed because the authors wanted telephone assessors to remain blinded. GPs in the intervention group underwent online training on how to use the booklet. Training sessions lasted 40 minutes and included: audio, video, pictures, and links to further study material; description of the booklet content; and how to use communication skills to explore parents' concerns and expectations. Researchers monitored GPs' compliance with the online training via the study website. Both the booklet and GPs' training had a theoretical basis in Social Cognitive Theory (Bandura 1996) and the Theory of Planned Behaviour (Ajzen 1991). GPs randomised to the usual care group practiced usual care. The authors determined outcomes by telephone questionnaire 14 days after recruitment included: reconsultation within two weeks for the same illness (yes or no); antibiotics prescribed by the clinician (defined as antibiotics prescribed at initial consultation or at any time over the following two-week period); antibiotic use by the patient (self-reported ingestion of antibiotics over the same time period, including any further antibiotics prescribed); and parent satisfaction with the consultation (dichotomised to 'very satisfied' or 'satisfied' versus 'neutral', 'dissatisfied' or 'very dissatisfied'). The study authors also measured future consultation intentions, reassurance, and enablement. However, we did not extract this data because they did not meet our review criteria.

Mainous 2000 conducted a four-arm factorial study. We extracted data for two comparisons that were relevant to this review: written information compared to usual care; and written information plus prescribing feedback to clinicians compared to feedback alone. All interventions were aimed at clinicians.

1. Written information (53 clinicians): Clinicians received letters about the study 'without information on costs and profiling' along with 25 two-page patient education pamphlets entitled 'Your child and antibiotics' produced by the Centers for Disease Control and Prevention (CDC) and the American Society for Microbiology. Clinicians also received information about where to access further copies of the CDC pamphlet. Content of the letter was not defined and fidelity was not assessed.
2. Prescribing feedback to clinicians (49 clinicians): Study authors provided clinicians with their antibiotic prescribing profile for paediatric acute URTIs (common cold), acute bronchitis, and purulent rhinitis for a period prior to the intervention. The prescribing profile consisted of total number of episodes of care for stated paediatric respiratory conditions, the number and proportion that received antibiotics, the total cost of the episode, and the proportionate cost of antibiotics in the cost of evaluation and managing these conditions (as per Medicaid). Clinicians also received their percentile rank for antibiotic prescribing compared with their peers.
3. Written information plus prescribing feedback to clinicians (52 clinicians).
4. Usual care (62 clinicians).

Excluded studies

We excluded 51 full-text studies (Figure 1, Characteristics of excluded studies). Of these, 17 studies were excluded because they contained multiple components and the effect of written information could not be determined. Common co-interventions included clinician education and training (Altiner 2007; Doyne

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2004; Flottorp 2002; Gonzales 1999; Gonzales 2013; Hickman 2003; Jenkins 2013; Légaré 2011; Metlay 2007; Price 2011; Ratchina 2011; Rubin 2005; Smabrekke 2002; Smeets 2009; Trepka 2001; Welschen 2004), clinical champions and leaders (Gonzales 2013; Metlay 2007; Price 2011), increases in fees for telephone consultation (Flottorp 2002), decision support aids and reminders (Flottorp 2002; Gonzales 2013), monitoring, audit and feedback on prescribing (Doyne 2004; Gonzales 2004; Gonzales 2013; Welschen 2004), and education for non-clinicians (Welschen 2004).

We excluded 14 studies because they were not RCTs (Adinoff 2006; Agnew 2013; Allaire 2011; Becker 2002; Briel 2010; Farquhar 2002; Formoso 2011; Hay 2010; Linder 2008; Moore 2010; Rodis 2004; Shaughnessy 2002; Vega 2015; Wright 2002). Twelve studies did not include data on patients with URTIs (Bauchner 2001; Everitt 2006; Hallsworth 2016; Kullgren 2016; Macfarlane 2002; Moore 2009; Olives 2016; Schnellinger 2010; Sustersic 2012; Taylor 2003; Taylor 2005; Yu 2015). Four of these studies offered written information to patients presenting to primary care for any reason (Bauchner 2001; Taylor 2003; Taylor 2005; Schnellinger 2010). We contacted the authors of these four studies and found that data for URTIs were no longer available (Bauchner 2001; Schnellinger 2010); or we did not receive responses (Taylor 2003; Taylor 2005). Two studies recruited patients with LRTIs (Macfarlane 2002; Moore 2009), and one recruited patients with infective conjunctivitis (Everitt 2006).

Eight studies did not deliver written information or delivered the information but not at the time of prescribing. Dolovich 1999, Gonzales 2005, Teng 2006, and Turnbull 2015 directed the intervention to clinicians; Finkelstein 2001 mailed information to patients after the consultation; Formoso 2013 used advertisements in local media; Sahlan 2008 assessed patients' views; and Segador 2005 provided information stating the importance of completing an antibiotic course.

We classified one study as awaiting classification (Alder 2005). This study measured the number of antibiotics prescribed by clinicians and parental satisfaction following the delivery of written information about antibiotics, but they did not report how they measured this nor did they provide the outcome data. We contacted the study authors to obtain these data, but did not receive a reply. We will re-contact these authors when updating this review.

Risk of bias in included studies

Risk of bias assessments are summarised below and are described in detail in the Characteristics of included studies tables.

Allocation

Selection bias varied between studies. We rated Francis 2009 at low risk of bias because we considered their randomisation and allocation concealment procedures appropriate. We assessed Mainous 2000 at high risk of bias because randomisation and concealment were poorly reported, and baseline differences between groups implied inadequate randomisation.

Blinding

It was not possible to blind clinicians or participants to the intervention in either study (Francis 2009; Mainous 2000). Although Francis 2009 used blinded telephone assessors, participants self-reported the subjective outcomes, introducing a high risk of bias. Mainous 2000 used an objective measure of antibiotic prescribing by clinicians, indicating a low risk of bias.

Incomplete outcome data

Attrition varied between the included studies. Francis 2009 had a low risk of bias (< 20% attrition, equal in both groups and analysed using an intention-to-treat analysis). In contrast, Mainous 2000 had a high risk of bias because 53 clinicians were excluded, but the study did not report when they were excluded or from which arm, and intention-to-treat analysis was not conducted.

Selective reporting

The risk of reporting bias varied between the included studies. A published study protocol (Francis 2008) was available for Francis 2009 and the study was reported as planned. A protocol was not available for Mainous 2000 and we assessed the risk of bias for selective reporting as unclear.

Other potential sources of bias

In Mainous 2000, clinicians received 25 pamphlets as part of the intervention and the study authors did not assess fidelity of distributing pamphlets to patients or ordering more copies. We assessed the risk of clustering in this study as high because the study authors randomised clinicians rather than patients, but did not adjust for this in their analysis. Francis 2009 received an educational grant to fund the GP training website; however, we rated this as a low risk of bias as they declared no conflicts of interest and stated the study was conducted independently of the funder.

Effects of interventions

See: **Summary of findings for the main comparison** Written information for patients (or parents of child patients) compared to usual care; **Summary of findings 2** Written information for patients (or parents of child patients) plus prescribing feedback to clinicians compared to prescribing feedback alone

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Written information compared to usual care

Primary outcome

1. Antibiotic use: written information significantly reduced the number of antibiotics used by patients (RR 0.53, 95% CI 0.35 to 0.80; ARR 20% (22% versus 42%); n = 220; Analysis 1.1; Figure 2; Francis 2009). Written information also significantly reduced the number of antibiotics prescribed by clinicians in Francis 2009 (RR 0.47, 95% CI 0.28 to 0.78; ARR 21% (20% versus 41%), n = 170) and Mainous 2000 (RR 0.84, 95% CI 0.81 to 0.86; 9% ARR (45% versus 54%), n = 18,643; Figure 3) (Analysis 1.2). We could not combine these data due to methodological and statistical heterogeneity (I^2 statistic = 80%, P < 0.00001).

Figure 2. Forest plot of comparison: 1 Written information versus control, outcome: 1.1 Antibiotics used by patients.

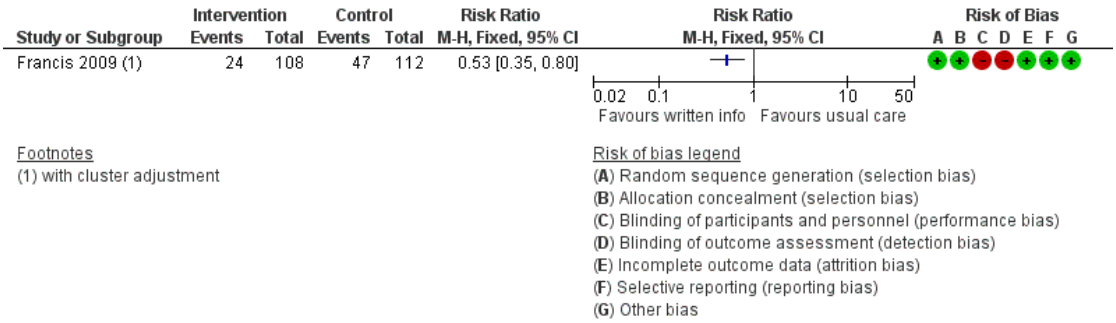
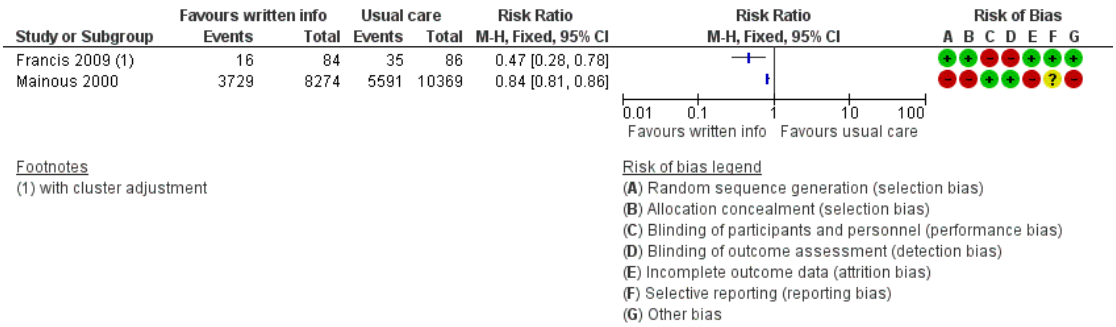


Figure 3. Forest plot of comparison: 1 Written information versus usual care, outcome: 1.2 Antibiotics prescribed by clinicians.



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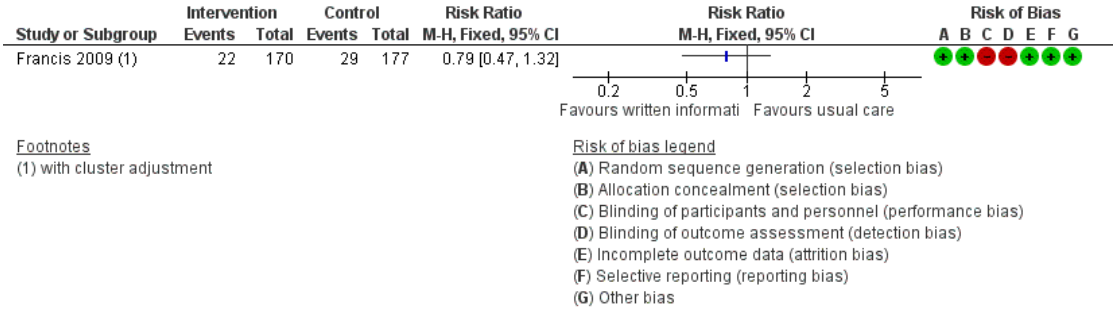
Secondary outcomes

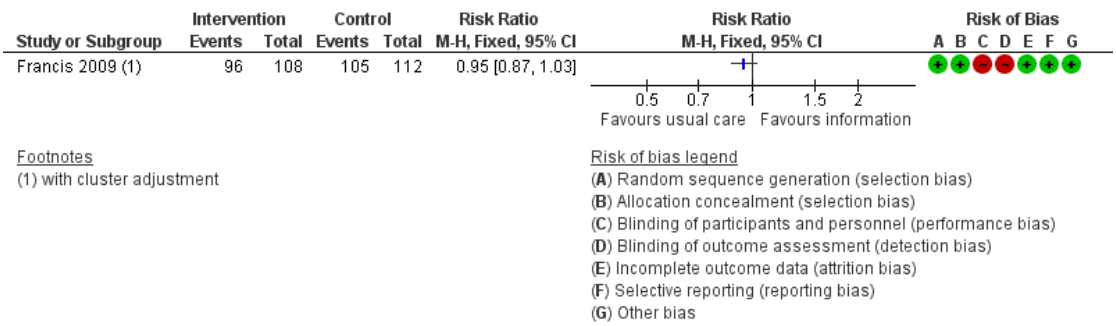
1. Reconsultation rate: written information had no significant effect on reconsultation rates (RR 0.79, 95% CI 0.47 to 1.32; ARR 3% (13% versus 16% reconsulted); n = 347; Analysis 1.3; Figure 4). Francis 2009 did not reach the predetermined study threshold for clinical significance of 10% reduction in reconsultation rates.

Figure 4. Forest plot of comparison: 1 Written information versus usual care, outcome: 1.3 Reconsultation.



1. Resolution of symptoms: neither of the included studies addressed this outcome.
2. Patient knowledge about antibiotics for acute URTIs: neither of the included studies addressed this outcome.
3. Patient satisfaction with consultation: written information had no significant effect on parent satisfaction postconsultation (RR 0.95, 95% CI 0.87 to 1.03; absolute risk difference 5% (89% satisfied in written information group compared to 94% in the usual care group); n =220; Analysis 1.4; Figure 5).

Figure 5. Forest plot of comparison: 1 Written information versus usual care, outcome: 1.4 Patient satisfaction with consultation.



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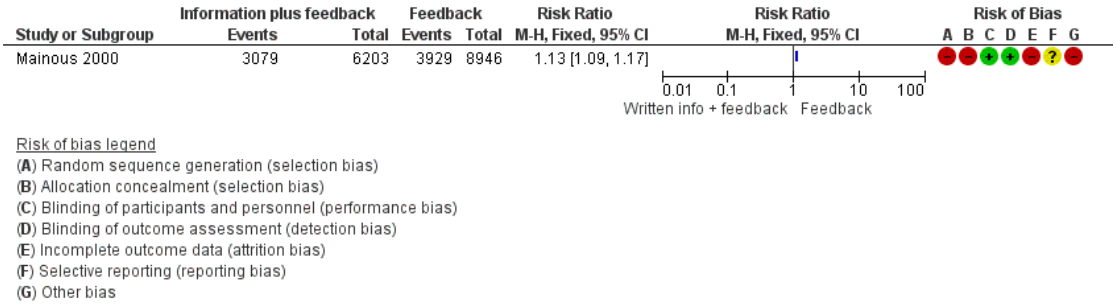
1. Complications: neither of the included studies measured adverse drug reaction due to the prescribed antibiotics or disease complications, such as pneumonia or mastoiditis.

Written information plus prescribing feedback to clinicians compared to prescribing feedback alone

Primary outcome

1. Antibiotic use: written information plus feedback significantly increased the number of antibiotics prescribed by clinicians (RR 1.13, 95% CI 1.09 to 1.17; absolute risk increase 6% (50% versus 44%); n = 15,149; Analysis 2.1; Figure 6).

Figure 6. Forest plot of comparison: 2 Written information plus prescribing feedback versus prescribing feedback alone, outcome: 2.1 Antibiotics prescribed by clinicians.



Secondary outcome

Neither study measured reconsultation rate, resolution of symptoms, patient knowledge about antibiotics for acute URTIs, patient satisfaction with consultation or complications for this comparison.

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ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Written information for patients (or parents of child patients) plus prescribing feedback compared with prescribing feedback alone to reduce the use of antibiotics for acute upper respiratory tract infections in primary care

Patient or population: patients (or parents of child patients) with acute upper respiratory tract infections
Settings: primary care
Intervention: written information on antibiotics plus prescribing feedback to clinicians
Comparison: prescribing feedback to clinicians

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Clinician feedback	Written information plus clinician feedback			
Antibiotics prescribed by clinicians	439 per 1000	496 per 1000 (479 to 514)	RR 1.13 (1.09 to 1.17)	15,149 (1 RCT)	⊕⊕◯◯ **low**[1,2]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded due to indirectness. This study Included children with acute URTIs and provided a letter to clinicians. The effect of using written information with adults and delivering it without additional a letter to clinicians is not known.
[2]Downgraded due to risk of bias: high risk of selection, attrition and other bias.

DISCUSSION

Summary of main results

Compared to usual care, moderate quality evidence from one study showed that GPs who provide written information to parents of children with acute upper respiratory tract infections (URTIs) in primary care can reduce absolute rates of patient antibiotic use by 20% and halve the risk of patients using antibiotics, without any negative impact on reconsultation rates or parental satisfaction (Francis 2009). Low quality evidence from two studies shows that, compared to usual care, GPs prescribe fewer antibiotics for acute URTIs but prescribe more antibiotics when written information is provided alongside prescribing feedback (compared to prescribing feedback alone). The effect of written information on complications, patient knowledge, and resolution of symptoms has not been investigated.

Overall completeness and applicability of evidence

The available evidence partly addressed our research question. The two included studies recruited children and directed the intervention to their parents. We did not identify any eligible studies that targeted adult patients or that took place in low-income countries. This limits the generalisability of findings because it is not known if using written information with these populations would result in a similar effect.

Both included studies had limitations in delivery of interventions. Francis 2009 trained GPs to explain the booklet to parents and elicit parents' expectations, and Mainous 2000 sent clinicians a letter with a limited number of patient education (written information) pamphlets. The effect of written information about antibiotics provided to patients without any additional interaction and/or in another format (e.g. electronic) is not known. It is also not possible to determine from the included studies which are the most important elements of the written information interventions used, and which elements, if any, are redundant.

Francis 2009 focused more on patient understanding and behaviour, whereas the intervention investigated by Mainous 2000 focused more on prescriber behaviour. Francis 2009 and Mainous 2000 measured patient antibiotic use or antibiotics prescribed by clinicians; in addition, Francis 2009 measured satisfaction and reconsultation. The effect of written information on complications, patient knowledge, and resolution of symptoms has not been measured. It should be further noted that the uptake of this intervention in different healthcare settings (publicly funded compared with private, insurance-based systems) may vary.

One study met our criteria for participants, interventions, and comparators but did not report how they measured our primary outcome (antibiotic use) nor did they provide the outcome data (Alder 2005). We contacted the authors to obtain these data but did not receive a reply. Consequently, we classified the study as awaiting classification and plan to contact the authors again when updating this review.

Quality of the evidence

For comparison one (written information compared to usual care), we graded the evidence as moderate quality for antibiotic use by patients, reconsultation, and satisfaction (Francis 2009). We downgraded these outcomes on risk of bias and indirectness. We assessed Francis 2009 at high risk of performance and detection bias because unblinded GPs delivered the intervention and unblinded parents self-reported outcomes (risk of bias). Francis 2009 included only children with acute URTIs and trained GPs to deliver the intervention (indirectness). The effect of this intervention on adults or when delivered without clinician training or explanation is not known. We graded the evidence as low quality for antibiotic prescribing by clinicians (Francis 2009; Mainous 2000). We downgraded this assessment based on risk of bias, inconsistency, indirectness, and precision. We assessed Francis 2009 at high risk of performance bias and Mainous 2000 at high risk of selection, attrition, and other bias (providing only 25 pamphlets to the intervention clinicians, which was considered a risk of bias because clinicians could rapidly run out of the intervention tool with no clear way of attaining more). We found significant heterogeneity (inconsistency), studies only included children and their parents, and provided training or a letter to clinicians (indirectness) and Francis 2009 had a relatively small sample size with relatively wide confidence intervals, and we could not adjust for clustering in Mainous 2000 (precision). Similarly, we graded the quality of the evidence as low for antibiotic prescribing by clinicians in comparison two (written information plus prescribing feedback compared to feedback alone).

Potential biases in the review process

We employed a robust and comprehensive search strategy to identify RCTs testing written information compared to no information, with no restrictions on language. Two review authors extracted data and appraised risk of bias. We adjusted for clustering in our analysis, where possible. For this adjustment, we calculated ICCs for two outcomes which may have affected our findings (Francis 2009). We could not adjust the sample size for clustering in Mainous 2000 because the study authors did not report any data on cluster size or ICC. Episodes of care could be correlated in this study because the same parent and child could return to see their physician on more than one occasion during the data collection period but these would be counted as separate episodes of care.

One study met our criteria for participants, interventions, and comparators but we did not included it in this review because it

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did not report outcome data (Alder 2005). We included Mainous 2000, although study selection criteria included acute bronchitis (typically classified as a lower respiratory tract infection (LRTI)). We included this study because most participants included had acute URTIs (86% for the written information group, 87.1% for the prescribing feedback to clinicians group, 89.5% for the written information plus prescribing feedback to clinicians group, and 85% for usual care group) and the investigators excluded illnesses that we also set out to exclude from our review, most notably pneumonia. We contacted the study authors to request data excluding patients with acute bronchitis, but these were unavailable.

We excluded studies that included patients with LRTIs, however, in clinical practice it is often hard to determine confidently between a LRTI and URTI. Written information about antibiotics for LRTIs could also be relevant for the management of URTIs.

We also excluded multicomponent interventions, which greatly limited the number of studies we could include. However, this was the most appropriate method to enable us to determine the effect of written information alone. Another potential bias is the effect of training clinicians in the use of the written information intervention. In both included studies, clinicians were given either formal online training on use of the intervention booklet (Francis 2009), or from an ill-defined letter (Mainous 2000). As such, the effect of the intervention is unclear and our reported results should be interpreted as such.

Agreements and disagreements with other studies or reviews

Five systematic reviews with similar aims have been conducted (AHRQ 2015; Andrews 2012; Arnold 2005; de Bont 2015; Vodicka 2013). Findings are broadly in agreement with this review: there is limited and conflicting evidence of the benefit of written information on antibiotic prescribing for acute URTIs. Two reviews included both Francis 2009 and Mainous 2000 (AHRQ 2015; Vodicka 2013); two other reviews did not include Mainous 2000, although it met inclusion criteria (Andrews 2012; de Bont 2015); and one review, Arnold 2005, did not include Francis 2009 because it was published after the review.

We identified a number of key differences in inclusion criteria. AHRQ 2015 and Arnold 2005 reviewed the evidence for any intervention aimed at changing antibiotic prescribing in outpatient settings. de Bont 2015 reviewed the evidence for patient information leaflets in reducing antibiotic use by patients, antibiotic prescribing by clinicians, and reconsultation rates in general practice for any infection. Vodicka 2013 included randomised and non-randomised trials of primary care interventions for children with any respiratory tract infection. Andrews 2012 reviewed the evidence for any intervention influencing antibiotic use and consultation in children with respiratory tract infection delivered at any point, including prior to the child becoming unwell.

AUTHORS' CONCLUSIONS

Implications for practice

Compared to usual care, moderate quality evidence from Francis 2009 showed that GPs trained to provide written information to parents of children with acute URTIs in primary care can reduce patients' antibiotic use by 20% without any negative impact on reconsultation rates or parental satisfaction. Primary care clinicians could implement this intervention by completing the 40 minute online training and downloading the information resource from www.whenshouldiworry.com for parents of children with URTIs.

Low quality evidence from two studies shows that, compared to usual care, GPs prescribe fewer antibiotics for acute URTIs but prescribe more antibiotics when written information is provided alongside prescribing feedback (compared to prescribing feedback alone). There was no evidence addressing resolution of patients' symptoms, patient knowledge about antibiotics for acute URTIs, or frequency of complications.

Implications for research

Two very different written information interventions were tested: one that provided 25 copies of a two-page pamphlet to clinicians for dissemination to patients and another that used an eight-page booklet delivered by GPs who had undergone a 40-minute training session. The written information booklet provided by Francis 2009 has been tested in general practice in the UK. This study requires replication in other primary care settings globally. Further RCTs are also needed that test written information in adults with acute URTIs, in both high- and low-income countries, without clinician training and that is delivered in different formats (e.g. electronic), blinds outcome assessors to group allocation, and measures the effect of written information on antibiotic use by patients or antibiotic prescribing by clinicians, satisfaction, reconsultation, knowledge, resolution of symptoms, and complications.

A broader research implication raised by this study is that even with the 20% absolute reduction in prescribing for acute URTIs demonstrated by Francis 2009, 22% of children with URTIs still consumed an antibiotic. Given the overwhelming evidence suggesting antibiotics are not effective in this population (Reveiz 2015; Smith 2014; Spinks 2013; Spurling 2013; Venekamp 2015), ideally few, if any, of these patients should be prescribed antibiotics. Therefore, two questions remain prominent: what percentage of patients with acute URTIs receiving antibiotics is acceptable; and can written patient information, either in isolation or combination with other interventions, achieve this?

ACKNOWLEDGEMENTS

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Thanks to Sarah Thorning and Justin Clark for help with the search strategy, and Liz Dooley for help with details of the protocol and review. We also thank the following people for commenting on the draft protocol: Elizabeth Ayres, Karen Parris, Peter Knapp, Sabina Ciciriello, Elaine Beller, and Jenny Doust. Further thanks goes to all the reviewers who commented on this manuscript: Jenny Negus, Sheila Page, Peter Knapp, Helena Liira, Elaine Beller and Jenny Doust.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Francis 2009

Methods	Cluster-RCT with general practices as the unit of allocation. Authors recruited general practices from England and Wales via mail and then phone, over an 18-month period (October 2006 to April 2008). In Wales, general practices were selected randomly; it is unclear how selection occurred in England. A statistician randomised general practices by block randomisation and then stratified by list size, antibiotic prescribing rate and country (Wales, England). Randomised general practices sequentially recruited eligible patients upon presentation to their practice. South-East Wales Local Research Ethics committee granted ethics approval
Participants	49 general practices in Wales were randomised, 36 recruited participants. 34 general practices in England were randomised, 25 recruited participants. Eligible participants included otherwise well children of any gender, aged between 6 months and 14 years with acute URTIs (cough, cold, sore throat, earache) for < 7 days. Mean age of recruited children was five years and they had a mean of three days of symptoms at baseline. The written information group had slightly fewer males (45%) compared to the usual care group (54%). General practices in both the written information and the usual care group had similar median (IQR) list sizes of 6750 (IQR 4400 - 9000) and 6800 (3700 - 8700) , respectively. Each group had a similar number of practices with above average rates of prescribing (intervention: 9, control: 10) and a similar number recruiting patients from England (intervention: 14, control: 11). 274 participants were randomised to the written information group and 284 to the usual care group
Interventions	Parents of children in the intervention group received an eight-page booklet on acute URTIs in children during a clinical consultation with their GP. The booklet included: prompts to discuss parent's concerns and expectations; information on how to manage a fever; advice about temperature fits (febrile convulsions); information about antibiotic effectiveness for cough, green phlegm, sore throat, earache and croup; when not to take antibiotics; and, when further help should be sought. Parents could take the booklet home following the consultation. GPs received online training on how to use this resource. It included education on: the content and aims of the booklet; encouraged its use within the consultation; and, the use of communication skills to explore parental concerns and expectations. The content of the booklet could not be tailored to individual patients
Outcomes	Reconsultation rate was the primary outcome (attending a face-to-face consultation about the same illness within 2 weeks of the index consultation). Relevant secondary outcomes included: antibiotics prescribed by clinicians, antibiotics used by patients, and parental satisfaction
Notes	Funded by Medical Research Council, Welsh Assembly Government and Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement

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Random sequence generation (selection bias)	Low risk	Quote: 'Practices were randomised by a statistician using block randomisation with random block sizes and stratification by practice list size, antibiotic prescribing rate for 2005, and country.' Comment: The randomisation technique was adequate and well described. The study statistician created the randomisation table using random permuted block sizes. Groups were comparable at baseline Quote: 'Participating clinicians were asked to recruit sequential eligible children (6 months to 14 years) consulting with an upper respiratory tract infection (cough, cold, sore throat, earache for seven days or less) and their parents.' Comment: Individual children could not be randomised as GPs cannot go from a trained to untrained state. The authors noted the potential bias in cluster randomisation and put measures in place to identify any selection bias: they requested GPs to record non-identifiable data for eligible patients not recruited. They did not identify any important differences between those recruited and those not recruited. There was also similar recruitment rates between written information and usual care groups
Allocation concealment (selection bias)	Low risk	Quote (from Protocol: Francis 2008): 'the study statistician will create a randomisation table using random permuted block sizes. These tables will be kept securely and allocation for each practice will be provided only after the practice has agreed to participate and the practice ID and stratification variables are provided to the statistician.' Comment: Clinicians could not foresee which group that were allocated to Comment: Figure 1 from protocol Francis 2008 shows method of patients consenting prior to delivery of intervention Comment: Patients and parents did not know which group they were enrolled in prior to informed consent
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: 'Neither clinicians nor participants were blinded as to study group.' Comment: Neither clinicians nor partici-

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		pants were blinded and outcomes were self-reported and thus, subjective
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: 'Follow-up was via a telephone administered questionnaire with the child's parent or guardian, 14 days after recruitment.' Comment: Although telephone interviewers were blinded when collecting outcome data, the outcomes were self-reported. Therefore, the true assessors of outcomes were the parents themselves, who were unblinded and reported subjectively
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: 'The primary analysis was intention to treat.' Quote: 'We achieved a follow-up rate of 94.6% (93.4% intervention, 95.8% control) for the primary outcome data.' Comment: Attrition was similar in written information (intervention) and usual care (control) groups: 11 practices failed to recruit in both groups; no practices were lost to follow-up; one patient withdrew from the written information group and two from the usual care group; 17 were lost to follow-up in the written information group and 10 in the usual care group. The authors used an intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Comment: All outcomes were reported as outlined in the study protocol (Francis 2008)
Other bias	Low risk	Quote: 'All participating clinicians were provided with information about the aims of the study. However, antibiotic use was listed fourth in a long list of outcome measures and is therefore unlikely to have resulted in meaningful changes in prescribing behaviour.' 'Funding for the development of the training website was from an educational grant from Pfizer UK...All authors declare that this work was conducted independently of the study funders.' Comment: Authors acknowledged a potential Hawthorne effect and mitigated this by disguising desired outcomes among a

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		long list of study outcomes. Pfizer supplied funding for the educational website but report the work was conducted independently and do not declare any competing interests

Mainous 2000

Methods	4-arm factorial randomised control trial using primary care clinicians as unit of allocation. Data from Medicaid was matched with Kentucky Medical Licensure Board (KMLB) to select primary care clinicians with experience in managing paediatric acute URTIs. Eligible clinicians that had billed for at least 75 episodes of any combination of the paediatric acute URTIs (see participants below) and at least 25 URTI episodes between 1 July 1995 and 30 June 1996. Individuals with this level of service were initially included in the study; however, individuals were kept in the study if they managed at least 5 acute URTIs/purulent rhinitis/acute bronchitis episodes in each of the 3 study periods of Autumn 1996, Winter/Spring 1997, and Autumn 1997 The intervention period of the study was from 1 July 1997 to 30 November 1997
Participants	269 primary care clinicians who provided primary care in either private or hospital-based practice and were family physicians (GPs), paediatricians or 'other primary care'. Otolaryngology specialists were excluded Patients (and their parents) aged less than 18 years old of any gender who were diagnosed with any of nonsuppurative otitis media, suppurative otitis media, sinusitis, streptococcal pharyngitis, pharyngitis/tonsillitis, rhinitis, acute URTI (common cold) or acute bronchitis were included. Patient presentations were measured as 'episodes of care', allowing multiple presentations for individual patients. A total of 33,792 episodes of care were reported (8274 (written information), 8946 (prescribing feedback to clinicians), 6203 (written information plus prescribing feedback to clinicians), 10,369 (usual care)) . Baseline differences evident in the number of URTI episodes (written information: 71. 3 +/- 84.2, usual care: 89.5 +/-125.2; written information and prescribing feedback to clinicians: 44.3 +/- 48.5, prescribing feedback: 70.9 +/- 89.2); and the geographical location of the clinicians targeted (written information: 81.1% rural, prescribing feedback to clinicians: 49.0% rural; written information plus prescribing feedback to clinicians: 76. 9% and usual care: 80.7% rural). Most episodes of care were for the common cold (86% for written information; 87% for prescribing feedback to clinicians; 90% for written information plus prescribing feedback to clinicians; and 85% for usual care)
Interventions	Selected clinicians (and respective patients) were randomised to one of four groups: 1. Prescribing feedback to clinicians: Clinicians received a copy of their antibiotic prescribing profile for paediatric acute URTI (common cold), acute bronchitis and purulent rhinitis for the period prior to the intervention (1 July 1995 to 30 June 30 1997) . Prescribing profile consisted of: total number of episodes of care for stated paediatric respiratory conditions, the number and proportion that received antibiotics, the total cost of the episode and the proportionate cost of antibiotics in the cost of evaluation and managing these conditions (as per Medicaid). In addition to the prescribing profile, clinicians also received their percentile rank for antibiotic prescribing compared to their peers 2. Written information: Clinicians received 25 x 2-page patient education pamphlets -

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	'Your Child and Antibiotics' - produced by the Centres for Disease Control and Prevention (CDC) and the American Society for Microbiology, along with an accompanying letter 'without information on costs and profiling. Clinicians could access further pamphlets if required. Fidelity to intervention or how pamphlets were given to parents has not been reported 3. Written information plus prescribing feedback to clinicians: Clinicians (and their patients, in the patient education arm) received both prescribing feedback and written information 4. Usual care: no intervention
Outcomes	Antibiotic prescribing by clinicians
Notes	Funded by Department of Public Health, Commonwealth of Kentucky

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: 'The physicians in the four groups were randomised.' Comment: Participants were randomised, however it is not clear how selected participants were randomised Further, there were differences between groups at baseline, implying randomisation attempts were inadequate
Allocation concealment (selection bias)	High risk	It is not clear if any allocation concealment was attempted. Further, as the randomisation methodology was unclear we assumed this risk of bias to be high
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Any blinding attempts were not reported. It was not possible to blind clinicians or participants. Outcomes, however, were objective, which mitigates need for blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcomes, not clear who searched through Medicaid data and if they were blinded or not, however objective outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: 'Fifty-three of those physicians were excluded from the final analysis because we could not document that each had five or more episodes of care for children for URIs, purulent rhinitis, or acute bronchitis in each of three study periods.' Comment: 53 physicians were excluded as

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Mainous 2000 (*Continued*)

		they did not meet the extended inclusion criteria, it is not clear at what time point they were excluded and from which arm they were excluded from. Further, no intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Given there was no prior published protocol, we cannot determine if other outcomes were measured and then not reported
Other bias	High risk	Quote: 'Each physician received 25 pamphlets and instructions that additional pamphlets could be obtained from the CDC.' Comment: Fidelity was not assessed. Quote: 'Prescribing for an illness was attributed to an individual physician. However, a specific respiratory infection may result in more than one physician contact. Therefore, it was necessary to create an episode of care for any particular respiratory infection.' Comment: Given physicians were randomised and then outcomes assessed via individual episodes of care, the risk of clustering is high, the authors do not acknowledge this, nor provide adequate data to adjust for clustering

IQR: inter-quartile range
URTIs: upper respiratory tract infections

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adinoff 2006	Not RCT
Agnew 2013	Not RCT
Allaire 2011	Not RCT
Altiner 2007	Mutlicomponent intervention
Bauchner 2001	Incorrect patient population

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(*Continued*)

Becker 2002	Not RCT
Briel 2010	Not RCT
Dolovich 1999	Wrong intervention
Doyne 2004	Multicomponent intervention
Everitt 2006	Incorrect patient population
Farquhar 2002	Not RCT
Finkelstein 2001	Wrong intervention
Flottorp 2002	Multicomponent intervention
Formoso 2011	Not RCT
Formoso 2013	Wrong intervention
Gonzales 1999	Multicomponent intervention
Gonzales 2004	Multicomponent intervention.
Gonzales 2005	Wrong intervention
Gonzales 2013	Multicomponent intervention
Hallsworth 2016	Incorrect patient population
Hay 2010	Not RCT
Hickman 2003	Multicomponent intervention
Jenkins 2013	Multicomponent intervention
Kullgren 2016	Incorrect patient population
Linder 2008	Not RCT
Légaré 2011	Multicomponent intervention
Macfarlane 2002	Incorrect patient population
Metlay 2007	Multicomponent intervention
Moore 2009	Incorrect patient population

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(*Continued*)

Moore 2010	Not RCT
Olives 2016	Incorrent patient population
Price 2011	Multicomponent intervention
Ratchina 2011	Multicomponent intervention
Rodis 2004	Not RCT
Rubin 2005	Multicomponent intervention
Sahlan 2008	Wrong intervention
Schnellinger 2010	Incorrect patient population
Segador 2005	Wrong intervention
Shaughnessy 2002	Not RCT
Smabrekke 2002	Multicomponent intervention
Smeets 2009	Multicomponent intervention
Sustersic 2012	Incorrect patient population
Taylor 2003	Incorrect patient population
Taylor 2005	Incorrect patient population
Teng 2006	Wrong intervention
Trepka 2001	Multicomponent intervention
Turnbull 2015	Wrong intervention
Vega 2015	Not RCT
Welschen 2004	Multicomponent intervention
Wright 2002	Not RCT
Yu 2015	Incorrect patient population

RCT: randomised controlled trial

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Characteristics of studies awaiting assessment *[ordered by study ID]*

Alder 2005

Methods	A four-arm factorial RCT in two suburban primary care clinics in Salt Lake City, Utah. Parents of children presenting to clinics were the unit of allocation. The randomisation technique was not described and it is unclear how these primary care clinics were selected. The study period ran from August to December 2000
Participants	Recruited 80 (20 per group) parents of children aged 1 to 10 years presenting to the GP with ear pain, sore throat, cough, congestion and/or fever who had not received antibiotics during the previous two weeks. Age of parents and age of children were similar between groups, only significant difference at baseline was the number of parents who were the child's primary caregiver (difference between groups P = 0.009)
Interventions	Parents of child patients were randomised into one of four groups: 1. Communication only intervention: Parents were asked to review and then ask their clinicians four questions. These questions were adapted from the *Talk to your Doctor* approach used in the Centres for Disease Control and Prevention's (CDC) *Use Antibiotics Wisely* campaign and were designed to enable parents to obtain necessary information about the illness affecting their child. 2. Information only intervention: Parents received a pamphlet *Antibiotics and Your Child (*published by CDC) and a fact sheet adapted from the *Use Antibiotics Wisely* campaign. Topics such as 'how bacteria become resistant, when antibiotics are and are not needed, and following recommended instructions if an antibiotic is prescribed' were covered in this material. 3. Combined intervention: Parents received both the communication and information intervention. 4. Control arm: Parents received an intervention focused on appropriate nutrition for children. It was not stated whether this intervention was verbal or written information, but was based on the US Food and Drug Administration (FDA) *TIPS for using the FOOD GUIDE PYRAMID for Young Children 2 to 6 years old*
Outcomes	Number of antibiotics prescribed by clinicians and parental satisfaction
Notes	This study measured the number of antibiotics prescribed by clinicians and parental satisfaction following the delivery of written information about antibiotics, but they did not report how they measured this nor did they provide the outcome data. We contacted the study authors to obtain these data, but did not receive a reply. We will re-contact these authors when updating this review

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DATA AND ANALYSES

Comparison 1. Written information versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antibiotics used by patients	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Antibiotics prescribed by clinicians	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Reconsultation rates	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Patient satisfaction with consultation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Written information plus prescribing feedback versus prescribing feedback alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antibiotics prescribed by clinicians	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

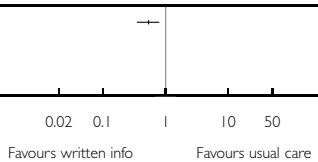
Analysis 1.1. Comparison 1 Written information versus usual care, Outcome 1 Antibiotics used by patients.

Review: Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care

Comparison: 1 Written information versus usual care

Outcome: 1 Antibiotics used by patients

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Francis 2009 (1)	24/108	47/112		0.53 [0.35, 0.80]



(1) with cluster adjustment

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Analysis 1.2. Comparison 1 Written information versus usual care, Outcome 2 Antibiotics prescribed by clinicians.

Review: Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care

Comparison: 1 Written information versus usual care

Outcome: 2 Antibiotics prescribed by clinicians

Study or subgroup	Favours written info n/N	Usual care n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Francis 2009 (1)	16/84	35/86		0.47 [0.28, 0.78]
Mainous 2000	3729/8274	5591/10369		0.84 [0.81, 0.86]

(1) with cluster adjustment

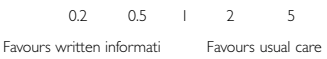
Analysis 1.3. Comparison 1 Written information versus usual care, Outcome 3 Reconsultation rates.

Review: Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care

Comparison: 1 Written information versus usual care

Outcome: 3 Reconsultation rates

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Francis 2009 (1)	22/170	29/177		0.79 [0.47, 1.32]



(1) with cluster adjustment

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Analysis 1.4. Comparison 1 Written information versus usual care, Outcome 4 Patient satisfaction with consultation.

Review: Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care

Comparison: 1 Written information versus usual care

Outcome: 4 Patient satisfaction with consultation

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Francis 2009 (1)	96/108	105/112		0.95 [0.87, 1.03]

(1) with cluster adjustment

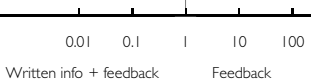
Analysis 2.1. Comparison 2 Written information plus prescribing feedback versus prescribing feedback alone, Outcome 1 Antibiotics prescribed by clinicians.

Review: Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care

Comparison: 2 Written information plus prescribing feedback versus prescribing feedback alone

Outcome: 1 Antibiotics prescribed by clinicians

Study or subgroup	Information plus feedback n/N	Feedback n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Mainous 2000	3079/6203	3929/8946		1.13 [1.09, 1.17]



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APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

1 exp Respiratory Tract Infections/
2 (respiratory adj3 infection*).tw.
3 (urti or lrti).tw.
4 Otitis Media/
5 otitis media.tw.
6 exp Sinusitis/
7 sinusit*.tw.
8 (acute adj3 (rhinosinusit* or nasosinusit* or rhinit*)).tw.
9 exp Pharyngitis/
10 (pharyngit* or nasopharyngit* or tonsillit*).tw.
11 sore throat*.tw.
12 exp Laryngitis/
13 laryngit*.tw.
14 croup.tw.
15 Cough/
16 cough*.tw.
17 Common Cold/
18 common cold*.tw.
19 coryza.tw.
20 Influenza, Human/
21 (influenza* or flu).tw.
22 Bronchitis/
23 bronchit*.tw.
24 exp Bronchiolitis/
25 bronchiolit*.tw.
26 or/1-25
27 exp Anti-Bacterial Agents/
28 antibiotic*.tw,nm.
29 27 or 28
30 Patient Education as Topic/
31 Pamphlets/
32 (pamphlet* or brochure* or leaflet* or booklet*).tw.
33 (flyer* or flier*).tw.
34 information pack*.tw.
35 information sheet*.tw.
36 (cards or postcard*).tw.
37 (handout* or guidebook*).tw.
38 (print* adj2 (material* or information* or guide or guides or instruction* or advice or advis*)).tw.
39 or/30-38
40 26 and 29 and 39

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Appendix 2. EMBASE (Elsevier) search strategy

#51 #42 AND #50
#50 #45 NOT #49
#49 #46 NOT #48
#48 #46 AND #47
#47 'human'/de
#46 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de
#45 #43 OR #44
#44 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR trial:ti OR allocat*:ab,ti OR (doubl* NEXT/1 blind*):ab,ti
#43 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#42 #24 AND #27 AND #41
#41 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#40 'health literacy'/de
#39 'consumer health information'/de
#38 'information dissemination'/de
#37 'persuasive communication'/de
#36 (patient* NEAR/3 (literatur* OR material* OR information* OR guide* OR guides OR instruction*)):ab,ti
#35 ((print* OR written OR text*) NEAR/3 (material* OR information* OR guide OR guides OR instruction* OR advice OR advis* OR messag* OR note OR notes)):ab,ti
#34 handout*:ab,ti OR guidebook*:ab,ti
#33 card:ab,ti OR cards:ab,ti OR postcard*:ab,ti
#32 (information NEAR/2 (pack* OR sheet*)):ab,ti
#31 flyer*:ab,ti OR flier*:ab,ti
#30 pamphlet*:ab,ti OR brochure*:ab,ti OR leaflet*:ab,ti OR booklet*:ab,ti
#29 'publication'/de
#28 'patient education'/de
#27 #25 OR #26
#26 antibiotic*:ab,ti
#25 'antibiotic agent'/exp
#24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#23 bronchit*:ab,ti OR bronchiolit*:ab,ti
#22 'bronchitis'/exp
#21 influenza*:ab,ti OR flu:ab,ti
#20 'influenza'/exp
#19 coryza:ab,ti
#18 'common cold'/de OR 'common cold symptom'/de
#17 cough*:ab,ti
#16 'coughing'/de
#15 croup:ab,ti
#14 ((throat* OR 'middle ear' OR tonsil* OR sinus* OR laryn* OR pharyn* OR bronch*) NEAR/3 (inflam* OR infect*)):ab,ti
#13 laryngit*:ab,ti
#12 'laryngitis'/de
#11 'sore throat'/de
#10 pharyngit*:ab,ti OR nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti OR tonsillit*:ab,ti
#9 'pharyngitis'/exp
#8 (acute NEAR/3 (rhinosinusit* OR nasosinusit* OR rhinit*)):ab,ti
#7 sinusit*:ab,ti
#6 'sinusitis'/exp
#5 'otitis media':ab,ti
#4 'otitis media'/exp

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#3 urti:ab,ti OR lrti:ab,ti
#2 (respiratory NEAR/3 infection*):ab,ti
#1 'respiratory tract infection'/exp

Appendix 3. CINAHL (Ebsco) search strategy

S52 S42 and S51 S
S51 S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50
S50 (MH "Quantitative Studies")
S49 TI placebo* OR AB placebo*
S48 (MH "Placebos")
S47 TI random* OR AB random*
S46 TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*))
S45 TI clinic* trial* OR AB clinic* trial*
S44 PT clinical trial
S43 (MH "Clinical Trials+")
S42 S25 and S28 and S41
S41 S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40
S40 (MH "Information Literacy")
S39 (MH "Communication")
S38 (MH "Consumer Health Information")
S37 TI (patient* N3 (literatur* or material* or information* or guide or guides or instruction*)) OR AB (patient* N3 (literatur* or material* or information* or guide or guides or instruction*))
S36 TI ((print* or written or text*) N3 (material* or information* or guide or guides or instruction* or advice or advis* or messag* or note or notes)) OR AB ((print* or written or text*) N3 (material* or
information* or guide or guides or instruction* or advice or advis* or messag* or note or notes))
S35 TI (handout* or guidebook*) OR AB (handout* or guidebook*)
S34 TI (card or cards or postcard*) OR AB (card or cards or postcard*)
S33 TI (information N2 (pack* or sheet*)) OR AB (information N2 (pack* or sheet*))
S32 TI (flyer* or flier*) OR AB (flyer* or flier*)
S31 TI (pamphlet* or brochur* or leaflet* or booklet*) OR AB (pamphlet* or brochur* or leaflet* or booklet*)
S30 (MH "Pamphlets")
S29 (MH "Patient Education")
S27 TI antibiotic* OR AB antibiotic*
S26 (MH "Antibiotics+")
S25 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or
S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24
S24 TI (bronchit* or bronchiolit*) OR AB (bronchit* or bronchiolit*)
S23 (MH "Bronchitis+")
S22 TI (influenza* or flu) OR AB (influenza* or flu)
S21 (MH "Influenza+")
S20 TI coryza OR AB coryza
S19 TI common cold* OR AB common cold*
S18 (MH "Common Cold")
S17 TI cough* OR AB cough*
S16 (MH "Cough")
S15 TI croup OR AB croup
S14 TI ((throat* or middle ear* or tonsil* or sinus* or laryn* or pharyn* or bronch*) N3 (inflam* or infect*)) OR AB ((throat* or middle ear* or tonsil* or sinus* or laryn* or pharyn* or bronch*) N3 (inflam* or infect*))
S13 TI laryngit* OR AB laryngit*
S12 (MH "Laryngitis+")
S11 TI sore throat* OR AB sore throat*

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S10 TI ((pharyngit* or nasopharyngit* or rhinopharyngit* or tonsillit*)) OR AB ((pharyngit* or nasopharyngit* or rhinopharyngit* or tonsillit*))
S9 (MH "Pharyngitis")
S8 TI (acute N3 (rhinosinusit* or nasosinusit* or rhinit*)) OR AB (acute N3 (rhinosinusit* or nasosinusit* or rhinit*))
S7 TI sinusit* OR AB sinusit*
S6 (MH "Sinusitis+")
S5 TI otitis media OR AB otitis media
S4 (MH "Otitis Media+")
S3 TI (urti or lrti) OR AB (urti or lrti)
S2 TI respiratory N3 infection* OR AB respiratory N3 infection*
S1 (MH "Respiratory Tract Infections+")

Appendix 4. LILACS (BIREME) search strategy

(MH:"Anti-Bacterial Agents" OR Antibacterianos OR Antibacterianos OR antibiotic$ OR MH:D27.505.954.122.085$ OR Antibacterianos OR Antibióticos) AND (MH:"Patient Education as Topic" OR "Educación del Paciente" OR "Educação de Pacientes" OR Pamphlets OR Folletos OR Folhetos OR Panfletos OR Libretes OR Livretos OR booklet$ OR brochur$ OR flyer$ OR flier$ OR card OR cards OR postcard$ OR handout$ OR guidebook$ OR MH:"Consumer Health Information" OR "Información de Salud al Consumidor" OR "Informação de Saúde ao Consumidor" OR MH:I02.233.332.186$ OR MH:N02.421.143.827.407.228$ OR N02.421.726.407.228$ OR MH:"Persuasive Communication" OR "Comunicación Persuasiva" OR "Comunicação Persuasiva" OR MH:"Information Dissemination" OR "Diseminación de Información" OR "Disseminação de Informação" OR "information sheet" OR "information sheets" OR "information pack" OR "information packs" OR "information package" OR "printed information" OR "printed instructions" OR "printed guides" OR "patient information" OR "patient instructions")

Appendix 5. Web of Science (Thomson Reuters) search strategy

# 6	#5 AND #4 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years*
# 5	**TOPIC:** (random* or placebo* or ((singl* or doubl*) NEAR/1 blind*) or crossover* or "cross-over" or allocat*) *OR* **TITLE:** (trial) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years*
# 4	#3 AND #2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years*
# 3	**TOPIC:** (pamphlet* or brochur* or leaflet* or booklet* or flyer* or flier* or (information NEAR/3 (pack* or sheet*)) or card or cards or postcard* or handout* or guidebook* or ((print* or written or text*) NEAR/3 (material* or information* or guide or guides or instruction* or advice or advis* or messag* or note or notes)) or ((patient* or consumer*) NEAR/3 (literatur* or material* or information* or guide or guides or instruction*))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years*
# 2	**TOPIC:** (antibiotic* or anti-bacterial*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years*
# 1	**TOPIC:** ((respiratory NEAR/3 infection*) or urti or lrti or "otitis media" or sinusit* or (acute NEAR/1 (rhinosinusit* or nasosinusit* or rhinit*)) or pharyngit* or nasopharyngit* or rhinopharyngit* or tonsillit* or "sore throat" or "sore throats" or laryngit* or ((throat* or "middle ear" or tonsil* or sinus* or laryn* or pharyn* or bronch*) NEAR/3 (infect* or inflam*)) or

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(*Continued*)

	croup or cough* or "common cold" or "common colds" or coryza or influenza* or flu or bronchit* or bronchiolit*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years*

Appendix 6. WHO International Clinical Trials Registry Platform Search Portal

Searched: 'information AND upper respiratory tract infections AND patient AND antibiotics'

Appendix 7. clinicaltrials.gov

Searched: 'information AND upper respiratory tract infections AND patient AND antibiotics

CONTRIBUTIONS OF AUTHORS

- PG conceived the idea for the review.
- JOS, RT and AMcC screened abstracts and extracted data.
- JOS and AMcC analysed data.
- All authors drafted the review and agreed the final version for publication.

DECLARATIONS OF INTEREST

- Jack W O'Sullivan: none known.
- Robert T Harvey: none known.
- Paul P Glasziou: PG is supported by an NHMRC Research Fellowship (Ref: GNT1080042) and is a CI on an NHMRC Centre for Research Excellence award for the Centre for Research Excellence (CRE) in Minimising Antibiotic Resistance for Acute Respiratory Infections (CREMARA) (Ref: 1044904).
- Amanda McCullough: AMcC is supported by an NHMRC Centre for Research Excellence award for the Centre for Research Excellence in Minimising Antibiotic Resistance for Acute Respiratory Infections (CREMARA) (Ref: 1044904).

SOURCES OF SUPPORT

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Internal sources

- No sources of support supplied

External sources

- National Health and Medical Research Council (NHMRC), Australia.

PG is supported by an NHMRC Research Fellowship (Ref: GNT1080042) and is a CI on an NHMRC Centre for Research Excellence award for the Centre for Research Excellence (CRE) in Minimising Antibiotic Resistance for Acute Respiratory Infections (CREMARA) (Ref: 1044904). AMcC is supported by the same CRE. The funder did not have any role in the concept, design or undertaking of this review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Amanda McCullough has been changed to last author. Paul Glasziou has been changed to third author. The title of this review has been changed to: Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care. The following sentence was deleted from the 'Methods, Types of studies' section, because inclusion of these studies would not enable the effect of written information to be determined: "We will also include studies that compared information and another intervention with a control (for example, usual care)." We also changed the following sentence from: 'Trials that include information as the only intervention and those that include information as an add-on intervention will be included.' to 'We also included studies that included information as an add-on intervention.' Primary care was not defined in the protocol; a definition is included in the review. See Types of participants. GRADE methods were not mentioned in the protocol, but have been used in this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [*therapeutic use]; General Practice; Inappropriate Prescribing [*prevention & control; statistics & numerical data]; Pamphlets; Parents; Patient Education as Topic [methods]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [*drug therapy; virology]; Virus Diseases [drug therapy]

MeSH check words

Child; Humans

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